TITLE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis
Protocol Number:	ALXN1210-MG-306
Compound Number:	ALXN1210
USAN/INN:	Ravulizumab
Amendment Number:	2
Short Title:	Safety and Efficacy Study of Ravulizumab in Adults With Generalized Myasthenia Gravis
Sponsor Name	Alexion Pharmaceuticals, Inc. (Alexion)
Legal Registered Address:	121 Seaport Boulevard Boston, MA 02210 USA
Regulatory Agency Identifying Number:	IND: 140,115 EUDRACT: 2018-003243-39
Approval Date:	25 Oct 2019

Sponsor Signatory:

PPD

10/28/2019

Date

Medical Monitor Name and Contact Information can be found in the Study Contact list distributed to Study Sites.

24-hour Emergency Contact: PPD

INVESTIGATOR'S AGREEMENT

I have read the ALXN1210-MG-306 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	25 Oct 2019
Amendment 1.2 (France)	14 Oct 2019
Amendment 1.1 (Germany)	27 Jun 2019
Amendment 1	11 Dec 2018
Original Protocol	16 Nov 2018

Amendment 2 (25 Oct 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

To revise secondary and exploratory endpoints, to decrease burden to patients by reduction in assessment and visit frequency, to provide additional guidance for supplemental dosing, and to clarify minor operational aspects of the protocol.

Section # and Name	Description of Change	Brief Rationale
Title page	Updated legal registered address.	
Sponsor Signatory	Removed sponsor signatory's personal contact information.	Contact information is provided in the study contact list provided to sites.
Section 1.1 and Section 3 Objectives and Endpoints	Moved change from baseline in MG-QOL15r and Neuro-QOL Fatigue scores and MG-ADL and QMG responder from exploratory to secondary endpoints. PK/PD/ADA endpoints moved from under exploratory to new independent subheading. Expanded exploratory endpoints to include change from baseline in MG-ADL and QMG subcomponent scores as well as incidence of hospitalizations/MG-related hospitalizations and Clinical Deterioration/MG crisis. Clarified that endpoints will be evaluated throughout study.	To better characterize disease parameters associated with gMG and yield a clearer assessment of the impact of study intervention.
Section 1.3 Schedule of Activities	Removed evaluation of Myasthenia Gravis Foundation of America-Post-Interventional Status (MGFAPIS) on Day 1.	Post-intervention status cannot be evaluated before patients receive study intervention.
	Added serum pregnancy test at Day 183/ET.	To ensure patient safety.
	Removed visits at Weeks 3, 8, 14, 22, and 40; reduced number of visits at which MG-QOL15r, Neuro-QOL Fatigue, and EQ-5D-5L are collected, including removal from Clinical Deterioration visits; expanded visit window and reduced/moved PK/Free C5 and ADA collections during extension.	To reduce burden on patient.

Section # and Name	Description of Change	Brief Rationale
	Added body weight collection at all visits.	Needed to ensure that proper dosage is administered.
	Revised footnotes to specify data collected for MG history and C-SSRS, assessments needed at Clinical Deterioration visits, and requirement for Properly Trained Clinical Evaluator to perform QMC and MGC assessments.	Clarifications
Section 2.3 Study Rationale	Added approval of eculizumab for the treatment of neuromyelitis optica spectrum disorder.	Update.
Section 4.1.1 Screening Period	Clarified MG history data collection, including 2-year hospitalization history. Removed incorrect statement about retaining a patient who experiences Clinical Deterioration/MG crisis during the Screening Period (inconsistent with Section 5.4).	To enable assessment of pre-study hospitalizations. Correction.
Section 4.2.4 Responsibilities for Myasthenia Gravis Assessments	Noted that MG-ADL must be performed first, QMG second.	Clarification.
Section 4.4 Justification for Dose	Revised to reflect that the ravulizumab dosing regimen used in this study is approved for adult patients with PNH.	To inform on labeled dosing recommendation.
Section 5.1 Inclusion Criteria	Revised IC#2 and IC#3 to clarify that MG diagnosis must occur at least 6 months prior to screening, and that eligibility is confirmed by positive anti-AChR Ab test result at screening and by abnormal neuromuscular transmission test and/or improvement in MG signs with oral cholinesterase inhibitor treatment either historically or during screening.	To further clarify entry criteria for the investigator.
Section 5.2 Exclusion Criteria	Revised EC#1 to permit treated patients with stage 1 or 2 thymoma other than thymic carcinoma and EC#2 to exclude thymomectomy or any thymic surgery.	To clarify entry criteria for patients with thymoma.
	Added 3 new exclusion criteria for history of unexplained infections, active infections within 14 days of study drug administration, or fever within 7 days of study drug administration.	To exclude enrollment of patients with active systemic infections.
Section 6.1 Study Drug Administration	Added instruction for action to be taken if a patient's body weight drops below 40 kg during treatment.	Clarification.
Section 6.4 Concomitant Therapy	Added that MG-specific medication or therapy (eg, thymectomy, ISTs including corticosteroids, IVIg, and PE/PP) within 2 years prior to screening will be recorded.	Clarification regarding data collection.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.1.4 PE/PP/IVIg	In Table 7 and Table 8, applicable supplemental dosing day range has been added, and doses and corresponding diluent and total volumes have been corrected in the Placebo group Open Label Extension associated with the Blinded ravulizumab loading dose administered on Day 183. Details in text on supplemental dose timing.	To clarify timing of supplemental dosing and to maintain blind on Day 183.
Section 6.5.1.5 Disallowed Medications and Therapies	Added chronic PE/PP and IVIg therapies.	To clarify that only acute treatment is permitted.
Section 8.1.1 Hospitalization	Reduced information to be collected to include only that required for meaningful assessment.	To reduce burden on patients.
Section 8.1.2 Clinical Deterioration	Replaced text description of PK/PD sampling during Clinical Deterioration with a figure that provides instructions more clearly. Changed numbering to bullets.	Clarification. Specific order of procedures is not required.
Section 8.1.9 MGFA Clinical Classification	Added new section describing Day 1 assessment of MGFA Clinical Classification.	Correction.
Section 8.1.10 MGFA Post-Intervention Status	Noted that modified version of MGFA-PIS does not include categories of Exacerbation or Died of MG.	Clarification.
Section 8.2.3 Electrocardiogram	Indicated that QT interval will be corrected for heart rate using Fridericia's formula.	Clarification.
Section 8.2.4.1 Urinalysis and Urine Chemistry	Removed statement regarding protein:creatinine ratio, which will not be performed in this study.	Correction.
Section 8.2.5.1 Columbia-Suicidal Severity Rating Scale	Added timepoints (lifetime and past 1 year [12 months]) for assessing suicidal ideation and behaviors	To provide specific time points for data collection that have been implemented in the eCRF.
Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	All adverse events that occur after the informed consent form (ICF) is signed must be recorded in the adverse event case report form, not in the medical history form.	To ensure appropriate collection of pretreatment adverse events.
Section 8.8 Biomarkers	Noted that unused PK/PD/ADA/AChR samples may be stored for future biomarker research.	To allow for future studies to understand drug/disease mechanisms.
Section 8.9 Healthcare Resource Utilization	Data collected will be the type of facility (hospital, rehabilitation center, or hospice), whether the primary reason for admission was related to MG, and the duration of hospitalization.	To reduce data collection to only those elements needed for analysis.
Section 9 Statistical Considerations	Added description of plans for CSR preparation.	Clarification.
Section 9.1 Statistical Hypotheses	Re-ordered secondary and exploratory hypotheses and estimation of treatment effect to align with changes made in Section 1.1 and Section 3 Objectives and Endpoints.	To better characterize disease parameters associated with gMG and yield a clearer assessment of the impact of study intervention.
Section 9.4.5.4 Multiplicity Adjustment for Primary and Secondary Endpoints	Added description of secondary hypothesis testing.	To inform on statistical methods.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.6.4 Analysis of PK and PD	Revised description of analyses to be performed.	To inform on statistical methods.
Section 10.1.3 Data Protection	Described storage of anonymized data.	To inform on data protection.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Deleted creatinine and added leukocyte esterase, ADA, and AChR Ab.	Correction.
Section 10.8 Appendix 8 Myasthenia Gravis Composite Scale	Replaced with updated image.	Correction.
Section 10.11 Appendix 11: Neurology Quality of Life Fatigue	The last 3 questions of the Neurology Quality of Life Fatigue questionnaire were added to Appendix 11.	Page 2 of the sample document was missing in prior versions of the protocol.
Section 10.12 Appendix 12: Myasthenia Gravis Foundation of America Clinical Classification	MGFA clinical classification is added as Appendix 12.	In this trial, MGFA classification is utilized to assess the MG clinical state of patients. It was missing in prior versions of the protocol.
Section 10.16 Appendix 16: Statistical Considerations	Expanded description of sample size determination.	To inform on statistical methods.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: Safety and Efficacy Study of Ravulizumab in Adults With Generalized Myasthenia Gravis

Rationale: Ravulizumab (ALXN1210) was engineered from eculizumab (h5G1.1-mAb), humanized monoclonal antibody that specifically binds with high affinity to the human terminal complement component (C5), inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic complement activation products, C5a, and the cytolytic and proinflammatory/prothrombotic membrane attack complex, C5b-9, which are responsible for the antibody-mediated destruction of the neuromuscular junction (NMJ), loss of acetylcholine receptors, and failure of neuromuscular transmission associated with generalized myasthenia gravis (gMG). Eculizumab is approved for the treatment of gMG, paroxysmal nocturnal hemoglobinuria, and atypical hemolytic uremic syndrome in many countries worldwide, including Japan, the USA, and countries in the European Union under the trade name Soliris®.

Ravulizumab preserves immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval; it was specifically designed (and has subsequently been proven) to have an increased half-life relative to eculizumab. Therefore, ravulizumab requires less frequent (once every 8 weeks [q8w]) infusions than eculizumab (once every 2 weeks [q2w] infusions). Given that gMG is a chronic disease with a significant treatment burden, the relative convenience of the ravulizumab dosing regimen may increase patient satisfaction and treatment adherence, and ultimately, lead to improved health outcomes.

Ravulizumab was designed based on comprehensive modelling and simulation analyses to maintain efficacious concentrations across an extended dosing interval. The enhanced pharmacokinetic (PK)/pharmacodynamic profile of ravulizumab, with fewer PK troughs than eculizumab, has the potential to improve therapeutic efficacy while maintaining a safety profile similar to that of eculizumab. Furthermore, the q8w dosing regimen minimizes the risk of incomplete complement inhibition.

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.

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

infusion. Patients will be centrally randomized using interactive response technology. The randomization will be stratified by region (North America, Europe, Asia-Pacific, and Japan).

Patients randomized to the ravulizumab group will receive a blinded loading dose of ravulizumab on Day 1, followed by blinded maintenance doses of ravulizumab on Day 15 (Week 2) and q8w thereafter, for a total of 18 weeks of treatment. Patients randomized to placebo will receive a blinded dose of placebo on Day 1, followed by blinded doses of placebo on Day 15 (Week 2) and q8w thereafter, for a total of 18 weeks. Both ravulizumab and placebo will be administered by intravenous infusion.

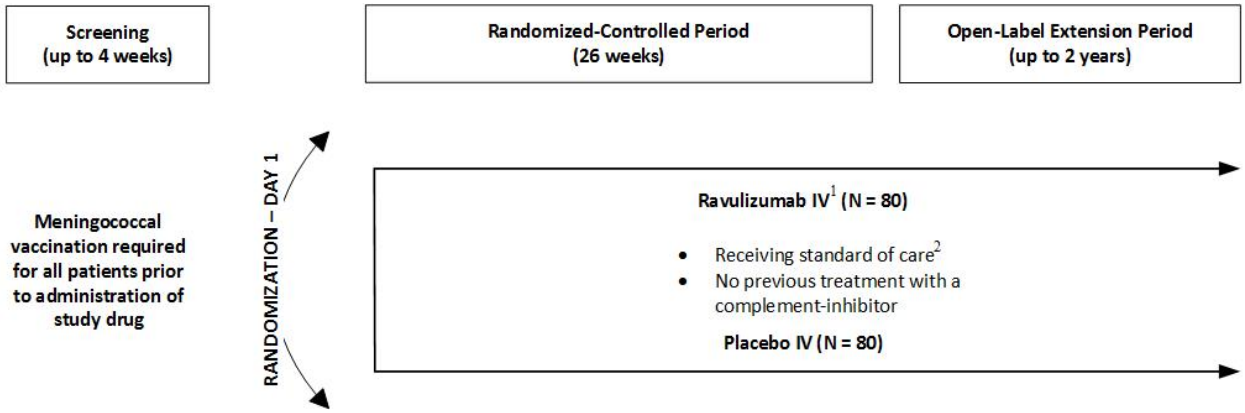
After the 26-Week Randomized-Controlled Period and assessments on Day 183 (Week 26), patients in the placebo group will receive a blinded loading dose of ravulizumab and patients in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg; the 900-mg dose was chosen to ensure maintenance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

Data Monitoring Committee: No.

1.2. Schema

Study ALXN1210-MG-306 Schematic



[1] Ravulizumab dosage regimen:

LOADING DOSE (Day 1) =

2400 mg for patients weighing ≥ 40 kg to < 60 kg
2700 mg for patients weighing ≥ 60 kg to < 100 kg
3000 mg for patients weighing ≥ 100 kg

MAINTENANCE DOSE (Day 15 and every 8 weeks [q8w] thereafter) =

3000 mg for patients weighing ≥ 40 kg to < 60 kg
3300 mg for patients weighing ≥ 60 kg to < 100 kg
3600 mg for patients weighing ≥ 100 kg

[2] Standard of care treatment to remain stable throughout the Randomized-Controlled Period

Abbreviations: IV = intravenous; N = number [of patients]

1.3. Schedule of Activities

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

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**	
Informed Consent	X									
Assessment of Inclusion/ Exclusion Criteria	X	X								
Medical History	X									
MG History[3]	X									
MGFA Clinical Classification[4]	X	X								
Weight	X		X		X	X	X	X	X	
Height	X									
HIV-(1 and 2) testing	X									
Vital Signs & Pulse Oximetry[5]	X	X	X	X	X	X	X	X	X	X
Physical Examination	X								X	X
Abbreviated Physical Examination[6]		X	X	X	X	X	X	X		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Non-Drug Therapy	X	X	X	X	X	X	X	X	X	X
MG Therapy Status	X	X	X	X	X	X	X	X	X	X
Hospitalization Status		X	X	X	X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X	X	X	X	X
MG-ADL[4,7]	X	X	X	X	X	X	X	X	X	X
QMG[4,8]	X	X	X	X	X	X	X	X	X	X
MG-QOL15r	X	X			X		X	X	X	
Neuro-QOL Fatigue	X	X			X		X	X	X	
EQ-5D-5L	X	X			X		X	X	X	
MGC[4,8]	X	X	X	X	X	X	X	X	X	X
MGFA-PIS[4]					X		X	X	X	
C-SSRS Baseline/Screening Version[9]		X								
C-SSRS Since Last Visit Version							X		X	
ECG	X								X	
AChR Ab	X						X		X	X

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.

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).

Table 2: Schedule of Activities: Extension Period

Period	Open-Label Extension																	Clinical Deterioration[1]
Study Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Study Days[2]	**D183**	**D197**	**D211**	**D253**	**D267**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**	**D925/ ET[3]/ EOS**	
Weeks	**W26**	**W28**	**W30**	**W36**	**W38**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**	**W 132**	
Window (day)		**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs & Pulse Oximetry[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination																	X	X
Abbreviated Physical Examination[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-Drug Therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG Therapy Status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalization Status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[6, 7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QMG[6, 8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-QOL15r			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Neuro-QOL Fatigue			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
MGC[6, 8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MGFA-PIS[6]					X	X		X		X		X		X		X	X	
C-SSRS Since Last Visit Version					X	X		X		X		X		X		X	X	
ECG																	X	
AChR Ab						X		X		X		X		X		X	X	X
Clinical Lab Tests[9]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Activities: Extension Period (Continued)

Period	Open-Label Extension																	Clinical Deterioration[1]
Study Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Study Days[2]	**D183**	**D197**	**D211**	**D253**	**D267**	**D309**	**D365**	**D421**	**D477**	**D533**	**D589**	**D645**	**D701**	**D757**	**D813**	**D869**	**D925/ ET[3]/ EOS**	
Weeks	**W26**	**W28**	**W30**	**W36**	**W38**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	**W124**	**W 132**	
Window (day)		**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Pregnancy Test[10]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
PK, Free C5[11]	P	T/P		T/P		T/P	T/P		T/P		T/P		T/P		T/P		T	X
ADA[11]				X		X			X				X				X	X
Patient Safety Information Card[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Ravulizumab Infusion[13]	X	X		X		X	X	X	X	X	X	X	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 can be scheduled at the discretion of the Investigator.

[2] Extension Period begins at the start of Day 183 (Week 26) dosing.

[3] If a patient withdraws early from the study during the Extension Period an Early Termination Visit will be performed.

[4] 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.

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

[6] Refer to Section 4.2.4.

[7] The MG-ADL is required to be performed first, followed by the QMG. The MG-ADL 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] Clinical laboratory tests will be performed at the central laboratory.

[10] Pregnancy tests must be performed on all patients of child-bearing potential at the specified time points. Serum pregnancy tests will be performed at Day 925/ET/EOS; 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.

Table 2: Schedule of Activities: Extension Period (Continued)

[11]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 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, a blood sample for serum PK/PD and ADA analyses will be collected if supplemental dosing is provided (see Section 8.1.2).

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

[13]Ravulizumab will be administered intravenously via infusion after completion of all other tests and procedures, excluding the peak blood sampling for PK, 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; ECG = electrocardiogram; EOS=End of Study; EQ-5D-5L = Euro Quality of Life; ET = Early Termination; ICU = Intensive Care Unit; MG = Myasthenia Gravis; MG-ADL = MG Activity 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 = pharmacokinetics/pharmacodynamics; QMG = Quantitative Myasthenia Gravis score for disease severity; QoL = quality of life; T = trough sample.

2. INTRODUCTION

2.1. Generalized Myasthenia Gravis

Generalized myasthenia gravis (gMG) is a rare disorder, which based on studies conducted in Europe, has an estimated prevalence between 145 to 278 per million inhabitants (Cetin, 2012; Fang, 2015; Heldal, 2009). Patients with gMG suffer from a devastating inflammatory neuromuscular disorder with limited therapeutic options.

Generalized myasthenia gravis patients differ from the ocular myasthenia gravis (MG) population in that neuromuscular inflammation and the resultant clinical findings are not just limited to the ocular muscles, but involve all voluntary muscle groups: the bulbar, respiratory, head, neck, trunk, or peripheral muscles with or without involvement of the eyes. Profound weakness and devastating consequences, including slurred speech, dysarthria, dysphagia, disorienting vision, shortness of breath (both with activity and at rest), weakness of the upper and lower extremities, impaired mobility, marked reductions in the ability to perform activities of daily living (ADLs), extreme fatigue, and episodes of pulmonary failure requiring mechanical ventilation are hallmarks of gMG. Compared with patients with isolated ocular MG, patients with gMG have a greater incidence of morbidities and a higher burden of disease (Engel-Nitz, 2018).

Hospitalizations for gMG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (eg, myasthenic crisis) and gastrointestinal tube placement for nutritional support and prevention of dysphagia-associated aspiration. Patients with more advanced gMG have been reported to experience increased mortality of up to 40% at 10 years following diagnosis (Christensen, 1998).

2.2. Background

2.2.1. Unmet Medical Need in Patients With Generalized Myasthenia Gravis

In difficult-to-control cases, patients with gMG experience unrelenting inflammation, tissue destruction, and consequent severe morbidities including profound muscle weakness, impaired mobility, shortness of breath, pulmonary failure, extreme fatigue, risk for aspiration, and markedly impaired ADLs (Sahashi, 1978; Silvestri, 2014; Suh, 2013). These patients are typically diagnosed in the prime of their adult lives, with a median age of onset ranging from 36 to 60 years (Suh, 2013). As a result of the morbidities associated with gMG, many patients cannot work or have diminished work-capacity, experience difficultly caring for themselves and others, and require assistance speaking, eating, ambulating, breathing, and performing ADLs.

2.2.2. Role of Complement in Myasthenia Gravis

Uncontrolled terminal complement activation has been implicated in animal models of experimental autoimmune gMG (Sahashi, 1978; Fitch, 1999; Dalakas, 2004; Keshavjee, 2005; Patel, 2005) as well as in other forms of autoimmune neuropathy in humans. Autoantibodies recognize targeted neural or muscle tissues, including the acetylcholine receptor (AChR), leading to uncontrolled terminal complement activation at the neural or muscle surface (Ha, 2015).

Autoantibody-driven uncontrolled terminal complement activation with membrane attack complex (MAC)-dependent lysis and activation, and C5a-dependent inflammation at the neuromuscular junction (NMJ) causes AChR loss and failure of neuromuscular transmission. Consistent with this model, both complement component (C) 3 (C3a and C3b) fragments and the MAC C5b-9 have been found in NMJs of MG patients (Sahashi, 1978).

Taken together, the data support that uncontrolled terminal complement activation at the NMJ plays a role in the destruction of post-synaptic structure. Rapid, complete, and sustained inhibition of terminal complement activation is a biologically rational approach to prevent the damage caused in patients with gMG.

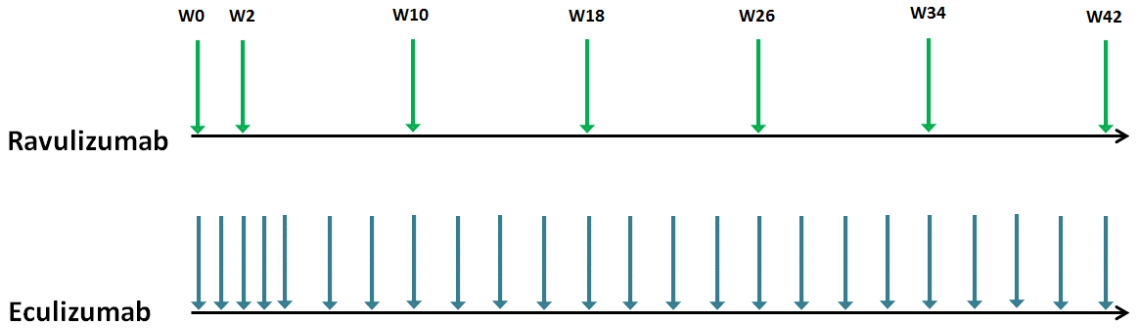
2.3. Study Rationale

Ravulizumab (ALXN1210) was engineered from eculizumab (h5G1.1-mAb), a humanized monoclonal Ab (mAb) that specifically binds with high affinity to the human terminal C5, inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic mediators, such as MAC C5b-9, which are responsible for the inflammatory consequences of terminal complement activation. Eculizumab is approved for the treatment of gMG, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and neuromyelitis optica spectrum disorder (NMOSD) in many countries worldwide under the trade name Soliris®.

Ravulizumab preserves immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval; it was specifically designed (and has subsequently been proven) to have an increased half-life relative to eculizumab. Therefore, ravulizumab requires less frequent (once every 8 weeks [q8w]) infusions relative to eculizumab (once every 2 weeks [q2w] infusions). Given that gMG is a chronic disease with a significant treatment burden, the relative convenience of the ravulizumab dosing regimen may increase patient satisfaction, increase treatment adherence, and ultimately, lead to improved health outcomes.

Ravulizumab was designed based on comprehensive modelling and simulation analyses to maintain efficacious concentrations across a longer dosing interval. The enhanced pharmacokinetic (PK)/pharmacodynamic (PD) profile of ravulizumab, with fewer PK troughs, than eculizumab, has the potential to improve therapeutic efficacy while maintaining a safety profile similar to that of eculizumab. Furthermore, the q8w dosing regimen minimizes the risk of incomplete complement inhibition. The infusion frequency is relatively low (6 infusions per year) (Figure 1), which offers the potential for improved quality of life (QoL) through fewer missed days of work or school, better treatment adherence, and improved accessibility.

Figure 1: Ravulizumab Every 8 Weeks Dosage Regimen Versus Eculizumab Every 2 Weeks Dosage Regimen



Ravulizumab offers a convenient dosing and immediate onset of action with effective and complete terminal complement inhibition at the end of the first infusion. Additionally, the dose regimen of ravulizumab has been optimized to reduce the exposure differences across the adult body-weight range by utilizing a weight-based dosing paradigm that provides immediate, complete, and sustained C5 inhibition over the entire dosing interval. Therefore, ravulizumab minimizes the risk of inflammation, including C5a recruitment and activation of inflammatory cells as well as direct MAC-complex induced damage of the motor neural endplate (Kusner, 2008).

The proposed rationale for the ravulizumab posology for the gMG indication is highly consistent with the approach used in dose-selection for eculizumab in the aHUS and gMG indications.

2.4. Benefit/Risk Assessment

Ravulizumab provides patients and physicians with an option for less frequent dosing, which allows greater access to care for those patients who may not initiate treatment on eculizumab, may discontinue eculizumab due to frequency of dosing, or who are currently receiving eculizumab every 2 weeks.

2.4.1. Identified and Potential Risks

2.4.1.1. Identified Risk

2.4.1.1.1. *Neisseria meningitidis*

Increased susceptibility to infection caused by *Neisseria meningitidis (N meningitidis)* is a known risk associated with complement inhibition. The main risk associated with ravulizumab is the risk of meningococcal infections. Specific risk mitigation measures are in place to address this risk, as described in Section 8.3.6.

2.4.1.2. Potential Risks

2.4.1.2.1. Immunogenicity

Administration of any therapeutic protein, including ravulizumab, may induce an immunogenic response potentially resulting in antidrug antibodies (ADA). The spectrum of potential clinical

consequences may include severe hypersensitivity-type reactions and decrease in efficacy (PK and/or PD neutralization) due to development of neutralizing ADA (Casadevall, 2002; Li, 2001).

Of the 261 patients with PNH who were treated with ravulizumab in the ravulizumab IV clinical studies, 1 patient developed a treatment-emergent ADA. Treatment-emergent ADAs have been observed in 3 healthy subjects treated with ravulizumab subcutaneous (SC) and 1 healthy subject treated with ravulizumab IV in Study ALXN1210-HV-104. All ADA positive titer values were low and negative for eculizumab cross-reactivity. There was no apparent impact of immunogenicity on the PK or PD of ravulizumab. More information about the immunogenicity of ravulizumab may be found in the current edition of the Investigator's Brochure (IB).

Monitoring of immunogenicity for this study will be conducted as described in Section 1.3 and Section 8.2.4.3.

2.4.1.2.2. Local and Systemic Reactions

Protein therapies administered IV have the potential risk of causing local (infusion-site reactions) and systemic reactions (infusion-associated reactions). Infusion-site reactions are those localized to the site of IV drug administration and may include reactions 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 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 (Section 8.3.7).

2.4.1.2.3. Pregnancy Exposure

No studies of ravulizumab have been conducted in pregnant women. Pregnant or nursing patients will be excluded from the clinical study. Patients enrolled in the study, and their spouses/partners, will use a highly effective or acceptable method of contraception as required in Section 10.4 (Appendix 4). In the event of a pregnancy, the patient will be discontinued from study drug (Section 7).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ravulizumab may be found in the IB.

3. 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.

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).

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.

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

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.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers are not allowed.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Male and female patients must be aged ≥ 18 years of age at the time of signing the informed consent

Type of Patient and Disease Characteristics

2. Diagnosed with MG at least 6 months (180 days) prior to the date of the Screening Visit
3. Confirmation of eligibility by:
   a. Positive serologic test for anti-AChR Abs as confirmed at screening, and
   b. One of the following (either historical or during screening):
      - Abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation
      - Positive anticholinesterase test (eg, edrophonium chloride test)
      - Demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician
4. Myasthenia Gravis Foundation of America Clinical Classification Class II to IV at screening
5. MG-ADL profile must be ≥ 6 at screening and randomization (Day 1)
6. Patients receiving treatment with any of the following must have been receiving treatment and on a stable dose for the time periods specified below prior to the date of the Screening Visit:
   - Azathioprine (AZA): Must have been on AZA for ≥ 6 months (180 days) and have been on a stable dose for ≥ 2 months (60 days)
   - Immunosuppressive therapies (ie, mycophenolate mofetil [MMF], methotrexate [MTX], cyclosporine [CYC], tacrolimus [TAC], or cyclophosphamide [CY]), must have been on the IST for ≥ 3 months (90 days) and have been on a stable dose for ≥ 1 month (30 days)
   - Oral corticosteroids, must have been on a stable dose for ≥ 4 weeks (28 days)
   - A cholinesterase inhibitor, at the time of the Screening Visit, must have been on a stable dose for ≥ 2 weeks (14 days)
7. To reduce the risk of meningococcal infection (*N meningitidis*), 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

Weight

8. Body weight ≥ 40 kg at the time of screening

Pregnancy and Contraception

9. Patients of childbearing potential and patients with partners of childbearing potential must follow protocol-specified contraception guidance (Section 10.4, Appendix 4) for avoiding pregnancy while on treatment and for 8 months after last dose of study drug

Informed Consent

10. Capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any active or untreated thymoma or history of thymic carcinoma or thymic malignancy

   Note: Treated patients with history thymoma other than thymic carcinoma corresponding to clinical stage 1 and 2 with no evidence of recurrence as defined by a recent negative imaging study (CT scan with IV contrast or MRI scan within 6 months of randomization) are eligible for enrollment.

2. History of thymectomy, thymomectomy, or any thymic surgery within the 12 months prior to screening
3. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins
4. History of *N meningitidis* infection
5. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
6. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study
7. History of hospitalization for ≥ 24 hours, for any reason, within the 4 weeks (28 days) prior to screening
8. Clinical features that, in the opinion of the Investigator, consistent with MG crisis/exacerbation or Clinical Deterioration, at the time of the Screening Visit or at any time prior to randomization
9. Female patients who plan to become pregnant or are currently pregnant or breastfeeding

10. Female patients who have a positive pregnancy test result at screening or on Day 1

Prior/Concomitant Therapy

11. Use of the following within the time period specified below:
    - IVIg within the 4 weeks (28 days) prior to randomization (Day 1)
    - Use of PE within the 4 weeks (28 days) prior to randomization (Day 1)
    - Use of rituximab within the 6 months (180 days) prior to screening
12. Patients who have received previous treatment with complement-inhibitors (eg, eculizumab)

Prior/Concurrent Clinical Study Experience

13. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of the study drug, whichever is greater

Additional Medical Conditions

14. History of unexplained infections
15. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1
16. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1

5.3. Lifestyle Considerations

No restrictions are required in this study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to a treatment group. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once based on discussion and agreement between the Investigator and the Medical Monitor.

A patient who experiences a gMG Clinical Deterioration or exacerbation/crisis during the Screening Period will be considered a screening failure. Such patients may be rescreened with Sponsor approval once they are treated and medically stable, in the opinion of the Investigator. At least 28 days of clinical stability must exist prior to enrollment. The patient must meet all of the inclusion criteria and none of the exclusion criteria at the time of rescreening in order to enter the study.

6. STUDY DRUG

6.1. Study Drugs Administered

Ravulizumab is formulated at pH 7.0 and is supplied in 30 mL single-use vials. Each vial of ravulizumab contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. The comparator product is formulated as a matching sterile, clear, colorless solution with the same buffer components, but without active ingredient. Additional details are presented in Table 5.

Table 5: Study Drug Administered

Product Name	Ravulizumab	Placebo
Dosage Form	Concentrated sterile, preservative-free aqueous solution (10 mg/mL) in single-use 30 mL vials	Sterile, preservative-free aqueous solution in single-use 30 mL vials
Route of Administration	Intravenous infusion	Intravenous infusion
Dosing Instructions	Refer to pharmacy manual for dosing instructions	Refer to pharmacy manual for dosing instructions
Packaging and Labeling	Glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits.	Glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits.
Physical Description	Liquid solution practically free from particles	Liquid solution practically free from particles
Manufacturer	Alexion Pharmaceuticals, Inc. or Contracted Manufacturing Organization	Alexion Pharmaceuticals, Inc. or Contracted Manufacturing Organization

Source: product specifications

Study drug will be administered as indicated in Table 6.

During the Randomized-Controlled Period, patients in the ravulizumab or placebo treatment groups will receive a weight-based loading dose of ravulizumab or placebo, respectively, on Day 1 (Visit 2). At Visit 4 (Week 2), patients in the ravulizumab or placebo treatment groups will receive weight-based maintenance doses or ravulizumab or placebo, respectively, q8w through the completion of the Randomized-Controlled Period. After the completion of the Randomized-Controlled Period, patients will enter the 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; 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.

Table 6: Reference Chart for Weight-Based Dosing

Study Period	Ravulizumab or Placebo Dosing	Body Weight (kg)[1]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Ravulizumab Group							
Randomized-Controlled	Loading dose (Day 1)	≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3300	330	0	330	660
		≥ 100	3600	360	0	360	720
Open-Label Extension	Blinded dose[2] (Day 183)	≥ 40 to < 60	900	90	150	240	480
		≥ 60 to < 100	900	90	180	270	540
		≥ 100	900	90	210	300	600
	Open-label maintenance dose (Days 197 to 869 q8w)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3300	330	0	330	660
		≥ 100	3600	360	0	360	720
Placebo Group							
Randomized-Controlled	Loading dose (Day 1)	≥ 40 to < 60	0	0	240	240	480
		≥ 60 to < 100	0	0	270	270	540
		≥ 100	0	0	300	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 40 to < 60	0	0	300	300	600
		≥ 60 to < 100	0	0	330	330	660
		≥ 100	0	0	360	360	720
Open-Label Extension	Blinded loading dose[3] (Day 183)	≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
	Open-label maintenance dose (Days 197 to 869, q8w)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3300	330	0	330	660
		≥ 100	3600	360	0	360	720

[1] Dose regimen will be based on the patient's most recently recorded body weight from a previous study/screening visit. Contact the Alexion medical monitor if a patient's weight drops below 40 kg during the treatment period.

[2] Blinded dose on Day 183 (Week 26) for patients who were randomized to the ravulizumab group and are entering into the Open-Label Extension Period.

[3] Blinded loading dose on Day 183 (Week 26) for patients who were randomized to the placebo group and are entering into the Open-Label Extension Period.

6.2. Preparation/Handling/Storage/Accountability

Study drug will be released to the site upon receipt of all required essential documents based upon federal, state, and local regulations.

Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.1. Study Drug Preparation

Study drug will be prepared and administered by a trained member of the site study team. Study drug is to be administered only to enrolled patients who are confirmed eligible for participation.

Preparation of ravulizumab and placebo doses must be performed in accordance with study center-specific local standards by qualified and study-trained pharmacy personnel.

The handling and preparation of materials used to prepare and administer the study drug must be carried out using aseptic techniques for sterile products.

All study patients, investigative-site personnel, Sponsor staff, Sponsor designees, and all staff directly associated with the conduct of the study will be blinded to patient treatment assignments.

Further details on preparation and dose administration of study drug, as well as disposal of study drug, can be found in the pharmacy manual.

6.2.2. Storage

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and that any discrepancies are reported and resolved before use of the study drug.

Upon arrival at the investigative site, the study drug should be promptly removed from the shipping cooler and stored in refrigerated conditions at 2°C to 8°C (36°F to 46°F). The pharmacist should immediately record the receipt of the study drug and notify the distributor if vials are damaged and/or if temperature excursions have occurred during transportation. Study drug must be stored in a secure, limited-access storage area and temperature must be monitored daily.

Diluted solutions of study drug may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to administration. The solution should be allowed to warm to room temperature prior to administration.

The admixed drug product should be at room temperature prior to administration. The material must **not** be heated (eg, by using a microwave or other heat source) other than by ambient air temperature.

Please consult the pharmacy manual for further information regarding the storage conditions of reconstituted ravulizumab.

6.2.3. Packaging and Labeling

The primary packaging of ravulizumab consists of a 30-mL vial (Type I borosilicate glass) with a stopper and a seal. The secondary packaging consists of a single vial carton. Both primary (vial) and secondary (carton) packaging include a booklet label with relevant information. Additional details are presented in Table 5 and in the Pharmacy Manual. The placebo will have an identical appearance to that of ravulizumab.

6.2.4. Accountability

When a drug shipment is received at the site, the pharmacist should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the site monitor in the pharmacy binder. Additionally, study drug receipt (as well as condition of the study drug at the time of receipt) must be reported to the IRT system to allow drug randomization, resupply, estimations, and drug expiration control.

Unless notified otherwise, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy standard operating procedures for clinical study drugs. Destruction of used and unused vials, either locally or centrally, must be properly documented. Drug accountability will be managed through the IRT system and detailed instructions on managing the IRT drug accountability module will be included in the IRT User Guide. The IRT module will perform accountability in two stages, where site personnel will complete an initial accountability entry in the system followed by confirmation by the Study Monitor that the site has correctly entered the appropriate status for all study drug. The pharmacist or designee must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. These drug accountability records must be readily available upon request, and will be reviewed throughout the study.

Each kit will have a label and a place for the pharmacist to record the patient number and initials.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available to regulatory authorities, the local regulatory agency, or an independent auditor’s inspection at any time.

Refer to the Pharmacy Manual for additional information.

6.2.5. Handling and Disposal

All clinical study material provided to the Investigator will be stored in a secure place, and allocated and dispensed by appropriately trained personnel. Detailed records of the amounts of the study drug received, dispensed, and destroyed will be maintained.

To satisfy regulatory requirements regarding drug accountability, all remaining ravulizumab inventory will be reconciled and destroyed or returned to Alexion at the end of the study according to applicable regulations.

Refer to the Pharmacy Manual for further information.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Patients will be randomized on Day 1 after the Investigator has verified that they are eligible. Patients will be stratified by region (North America, Europe, Asia-Pacific, and Japan) and randomized 1:1 either to ravulizumab IV infusion or to placebo IV infusion. Patients will be centrally randomized using IRT.

6.3.2. Blinding

All investigative site personnel, Sponsor staff, Sponsor designees, staff directly associated with the conduct of the study, and all patients will be blinded to patient treatment assignments. The double-blind will be maintained by using identical study drug kits and labels for ravulizumab and placebo. The placebo will have an identical appearance to that of ravulizumab. The randomization code will be maintained by the IRT provider. 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 at 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).

Unblinding should only be considered for the safety of the patient. If unblinding is deemed necessary by the Investigator, the Investigator should make a reasonable attempt to contact the Sponsor to discuss possible unblinding. After a reasonable attempt has been made, the Investigator can unblind the patient's treatment allocation using an IRT. The Investigator must note the date, time, and reason for unblinding. The Investigator should also inform the Medical Monitor that the patient was unblinded; however, they should not reveal to the Medical Monitor the patients' treatment allocation.

When an adverse event (AE) is an unexpected or related and serious, the blind will be broken for that specific patient only. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigators, etc.) and those responsible for data analysis and interpretation of results, such as biometrics personnel.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), and/or Institutional Review Boards (IRBs).

Any patient who is unblinded during the Randomized-Controlled Period will be discontinued from the study.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

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.

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.

Table 7: Supplemental Dose When Plasmapheresis/Plasma Exchange is Administered as Rescue Therapy on Nonscheduled Dosing Visits

Study Period	Previous Ravulizumab or Placebo Scheduled Dosing Visit	Next Applicable Supplemental Dosing Day Range	Body Weight Used for Most Recent Scheduled Dose (kg)[1]	Ravulizumab Dose (mg)	Volume (mL)			
					Ravulizumab	Placebo	Diluent (0.9% sodium chloride)	Total
Ravulizumab Group								
Randomized-Controlled	Loading dose (Day 1)	Days 2 to 14	≥ 40 to < 60	1200	120	0	120	240
			≥ 60 to < 100	1500	150	0	150	300
			≥ 100	1500	150	0	150	300
	Maintenance dose (Days 15, 71, 127)	Days 16 to 70, Days 72 to 126, Days 128 to 182	≥ 40 to < 60	1500	150	0	150	300
			≥ 60 to < 100	1800	180	0	180	360
			≥ 100	1800	180	0	180	360
Open-Label Extension	Blinded dose[2] (Day 183)	Days 184 to 196	≥ 40 to < 60	600	60	60	120	240
			≥ 60 to < 100	600	60	90	150	300
			≥ 100	600	60	90	150	300
	Open-label maintenance dose (Days 197 to 869 q8w)	On intervals between scheduled visits	≥ 40 to < 60	1500	150	0	150	300
			≥ 60 to < 100	1800	180	0	180	360
			≥ 100	1800	180	0	180	360
Placebo Group								
Randomized-Controlled	Loading dose (Day 1)	Days 2 to 14	≥ 40 to < 60	0	0	120	120	240
			≥ 60 to < 100	0	0	150	150	300
			≥ 100	0	0	150	150	300
	Maintenance dose (Days 15, 71, 127)	Days 16 to 70, Days 72 to 126, Days 128 to 182	≥ 40 to < 60	0	0	150	150	300
			≥ 60 to < 100	0	0	180	180	360
			≥ 100	0	0	180	180	360
Open-Label Extension	Blinded loading dose[3] (Day 183)	Days 184 to 196	≥ 40 to < 60	1200	120	0	120	240
			≥ 60 to < 100	1500	150	0	150	300
			≥ 100	1500	150	0	150	300
	Open-label maintenance dose (Days 197 to 869, q8w)	On intervals between scheduled visits	≥ 40 to < 60	1500	150	0	150	300
			≥ 60 to < 100	1800	180	0	180	360
			≥ 100	1800	180	0	180	360

[1] Supplemental dose will be based on the patient's body weight used to determine the most recently administered scheduled dose.
[2] Blinded dose on Day 183 (Week 26) for patients who were randomized to the ravulizumab group and are entering into the Open-Label Extension Period.
[3] Blinded loading dose on Day 183 (Week 26) for patients who were randomized to the placebo group and are entering into the Open-Label Extension Period.

Table 8: Supplemental Dose When Intravenous Immunoglobulin is Administered as Rescue Therapy on Nonscheduled Dosing Visits

Study Period	Previous Ravulizumab or Placebo Scheduled Dosing Visit	Next Applicable Supplemental Dosing Day Range	Body Weight Used for Most Recent Scheduled Dose (kg)[1]	Ravulizumab Dose (mg)	Volume (mL)			
					Ravulizumab	Placebo	Diluent (0.9% sodium chloride)	Total
Ravulizumab Group								
Randomized-Controlled	Loading dose (Day 1)	Days 2 to 14	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120
	Maintenance dose (Days 15, 71, 127)	Days 16 to 70, Days 72 to 126, Days 128 to 182	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120
Open-Label Extension	Blinded dose[2] (Day 183)	Days 184 to 196	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120
	Open-label maintenance dose (Days 197 to 869 q8w)	On intervals between scheduled visits	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120
Placebo Group								
Randomized-Controlled	Loading dose (Day 1)	Days 2 to 14	≥ 40 to < 60	0	0	60	60	120
			≥ 60 to < 100	0	0	60	60	120
			≥ 100	0	0	60	60	120
	Maintenance dose (Days 15, 71, 127)	Days 16 to 70, Days 72 to 126, Days 128 to 182	≥ 40 to < 60	0	0	60	60	120
			≥ 60 to < 100	0	0	60	60	120
			≥ 100	0	0	60	60	120
Open-Label Extension	Blinded loading dose[3] (Day 183)	Days 184 to 196	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120
	Open-label maintenance dose (Days 197 to 869, q8w)	On intervals between scheduled visits	≥ 40 to < 60	600	60	0	60	120
			≥ 60 to < 100	600	60	0	60	120
			≥ 100	600	60	0	60	120

[1] Supplemental dose will be based on the patient's body weight used to determine the most recently administered scheduled dose.
[2] Blinded dose on Day 183 (Week 26) for patients who were randomized to the ravulizumab group and are entering into the Open-Label Extension Period.
[3] Blinded loading dose on Day 183 (Week 26) for patients who were randomized to the placebo group and are entering into the Open-Label Extension Period.

6.5.1.5. Disallowed Medications and Therapies

The following concurrent medications are prohibited during the study:

- Rituximab
- Chronic PE/PP therapy
- Chronic IVIg therapy
- Eculizumab (or other complement-inhibitors)

Patient-use of rituximab or eculizumab (or other complement inhibitors) at any point during the study will result in the patient being discontinued from the study.

6.5.2. Rescue Therapy

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. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

Should a patient require rescue therapy, every effort should be made to notify the Sponsor within 24 hours.

6.6. Intervention After the End of the Study

Patients will return to the care of their treating physician at the completion of study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. If a patient discontinues treatment from the study, the Investigator will attempt to perform (if the patient agrees) assessments specified for the ET Visit, or if not possible, a follow-up phone call to be conducted 8 weeks after the last dose of study drug has been administered (SoA, Section 1.3). Attempts should also be made to follow all patients for safety for a total of 8 weeks from the day the last dose of study drug is administered. The Sponsor and site monitor will be notified as soon as possible. If a patient is withdrawn from the study or withdraws consent no further data will be collected. Patients who withdraw from the study will not be replaced.

Patients should be discontinued from study drug if any of the following occur during the study:

1. Serious hypersensitivity reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to Section 10.5 [Appendix 5]) or serum sickness-like reactions manifesting 1 to 14 days after study drug administration;
2. Severe uncontrolled infection;
3. Pregnancy or planned pregnancy; or
4. Sponsor or Investigator deems it is in the best interest of the patient.
5. Use of rituximab, eculizumab (or other complement-inhibitors)

The Investigator should contact the Medical Monitor prior to discontinuing a patient from study drug. If a patient discontinues from treatment, the patient should be encouraged to return for the ET Visit (SoA, Section 1.3) 8 weeks after the patient's last dose of study drug.

The reason for the treatment discontinuation (ie, patient withdraws consent, patient withdrawal from procedures, physician decision, AE, or other reason specified in eCRF) will be recorded in the eCRF.

If a female patient is permanently discontinued from study drug due to pregnancy, the Investigator will make a reasonable attempt to follow-up, in accordance with local laws and regulations, until the outcome of the pregnancy is known (Section 10.4 [Appendix 4]).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use all data collected before such a withdrawal of consent.

If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records as well as inform the site monitor and Sponsor.

7.2. Lost to Follow Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

1. The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
2. Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
3. Should the patient continue to be unreachable, the patient will be considered to have withdrawn consent and future missed visits will not be considered protocol deviations.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Efficacy Assessments

8.1.1. Hospitalization

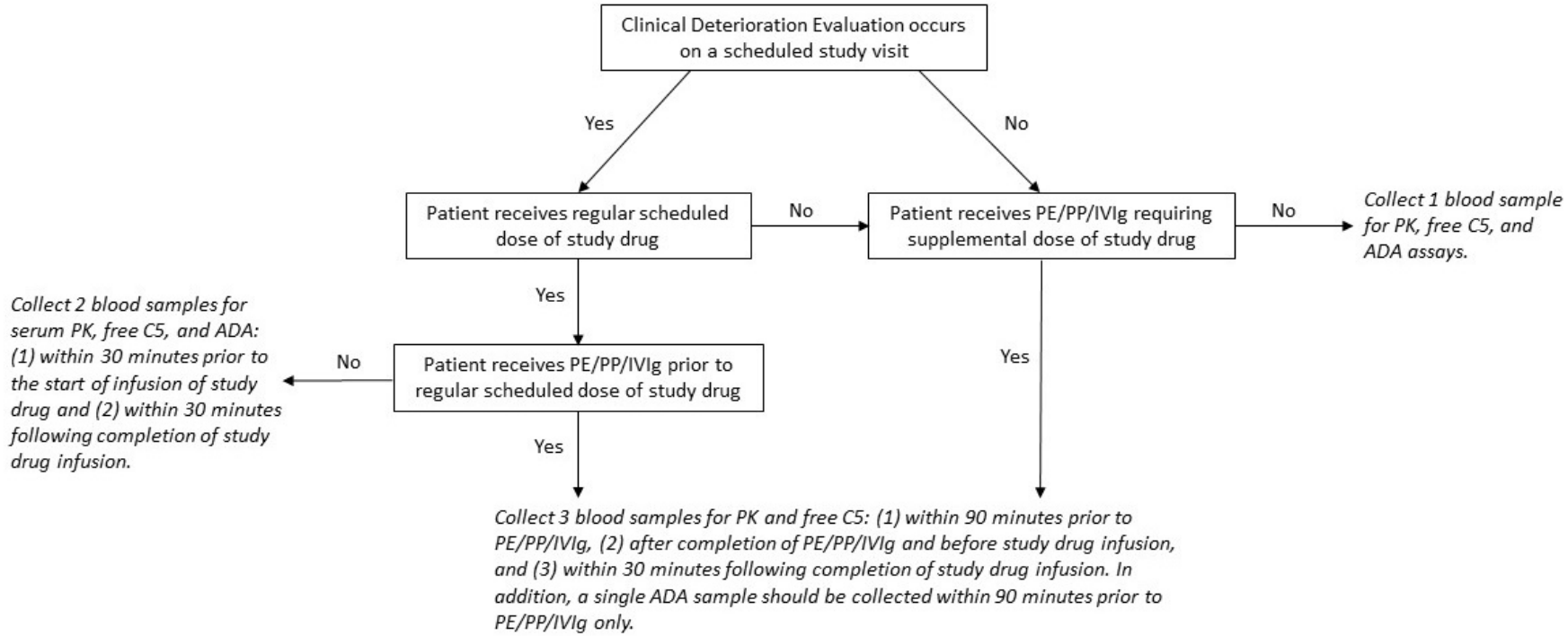
Information related to all-cause hospitalization, including those that occurred within the last 2 years prior to screening, will be collected through the OLE Period. Hospitalizations are defined as all admissions to a healthcare facility (hospital, rehabilitation center, or hospice), irrespective of the underlying relation to MG. Dates of admission/discharge, reasons for hospitalization, relationship to MG, and other relevant information will be collected on the eCRF.

8.1.2. Clinical Deterioration

Information related to Clinical Deterioration, as defined in Section 4.2.1, will be collected from patient signing of the ICF through the OLE Period. The evaluation visit for a Clinical Deterioration must be performed as soon as possible, within 48 hours of notification to the Investigator of the symptom onset. Additional Unscheduled Visits (Section 4.2.2) can be scheduled at the discretion of the Investigator. The following tests and procedures will be completed at this visit:

- Measure vital signs and pulse oximetry, including assessments of systolic and blood pressure (BP), temperature (°C or °F), oxygen saturation (SO_2), and heart rate (HR).
- Record any new medications or changes to concomitant medications, including all treatments for MG.
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Administer MG-ADL by a properly trained evaluator, preferably the same evaluator, throughout the study. The recall period is the preceding 7 days or since the last visit whichever occurs earlier.
- Administer clinical assessments QMG and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the study.
- Collect blood sample for the AChR auto-Abs test.
- Collect blood samples for clinical laboratory tests (see Section 10.2 [Appendix 2]).
- If medically indicated for evaluation of Clinical Deterioration, additional tests may be performed at the discretion of the Investigator.
- PK/PD/ADA sampling at or during Clinical Deterioration Visit is described in Figure 2.

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

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

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)

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

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

9.1.3. Hypotheses Related to Exploratory Efficacy Objectives

1. Ravulizumab is superior to placebo in improvement of MGC total score at Week 26.
2. Ravulizumab is superior to placebo in MGFA-PIS at Week 26.
3. Ravulizumab is superior to placebo in improvement of EQ-5D-5L index score at Week 26.
4. Ravulizumab is superior to placebo in improvement of MG-ADL subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.
5. Ravulizumab is superior to placebo in improvement of QMG subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.
6. Ravulizumab is superior to placebo in reducing incidence of hospitalizations/MG-related hospitalizations.
7. Ravulizumab is superior to placebo in reducing incidence of Clinical Deterioration/MG crisis.

9.1.4. Estimation of Treatment Effect for Secondary and Exploratory Hypotheses

The treatment effect corresponding to the change from Baseline continuous endpoints will be estimated similarly as the primary endpoint.

The treatment effect corresponding to the following dichotomous endpoints will be estimated by the odds ratio (OR) of the proportions of the corresponding endpoint in the ravulizumab group compared with the placebo group:

a. MG-ADL 3-point response at Week 26 irrespective of rescue therapy
b. QMG 5-point response at Week 26 irrespective of rescue therapy
c. Incidence of hospitalization/MG-related hospitalizations irrespective of rescue therapy
d. Incidence of Clinical Deterioration/MG crisis over 26 weeks irrespective of rescue therapy

An estimate of OR < 1 corresponding to the hospitalization and Clinical Deterioration endpoint will indicate a beneficial treatment effect, likewise an estimate of OR > 1 corresponding responder endpoints will indicate a beneficial treatment effect.

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.

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

9.4.5.2. Sensitivity Analyses for Primary Endpoint

Two sensitivity analyses will be performed for the primary efficacy endpoint to explore the robustness of the MMRM results for the primary efficacy analysis:

1. Placebo-based sensitivity analysis:

   The placebo-based sensitivity analysis will consider the Missing Not At Random (MNAR) mechanism for the missing data, where it will be assumed that patients who discontinue early from ravulizumab will follow the trajectory of outcomes similar to the one in the placebo group after discontinuation of ravulizumab, taking into account observed values prior to discontinuation.

2. Tipping point sensitivity analysis:

   This approach assumes that patients who discontinue from ravulizumab treatment experience worsening defined by a prespecified adjustment in the primary efficacy endpoint.

9.4.5.3. Analyses of Secondary and Exploratory Endpoints

All continuous secondary and exploratory endpoints related to change from Baseline will be analyzed similarly as the primary endpoint.

The QMG 5-point and MG-ADL 3-point responder endpoints will be analyzed using a mixed effect repeated measures model. The model will include response variable at each pre-specified time point as the dependent variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, and region; as well as fixed covariate of baseline QMG or MG-ADL total score (depending on the response variable). 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).

Clinical Deterioration/MG crisis and hospitalizations/MG-related hospitalizations will be analyzed using a logistic regression model with treatment group, region.

The MGFA-PIS endpoint at Week 26 will be considered as an ordinal scale. A logistic regression of the cumulative odds (cumulated over the categories starting from best outcome) will be performed using treatment as fixed categorical effect and adjusting for region.

Long-term efficacy data will be summarized descriptively based on OLE set.

9.4.5.4. Multiplicity Adjustment for Primary and Secondary Endpoints

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

1. Change from Baseline in QMG total score at Week 26

2. Proportion of patients with improvement of at least 5 points in the QMG total score from Baseline at Week 26
3. Change from Baseline in MG-QOL15r at Week 26
4. Change from Baseline in Neuro-QOL Fatigue at Week 26
5. Proportion of patients with improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26

The testing will proceed from (#1) to (#5) and if statistical significance is not achieved ($p \leq 0.05$), 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. 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.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the patient.
- The Investigator must retain the original version of the signed ICF(s). A copy of the signed ICF(s) must be provided to the patient.
- A patient who is rescreened is not required to sign another ICF unless an updated ICF is available.

10.1.3. Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Alexion will store anonymized data [ie, data that has been anonymized through removal of elements that will identify the individual directly so that the individual is no longer uniquely identifiable] in the study databases for no less than 15 years after the completion of the study or until the purposes of collection and use are attained, after which data will be destroyed. Health authorities and regulatory authorities may retain and utilize such information for the period set forth in applicable law or as duly determined at the relevant regulatory authority's discretion.

10.1.4. Dissemination of Clinical Study Data

Study-related information and study results may be posted on the US National Institutes of Health website www.clinicaltrials.gov, the EU website www.clinicaltrialsregister.eu/, or other publicly accessible websites as appropriate and in accordance with local regulations.

10.1.5. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements. Study monitors will communicate with investigative sites on a regular basis regarding the study and all protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigative site.
- The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each patient.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at their sole discretion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator

- Discontinuation of further ravulizumab development

10.1.8. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: Distribution width Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	BUN C-reactive protein Creatinine Chloride Potassium Bicarbonate Sodium Glucose (nonfasting)	AST/SGOT ALT/SGPT Alkaline phosphatase, Gamma glutamyltransferase	Total and direct bilirubin Total protein Albumin Uric acid
Coagulation	international normalized ratio, partial thromboplastin time, prothrombin time		
Urine	Appearance, color, specific gravity, pH, glucose, protein, leukocyte esterase, blood, ketones, bilirubin, urobilinogen, nitrite, microscopic examination (if blood or protein is abnormal)		
Other Screening tests	Serum/urine beta-hCG pregnancy test (as needed for patients of child-bearing potential) Serum follicle-stimulating hormone test (as needed for patients who consider themselves postmenopausal) HIV-1 and HIV-2 antibodies The results of each test must be entered into the eCRF.		
Complement activity	Free C5		
Other	Antidrug antibodies, AChR antibody		

Abbreviations: AChR = acetylcholine receptor; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C5 = complement component 5; eCRF = electronic case report form; hCG = human chorionic gonadotropin; HIV-1 = human immunodeficiency virus type 1; HIV-2 = human immunodeficiency virus type 2; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event

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

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study drug are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

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.

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).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4.3. Collection and Reporting of Pregnancy Information

No studies of ALXN1210 have been conducted in pregnant women. Pregnant or nursing female patients are excluded from the study. Patients enrolled in the study, and a spouse or partner, will use a highly effective or acceptable method of contraception.

In the event of a pregnancy event, pregnancy data will be collected during this study for all patients and a female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues study drug or withdraws from the study.

If a female patient or a patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GPV via facsimile or email (Section 10.3). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPV. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding" form) and any AEs experienced by the infant must be reported to Alexion GPV or designee via email or facsimile (Section 10.3).

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.5. Appendix 5: Management of Potential Infusion-Associated Adverse Events During Study Drug Administration

Intravenous and infusion-associated reactions are a potential risk with the use of mAbs; these reactions can be nonimmune or immune-mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration-, IV-, and infusion-associated reactions will be reported to the Investigator or qualified designee (Section 8.3). The Investigator or qualified designee are responsible for detecting, documenting, and recording events that meet the definition of 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).

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug. All AEs that may indicate an infusion-related response will be graded according to the CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed below, then administration of SC epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

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

10.6. 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

10.7. 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

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.

10.9. Appendix 9: Euro Quality of Life Questionnaire

Header to be completed by Study Site	
Study Number: ALXN1210-MG-306	Subject ID: _____
Date Completed: _____	Completed by: ☐ Patient

Health Questionnaire

English version for the USA

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

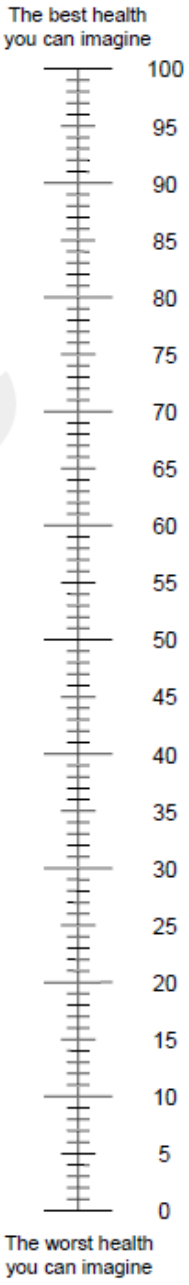
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

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 = ☐



3

10.10. Appendix 10: Myasthenia Gravis Quality-of-Life 15r Scale

Header to be completed by Study Site

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

Date Completed: _____ Completed by: ☐ Patient

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG.			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

Total MGQOL-R score

10.11. Appendix 11: Neurology Quality of Life Fatigue

Header to be completed by Study Site

Study Number: ALXN1210-MG-306

Subject ID: _____

Date Completed: _____

Completed by: ☐ Patient

Neuro-QOL Item Bank v1.0 –Fatigue

Fatigue

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NGFTGH3	I felt exhausted……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH1	I felt that I had no energy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH5	I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH6	I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH7	I was too tired to leave the house……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH10	I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH4	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH2	I had to limit my social activity because I was tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH1	I needed help doing my usual activities because of my fatigue……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH8	I needed to sleep during the day……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH4	I had trouble starting things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH5	I had trouble finishing things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH9	I was too tired to take a short walk…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH9	I was too tired to eat……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH2	I was so tired that I needed to rest during the day……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NGFTGH6	I felt weak all over……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
November 4, 2014

Page 1 of 2

Appendix 11: Neurology Quality of Life Fatigue (Continued)

Neuro-QOL Item Bank v1.0 –Fatigue

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG17	I needed help doing my usual activities because of weakness……....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG18	I had to limit my social activity because I was physically weak……....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG20	I had to force myself to get up and do things because I was physically too weak..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10.12. Appendix 12: Myasthenia Gravis Foundation of America Clinical Classification

MGFA Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

10.13. Appendix 13: Myasthenia Gravis Foundation of America Post-Interventional Status

Note that a modified version of Change in Status (excludes "Exacerbation" and "Died of MG") is used in this protocol (see Section 8.1.9).

MGFA Post-intervention Status (MGFA-PIS)

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).

10.14. Appendix 14: Columbia-Suicide Severity Rating Scale – Baseline/Screening (Version 1/14/09)

To be completed by Study Site	
Study Number: ALXN1210-MG-306	Subject ID: _____
Date Completed: _____	Completed by: ☐ Evaluator (initials): _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form,*** *developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS 1_eng-USori.doc

Appendix 14: Columbia-Suicide Severity Rating Scale – Baseline/Screening (Continued)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

Appendix 14: Columbia-Suicide Severity Rating Scale – Baseline/Screening (Continued)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

10.15. Appendix 15: Columbia-Suicide Severity Rating Scale - Since Last Visit (Version 1/14/09)

To be completed by Study Site	
Study Number: ALXN1210-MG-306	Subject ID: _____
Date Completed: _____	Completed by: ☐ Evaluator (initials):_____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

Appendix 15: Columbia-Suicide Severity Rating Scale - Since Last Visit (Continued)

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

Appendix 15: Columbia-Suicide Severity Rating Scale - Since Last Visit (Continued)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

10.16. Appendix 16: Statistical Considerations

10.16.1. Additional Details on Sample Size Determination

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

10.16.2. Additional Details on Sensitivity Analysis for Primary Endpoint

To assess the credibility of the primary analysis, the following sensitivity analyses are planned, based on assumptions that are unfavorable enough to the ravulizumab group to constitute a convincing stress test of the primary analysis.

10.16.2.1. Placebo-based Sensitivity Analysis

The placebo-based sensitivity analysis will consider the MNAR mechanism for the missing data, where it will be assumed that patients who discontinue early from the ravulizumab group will follow the trajectory of outcomes similar to the one in the placebo group after discontinuation of ravulizumab, taking into account observed values prior to discontinuation (Little, 1996); (Ratitch, 2013). Patients discontinuing early from placebo will be assumed to have unobserved outcomes similar to placebo patients who remain on their randomized treatment. The assumption that the efficacy profiles of dropouts after discontinuation of ravulizumab are similar to those of patients in the placebo group provides an estimand of efficacy attributable to patients in the ravulizumab group if received through the time point of interest, while limiting efficacy after early discontinuation to that of the placebo group.

10.16.2.2. Tipping Point Sensitivity Analysis

An additional sensitivity analysis will be performed based on the delta-adjusted stress testing method (tipping point analysis). This approach assumes that patients who discontinue from the active treatment experience worsening defined by a prespecified adjustment (delta) in the primary efficacy endpoint compared with the observed efficacy score of patients that continue the study to next visit (O'Kelley, 2014). Since a negative change in QMG total score indicates improvement, the prespecified value of delta will be a non-negative fixed quantity. For each value of delta, the treatment effect will be determined and the value of delta for which the

nominal 2-sided p-value crosses 0.05, will be considered as the ‘tipping point’ in the sense that the positive conclusion drawn from the primary analysis is reversed when patients who drop out are assumed to experience this fixed worsening after the discontinuation visit. After such a tipping point is determined, clinical judgment will be applied as to the plausibility of the assumptions underlying this tipping point. This methodology is expected to inform 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.

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)

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

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

10.18. Appendix 18: Protocol Amendment History

Amendment 1 (11 Dec 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

To change duration of safety follow-up after last dose; add additional details on assessments, align pregnancy and clinical laboratory testing frequency with infusions; change supplemental dosing recommendations and sample collection when rescue therapy is provided; and update adverse event and pregnancy/contraception language.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis; Section 4.1: Overall Design; Section 7.1: Discontinuation of Study Intervention; Section 8.3.1: Time Period and Frequency for Collecting Adverse Event and SAE Information	Patients will be followed for safety for 8 weeks after last dose of study drug.	A 24-week follow-up in patients is not feasible as safety data would likely be confounded by new treatments. To align with duration of safety follow-up for other ravulizumab programs.
Section 1.3: Schedule of Activities	Changed terminology of targeted physical examination to abbreviated physical examination throughout protocol. Clarification that C-SSRS Baseline/Screening Version assessment will occur on Day 1 and C-SSRS Since Last Visit Version assessment will occur on subsequent indicated visits. Added reference to section detailing assigned evaluator for assessment instruments. Frequency of Clinical Lab Test and Pregnancy Test assessments reduced and aligned with infusion visits. Clarified PK/PD and ADA sample collection should occur in the event of Clinical Deterioration.	To align with terminology for physical examination. To ensure appropriate C-SSRS versions are administered. To precisely specify appropriate evaluator for each assessment instrument. To align with infusion visits and reduce burden on patients. To ensure PK/PD and ADA analyses are performed consistently across events if Clinical Deterioration occurs.
Section 4.2.2: Unscheduled Visits	Specified that efforts will be made to map unscheduled visit data with the appropriate visit in the eCRF.	To ensure data is associated with the appropriate visit.
Section 4.2.3: Properly Trained Clinical Evaluator	Removed EQ-5D-5L and MG-QOL15r from section as these instruments are completed by patients.	To clarify as these assessments are completed by patients.
Section 4.2.4: Responsibilities for Myasthenia Gravis Assessments	Removed EQ-5D-5L and MG-QOL15r from Myasthenia Gravis Assessments and Responsibilities table.	To clarify as assessments are completed by the patient.

Section # and Name	Description of Change	Brief Rationale
Section 6.1: Study Drugs Administered	Updated Table 6 to indicate volumes needed for ravulizumab, placebo, and diluent.	To ensure proper preparation of placebo and ravulizumab doses.
Section 6.2.4: Accountability	Updated details for study drug accountability to reflect use of interactive response technology (IRT) and study monitors.	To ensure proper accountability of study drug while using IRT.
Section 6.2.5: Handling and Disposal	Provided details for study drug handling and disposal.	To provide additional details on proper handling and disposal of study drug.
Section 6.5.1.4: Plasma Exchange/Plasmapheresis/Intravenous Immunoglobulin	Updated timing and dosing levels for supplemental study drug administration when PE/PP or IVIg rescue therapy is provided.	To ensure proper and consistent dosing of supplemental study drug following PE/PP or IVIg.
Section 8.1.1: Hospitalization	Updated definition of hospitalization.	To ensure admission to facility overnight is collected as hospitalization.
Section 8.1.2: Clinical Deterioration	Section 10.2 (Appendix 2) referenced in clinical laboratory tests. MG Crisis or Clinical Deterioration Visit changed to Clinical Deterioration Visit.	To align with Section 10.2 (Appendix 2): Clinical laboratory tests. To provide consistency with Clinical Deterioration criteria.
Section 8.2.5.1: Columbia-Suicidal Severity Rating Scale	Updated to detail the C-SSRS will be administered by the Investigator or a properly trained designee.	To align with other sections of the protocol indicating the Investigator or a properly trained designee will administer the assessment.
Section 8.3.1: Time Period and Frequency for Collecting Adverse Event and SAE Information	Updated language on submission of SAE data.	To align with current practices.
Section 8.3.4: Regulatory Reporting Requirements for Serious Adverse Events	Added language on reporting of SUSARs.	To align with regulatory feedback on ravulizumab program.
Section 8.3.5: Pregnancy; Section 1.3: Schedule of Activities	Updated to indicate that serum pregnancy testing will occur at Screening and at the End of Study.	To align with Table 1 and Table 2 of Schedule of Activities.
Section 10.2 (Appendix 2): Clinical Laboratory Tests	Added serum follicle stimulating hormone and urine creatinine testing. Removed D-dimer and free hemoglobin testing.	To fix inconsistencies between protocol sections and remove D-dimer and free hemoglobin assessment.
Section 10.3.4 (Appendix 3): Recording and Follow-Up of Adverse Event and/or Serious Adverse Event	Updated to clarify that the expectedness and reporting criteria of an SAE will be based on the Reference Safety Document.	To ensure Reference Safety Document is used when recording an AE.
Section 10.4.1 (Appendix 4): Contraception Guidance	Updated to indicate that 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.	To align with current Alexion language.
Section 10.4.3 (Appendix 4): Collection and Reporting of Pregnancy Information	Updated language on collection and reporting of pregnancy information.	To align with current Alexion language.

Section # and Name	Description of Change	Brief Rationale
Section 10.5 (Appendix 5): Management of Potential Infusion-Associated Adverse Events During Study Drug Administration	Updated to indicate CTCAE v5.0 or higher will be used to grade an infusion-related response.	To align with proper CTCAE version planned for use.
Throughout	Minor editorial and document formatting revisions have been made throughout the document.	As these changes are minor, they have not been summarized.

Abbreviations: ADA = antidrug antibody; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; eCRF = electronic case report file; EQ-5D-5L = Euro Quality of Life; IRT = interactive response technology; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; MG-QoL15r = Revised Myasthenia Gravis Quality of Life 15-item scale; PD = pharmacodynamic; PE = plasma exchange; PK = pharmacokinetic; PP = plasmapheresis; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction

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