Endpoints:

Primary Efficacy Endpoint:

Change from Baseline in the QMG total score over time regardless of rescue treatment.

Secondary Efficacy Endpoints:

- Change from Baseline in the MG-ADL total score over time regardless of rescue treatment
- Proportion of patients with ≥ 3-point reduction in the MG-ADL total score over time with no rescue treatment
- Proportion of patients with ≥ 3-point reduction in the MG-ADL total score over time regardless of rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score over time with no rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score over time regardless of rescue treatment
- Change from Baseline in the MGC total score over time regardless of rescue treatment
- Change from Baseline in EQ-5D-Y over time regardless of rescue treatment
- Change from Baseline in Neuro-QoL Pediatric Fatigue over time regardless of rescue treatment
- MGFA Post-Interventional Status over time regardless of rescue treatment

Total number and percentage of patients with clinical deteriorations, myasthenic crises, and rescue therapy use over time

Extension Period Efficacy Endpoints:

- Total number and percentage of patients with clinical deteriorations and/or myasthenic crises during the study
- Total number and percentage of patients needing rescue therapy during the study
- Change from Baseline in the QMG total score regardless of rescue treatment
- Change from Baseline in the MG-ADL total score regardless of rescue treatment
- Change from Baseline in the MGC total score regardless of rescue treatment
- Change from Baseline in Neuro-QoL Pediatric Fatigue regardless of rescue treatment
- Change from Baseline in EQ-5D-Y regardless of rescue treatment
- Change from Baseline in MGFA Post-Interventional Status regardless of rescue treatment

Safety Endpoints:

- Frequency of adverse events (AEs) and serious adverse events (SAEs)
- Frequency of adverse events leading to discontinuation
- Incidence of antidrug antibodies (ADA)
- Changes from Baseline in vital signs
- Change from Baseline in electrocardiogram parameters
- Change from Baseline in laboratory assessments

Abbreviations and Terms	Definitions
PP	plasmapheresis
PT	preferred term
QMG	Quantitative Myasthenia Gravis
S pneumoniae	*Streptococcus pneumoniae*
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
TEAE	treatment-emergent adverse event
VAS	Visual Analog Scale
WHODrug	World Health Organization Drug Dictionary

4. STUDY DESIGN

4.1. Overall Design

Study ECU-MG-303 is an open-label, multicenter study to evaluate the efficacy, safety, PK, and PD of eculizumab for the treatment of pediatric patients aged 6 to < 18 years with AChR-Ab positive refractory gMG. At least 12 eligible patients aged 12 to < 18 years are planned to be enrolled in the study and receive eculizumab infusion to obtain at least 10 evaluable patients aged 12 to < 18 years for the primary endpoint taking into account potential dropouts. There will be 4 periods in this study:

- Screening Period (2-4 weeks)
- Primary Evaluation Treatment Period (26 weeks)
- Extension Period (up to an additional 208 weeks)
- Follow-up Period (8 weeks)

Patients may continue to receive AChI, IVIg, and ISTs during the study where applicable under certain restrictions. For patients who enter the study receiving any background therapy, the dose and frequency may not be changed during the Primary Evaluation Treatment Period before Week 12, unless deemed necessary per the Investigator based on clinical safety evaluation and Sponsor approval is obtained. Dose change with background medication is permitted after Week 12 at the Investigator's discretion and with Sponsor notification. During the Extension Period, changes in background medications will be permitted at the Investigator's discretion and with Sponsor notification.

If a patient withdraws from the study or discontinues eculizumab treatment at any time, the patient will be required to complete an Early Termination (ET) visit at the time of withdrawal and a Follow-up visit 8 weeks following the last dose of study drug. The overall study duration for an individual patient can be up to 246 weeks (approximately 4.7 years) from the Screening Period through the Follow-up Period.

This pediatric study is designed to assess the efficacy and safety of eculizumab in AChR-Ab positive refractory pediatric gMG patients, similar to what has been demonstrated in patients aged ≥ 18 years in Study ECU-MG-301 (a randomized, double-blind, placebo-controlled study). The similar pathogenic autoantibody profile (AChR-Ab), pathophysiology, clinical presentation, and treatment responses in AChR-Ab positive patients aged ≥ 18 years and pediatric patients, combined with the well-understood mechanism of action of eculizumab in inhibiting terminal complement, predict a similar efficacy profile of eculizumab in patients aged ≥ 18 years and pediatric patients with refractory gMG. Given the demonstration of the efficacy and safety of eculizumab in patients aged ≥ 18 years, randomizing pediatric patients to a placebo treatment arm may not be ethically acceptable, so a single arm open-label design was chosen.

This pediatric study is similar to the study conducted in patients aged ≥ 18 years (Study ECU-MG-301) in permitting background IST use. All patients may continue to receive ISTs during the study. Given the global nature of the study (multicenter) and experience from the study in patients aged ≥ 18 years, it is anticipated that different ISTs will be used based on local medical practice and local IST availability; thus, the use of ISTs will not be standardized in this study. In contrast to the study in patients aged ≥ 18 years, the number of eligible refractory

pediatric gMG patients aged 12 to < 18 years entering on maintenance IVIg therapy will be capped at 6 patients. These patients must have been on maintenance IVIg for at least 12 months and on a stable dose ≥ 3 months prior to Screening, with frequency and dose expected to remain stable during Screening and for 12 weeks following the first dose of study drug. Efforts will be made to enroll at least 1 patient in each geographic region (North America, EU, and APAC). There will be no limit on the number of patients aged 6 to < 12 years who may enter the study on maintenance IVIg. This change was made based on the higher prevalence of maintenance IVIg use in children.

4.1.1. Screening Period (2 to 4 weeks)

Patients will be screened for study eligibility only after obtaining the informed consent of the parent or other legal guardian, and the patient's informed assent, when applicable. Assessment will include confirmation of a refractory gMG diagnosis per protocol-defined inclusion/exclusion criteria, QMG total score, history of previous MG treatments and therapies, history of MG exacerbation or crisis and the treatment for each exacerbation/crisis, and a comprehensive review of medical history, including vaccination history, as well as any non-MG comorbid conditions. When an eligible patient meets all inclusion criteria, but none of the exclusion criteria, the Principal Investigator must notify the Sponsor to obtain Medical Monitor approval prior to enrolling the patient.

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. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement-inhibitors (eg, eculizumab). In addition to meningococcal vaccination, patients must be vaccinated against *Haemophilus influenzae* (*H influenzae*) and *Streptococcus pneumoniae* (*S pneumoniae*), if not already vaccinated, and strictly adhere to the national vaccination recommendations for each age group.

The site must notify the Sponsor if any patient experiences signs and symptoms of MG worsening that require rescue or foreseeable imminent change to the background medication during the Screening Period. Following discussion with the Sponsor, a decision will be made about whether the patient may be enrolled in the study or should be withdrawn. Patients whose MG is unstable (as determined by the Investigator) during the Screening Period may be rescreened at a later date based on discussion and agreement between the Investigator and the Alexion Medical Monitor.

4.1.2. Primary Evaluation Treatment Period (26 weeks)

All patients will receive eculizumab by IV infusion during the open-label Primary Evaluation Treatment Period. Dosing will be initiated with a weekly weight-based induction regimen and, thereafter, will be every 2 weeks. Weight may change for an individual patient during the study, and dose regimen will be based on the current visit's recorded body weight. If site/institution policies prohibit study drug to be prepared day-of visit, the weight from the most recent study visit should be used.

Sites must inform patients and their parent or legal guardian of potential signs and symptoms of MG worsening or clinical deterioration, including myasthenic crisis, and instruct them to contact the Investigator in the event these occur. The Investigator should make every effort to evaluate a patient reporting worsening signs and symptoms of MG as soon as possible and within 48 hours of notification. The Investigator will assess for clinical deterioration and treat the patient accordingly.

4.1.3. Extension Period (up to an additional 208 weeks)

After completing the 26-week Primary Evaluation Treatment Period, patients will continue receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks. Weight may change for an individual patient during the study, and dose regimen will be based on the current visit's recorded body weight. If site/institution policies prohibit study drug to be prepared day-of visit, the weight from the most recent study visit should be used. Patients may have an opportunity to receive study drug administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Principal Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

4.1.4. Follow-up Period: Safety Follow-up (8 weeks)

Patients who withdraw or discontinue treatment at any time and for any reason after receiving any amount of eculizumab will be required to complete both an ET Visit at the time of withdrawal and a Follow-up Visit at 8 weeks following the last eculizumab dose. Adverse events leading to patient discontinuation from the study are followed until resolution or are medically stable in the opinion of the Investigator.

Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit. The Investigator must confirm with the patient or their guardian/caregiver by telephone that the transition to commercially available eculizumab occurred within 2 weeks of the last scheduled dose during the study. In the event that treatment with commercially available eculizumab is delayed, an unscheduled safety Follow-up Visit should occur on the day of initiating commercial eculizumab treatment or as soon thereafter as feasible.

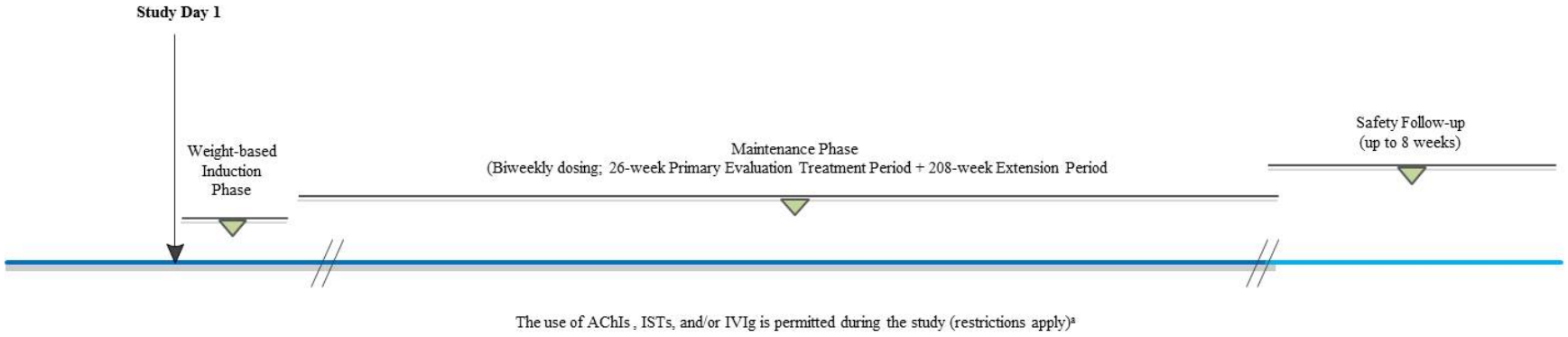
4.1.5. Post-Treatment Follow-up (up to 1 year)

The Sponsor may seek to collect follow-up information concerning MG status in patients post-treatment for up to 1 year from the end-of-study (EOS)/ET Visit (see Appendix 13).

4.1.6. Clinical Deterioration and Rescue Therapies

Allowed rescue therapy for clinical deterioration includes but is not limited to high-dose corticosteroids, PE, or IVIg and is at the discretion of the Investigator. Plasma exchange is not allowed for prophylaxis or routine maintenance. Every effort should be made to notify the Sponsor within 24 hours of administration of rescue therapy.

Figure 1: Flow Diagram for Study Design



[a] Patients may continue to receive AChI, IST, and/or IVIg during the study where applicable under certain restrictions. For patients who enter the study receiving any background therapy, the dose/schedule may not be changed during the Primary Evaluation Treatment Period before Week 12, unless deemed necessary per the Investigator based on clinical safety evaluation and if Sponsor approval is obtained. Dose change with background medication is permitted after Week 12 at the Investigator's discretion and with Sponsor notification. During the Extension Period, changes in background medications will be permitted at the Investigator's discretion and with Sponsor notification.

Abbreviation: AChI = acetylcholinesterase inhibitor; IST = immunosuppressant therapy; IVIg = intravenous immunoglobulin

5. STUDY POPULATION

The study will enroll at least 12 eligible refractory pediatric gMG patients 12 to < 18 years of age to receive open-label eculizumab infusion, in order to obtain at least 10 evaluable patients aged 12 to < 18 years for the primary endpoint, taking into account potential dropouts. Additional patients between the ages of 6 and 12 may be enrolled, but will not be included in the primary analysis. The number of eligible refractory pediatric gMG patients aged 12 to < 18 entering on maintenance IVIg treatment in this study will be capped at 6 patients. These patients must have been on maintenance IVIg for at least 12 months and on a stable dose ≥ 3 months prior to Screening, with frequency and dose expected to remain stable during Screening and for 12 weeks following the first dose of study drug. Efforts will be made to enroll at least 1 patient in each geographic region (North America, EU, and APAC).

After 6 patients complete their Week 26 assessments, if the observed standard deviation in change in QMG is 8 or higher, the final sample size will be re-estimated to be at least 14 instead of 12 to preserve adequate power for testing the primary endpoint.

Patients are eligible to be included in the study only if they satisfy all of the following inclusion/exclusion criteria. The Sponsor's Medical Monitor must approve enrollment for each eligible patient.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Male or female pediatric patients 6 to < 18 years of age at time of assent/consent.
2. Patient's legal guardian must be willing and able to give written informed permission and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional [or Independent] Ethics Committee [IEC]) and comply with the study visit schedule.
3. Parent or other legal guardian must be willing to comply with study requirements for the duration of the study.
4. Vaccinated against *N meningitidis* within 3 years prior to, or at the time of, initiating eculizumab. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until 2 weeks after the vaccination.
5. Documented vaccination against *H influenzae* and *S pneumoniae* infections prior to dosing as per local and country specific immunization guidelines for the appropriate age group.
6. Diagnosis of MG confirmed by positive serologic test for anti-AChR-Ab at Screening, and one of the following:
    a. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation, or

functional impairment. In this study, the MGC assessment will be administered at the protocol-specified time points at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the study.

7.4. Myasthenia Gravis Foundation of America Post-Intervention Status

The MG clinical state will be assessed using the MGFA Post-Intervention Status. Change in status categories of Improved, Unchanged, Worse, as well as the Minimal Manifestation will be assessed by the PI or the same neurologist skilled in the evaluation of MG patients throughout the study (Appendix 11).

7.5. European Quality of Life 5-Dimension

The EQ-5D-Y (Appendix 5) is a reliable and validated survey of health status in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which is completed by the patient for patients ≥ 12 years of age (at time of assessment) and completed by the patient's caregiver or with caregiver assistance for patients <12 years of age (Szende, 2014). Each area has 3 levels: Level 1 (no problems), Level 2 (some problems), and Level 3 (extreme problems). The EQ visual analogue scale (VAS) records the patient's self-rated health on a vertical, 20 cm VAS where the endpoints are labeled 'Best imaginable health state, marked as 100' and 'Worst imaginable health state, marked as 0'. Patients will continue to be evaluated based on the survey initially completed upon entry into the study. Change in age during the study will not constitute a patient changing the type of survey completed. Patients who are younger than the lowest age range of the survey (ie, patients < 8 years of age) will be evaluated using the proxy version of the EQ-5D-Y (Appendix 6). The parent or legal guardian (the proxy) will be asked to rate the child's health-related quality of life in their (the proxy's) opinion. The EQ-5D-Y assessment will be administered at the protocol-specified time points at approximately the same time of day throughout the study.

7.6. Neurological Quality of Life Fatigue Questionnaire

The Neuro-QoL Pediatric Fatigue questionnaire (Appendix 7) is a reliable and validated brief 11-item survey of fatigue, completed by the patient for patients ≥ 12 years of age (at time of assessment) and completed by the patient's caregiver or with caregiver assistance for patients <12 years of age (Cella, 2010). Higher scores indicate greater fatigue and greater impact of MG on activities. Patients will continue to be evaluated based on the survey initially completed upon entry into the study. Change in age during the study will not constitute a patient changing the type of survey completed. Patients who are younger than the lowest age range of the applicable scale (ie, patients < 8 years of age) will be evaluated using the PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a questionnaire (Appendix 8). The parent or legal guardian (the proxy) will complete the measure on the child's behalf following administration of these instructions: "The following questionnaires will ask about your child's symptoms and activity levels; his/her ability to think, concentrate and remember things; questions specific to his/her condition, and questions related to his/her quality of life. Please answer the following questions based on what you think your child would say." The Neuro-QoL Pediatric Fatigue questionnaire will be administered at the protocol-specified time points at approximately the same time of day throughout the study.

8. ADDITIONAL ASSESSMENTS

8.1. Myasthenia Gravis Disease Biomarker

Blood samples for assay of the AChR-Ab will be collected at Screening as specified in the Schedules of Assessments (Section 4.2).

8.2. Pharmacokinetics and Pharmacodynamics

Blood samples will be collected at specified time points to study the PK of eculizumab in pediatric patients with refractory gMG. Pharmacokinetic parameters such as maximum concentration and concentration after the first dose, and during the induction and maintenance treatment phase will be obtained. Clearance and terminal half-life will be estimated.

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

Baseline PK and PD samples will be collected 5-90 minutes prior to the first dose, and peak samples will be collected 60-120 minutes after the first dose and at other time points in the SoA. An intermediate blood sample will also be collected 24 hours after completion of the first dose. For the sample collected at 24 hours, there will be a window of ± 1 hour for collecting the sample. The date and exact time of collection must be recorded on the eCRF and the central laboratory requisition form.

Blood samples collected for PK and PD will be kept frozen and stored at Alexion Pharmaceuticals, Inc. for a maximum of 5 years after all the specified PK and PD data will have been collected for the study. The frozen samples may be used for future research related to eculizumab. Each sample will be given a code. This code will allow the patient sample to be used without the researchers knowing the patient's name. The results of the research may be presented at scientific meetings or in publications; however, patient identity will not be disclosed. All other blood and urine samples collected during the study will be destroyed after the tests have been completed.

9. ASSESSMENT OF SAFETY

The collection of AEs will be monitored from the signing of informed consent until study completion. Investigators are instructed to follow any AEs through to their conclusion (resolution or stabilization) as described in Section 9.6.8. In the event of patient withdrawal from the study, AE monitoring should continue through the last patient's last study visit if possible.

The timing of the clinical and laboratory assessments to be performed is specified in the Schedule of Assessments (Section 4.2). Any clinically significant abnormal results should be followed until resolution or stabilization.

9.1. Physical Examinations

Each examination will include the following assessments: general appearance of skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and general neurologic system. Physical growth (height [cm], weight [kg]) will be assessed. The accurate weighing of patients is vital as part of their management, as eculizumab dosing will depend on the patient's recorded body weight at the most recent dosing visit. It is recommended that patients should be weighed in the same amount of clothing in each instance where weight is assessed.

9.2. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). Vital signs will be taken prior to each administration of study drug.

9.3. Laboratory Assessments (Pregnancy Screen, Serum Chemistry, and Hematology)

Samples for urine pregnancy, hematology, and chemistry will be performed at the times specified for clinical laboratory tests in the Schedule of Assessments (Section 4.2). Specific laboratory assessments are provided in Appendix 12. For clinic visits indicating laboratory assessments as required, the samples for laboratory assessments will be collected before administration of study drug.

It is anticipated that some laboratory values may be outside the normal value range due to underlying disease. The Investigators should use their medical judgment when assessing the clinical significance of these values. Clinical significance is defined as any variation in laboratory measurements that has medical relevance and that results in a change in medical care. If clinically significant laboratory changes from Baseline resulting in medical intervention are noted, the changes will be documented as AEs on the AE eCRF. The Investigator will also assess the relationship to study drug for all clinically significant out-of-range values (Section 9.6.5). The Investigator will continue to monitor the patient through additional laboratory assessments until (1) values have returned to the normal range or baseline level, or (2) in the judgment of the Investigator, values that are outside the normal range are not related to the administration of study drug or other protocol-specific procedures.

9.4. Electrocardiograms

For each patient, 12-lead digital electrocardiograms (ECGs) will be collected according to the Schedule of Assessments (Section 4.2). Patients must be supine for approximately 5 to 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 to determine the clinical significance of the results. These assessments will be indicated on the CRF. For any clinically significant abnormal ECG results, the Investigator must contact the Medical Monitor to discuss the patient's continued eligibility to participate in this protocol.

9.5. Immunogenicity

Blood samples will be collected to test for the presence and titer of ADAs to eculizumab in serum as indicated in the Schedule of Assessments (Section 4.2). Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, to PK/PD, safety, and activity of eculizumab.

Refer to the Laboratory Manual for time windows for sample collection and detailed instructions for collecting, processing, storing, and shipping blood samples for immunogenicity analysis.

9.6. Adverse Event Management

9.6.1. Detection of Adverse Events

The Investigator is responsible for detecting, assessing, documenting, and reporting all AEs.

Adverse events reported by the patient and/or parent or legal guardian, identified in response to an open-ended question from study personnel, or revealed by observation, physical examination, or other study procedures must be collected and recorded as described in Section 9.6.3. The same parent or guardian is recommended to be available to accompany the patient to each visit, in order to reduce subjective variability in assessments.

9.6.2. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, and abnormal laboratory findings that are considered to be of clinical significance are all to be considered AEs.

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.

Situations where an untoward medical occurrence did not occur (social and/or elective admission to a hospital), and 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 are not AEs.

9.6.2.1. Procedure

Elective procedures that were preplanned prior to the time that written ICF was obtained are not AEs. Any complication or worsening of a pre-existing condition leading to the procedure must be considered an AE. In addition, any AE that could occur as an outcome of the planned procedure should be considered as an AE.

Diagnostic and therapeutic procedures (invasive and noninvasive), such as surgery or angiography, should not be reported as an AE or SAE. However, the medical condition or the diagnosis that was responsible for the procedure should be recorded. The procedure should be recorded in the narrative as treatment for the AE or SAE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder).

9.6.2.2. Abnormal Test Findings

Abnormal test findings may be considered AEs or SAEs; however, Investigators are strongly encouraged to report the diagnosis, sign, or symptom instead of just the abnormal result. The criteria for an abnormal test finding being classified as an AE or SAE are as follows:

- Test result is associated with a sign or symptom
- Test result requires additional diagnostic testing
- Test result requires a medical or surgical intervention
- Test result leads to a change in study dosing outside of the protocol defined dosing or discontinuation from the study
- Test result requires significant additional treatment (ie, addition of new medication, significant increase in dose of current medication)

9.6.2.3. Lack of Efficacy

Since eculizumab treatment in pediatric patients with refractory gMG is not an approved indication for this population, lack of efficacy should not be reported as an AE.

9.6.2.4. Development of Myasthenia Gravis Clinical Deterioration

Normal day-to-day fluctuations of the underlying study indication are not considered an AE unless it is so in the opinion of the Investigator. Worsening of underlying study indication that meets the SAE criteria should be reported as an SAE.

9.6.3. Recording Adverse Events

Cases of pregnancy that occur during maternal or paternal exposure to the 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.

All AEs (serious and nonserious) will be collected from the signing of the ICF. An AE reported after informed consent but before study drug administration will be considered a pretreatment AE.

Alexion has reporting standards for AEs that are to be followed as described in Section 9.6.8 regardless of applicable regulatory requirements that may be less stringent.

9.6.4. Severity Assessment

The severity (intensity) of an AE will be rated by the Investigator as mild, moderate, or severe using the following criteria:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific instructions 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 the criteria for an SAE (Section 9.6.6).

9.6.5. Causality Assessment

An Investigator causality assessment (not related or related) must be provided for all AEs, both serious and nonserious based upon the Investigator's medical judgement and the observed symptoms associated with the event (Table 18). This assessment must be recorded in the eCRF and any additional forms as appropriate.

Table 18: Causality Assessment Descriptions

Assessment	Description
Not Related	This relationship suggests that there is no causal association between the study drug and the reported event.
Related	This relationship suggests that there is causal association between the investigational product and the reported event

9.6.6. Definition of Serious Adverse Event

Any AE that fulfills any 1 of the criteria listed below must be recorded as an SAE. An SAE (experience) or reaction is described as any untoward medical occurrence that at any dose:

1. Results in death
2. Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.

3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

The expectedness of an SAE will be determined by Alexion, based on the current version of the eculizumab IB.

Information pertaining to the collection and reporting of SAEs is provided in Section 9.6.6.

9.6.7. Serious Adverse Event With Outcome of Death

If a patient experiences an SAE with an outcome of death:

- The SAE resulting in death should have an outcome documented as death/fatal with an end date being the date of death.
- If the patient had additional AE/SAEs that were ongoing at the time of death, these events would be documented as ongoing with no end date.
- Only one event should have an outcome of death/fatal unless an autopsy report or Investigator states otherwise.

9.6.8. Hospitalization

Adverse events that are associated with hospitalization or prolongation of hospitalization are considered SAEs. All admissions to a health care facility meet this criteria, even if less than 24 hours. Criteria for seriousness are also met if transfer within the hospital is done to receive more intense medical / surgical care (eg, medical floor to the intensive care unit [ICU]).

Hospitalization does not include the following:

- Rehabilitation facility
- Hospice facility
- Nursing facility
- Emergency Room
- Same day surgery

Hospitalization or prolongation of hospitalization not associated with an AE is not an SAE, examples include:

- Admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE

- Protocol-specified admission
- Pre-planned admission

9.6.9. Collection and Reporting of Adverse Events

9.6.9.1. All Adverse Events

All AEs (serious and nonserious) will be collected from the signing of the ICF until 8 weeks after the last dose of study drug for patients who discontinue or until 8 weeks after the last dose of study drug for patients who complete the study. All AEs must be recorded on the eCRF upon the Investigator or his/her staff becoming aware of their occurrence.

Investigators will be instructed to report the SAE including their assessment (eg, severity, seriousness, and potential relatedness to study drug) to Alexion Global Drug Safety (GDS) within 24 hours of first awareness of the event via the Safety Gateway.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly capture the circumstances and data leading to any such dose interruption or discontinuation of treatment in the AE and Exposure pages of the eCRF.

For patients who enter the trial on maintenance IVIg therapy, IVIg administered as part of routine maintenance therapy in an inpatient or outpatient setting should not be captured as AEs or SAEs, unless identified as such by the Investigator.

9.6.9.2. Serious Adverse Events

All SAEs must be recorded regardless of the Investigator's assessment of causality. No time limit exists on reporting SAEs that are thought to be causally related to the study drug. Investigators are at liberty to report SAEs irrespective of causality at any time.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious event(s)
- Seriousness criteria
- Treatment of/intervention for the SAE(s)
- Severity
- Outcome of the serious event(s)
- Supporting medical records and laboratory/diagnostic information

All SAEs must be reported to Alexion GDS 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 Safety Gateway.

In the event that either the electronic data capture or the Safety Gateway is unavailable at the site(s), the SAE must be reported utilizing the paper contingency form via Facsimile transmission or email.

Email: [redacted]

Facsimile: [redacted]

When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GDS via the Safety Gateway.

If applicable, additional information such as relevant medical records should be submitted to Alexion GDS via the email address or fax number noted above accompanied by the Investigator signed fax cover page.

All paper forms and follow-up information submitted to the Sponsor outside of the Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

9.6.9.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to the study drug or procedure. United States 21 CFR 312.32 and European Union Clinical Study Directive 2001/20/EC and the associated detailed guidances 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 guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs or IECs where applicable.

9.6.10. Sponsor Reporting Requirements

Alexion GDS or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the current eculizumab IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Document.

9.6.11. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for study Investigators. It is the PI's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

9.7. Exposure During Pregnancy and Breastfeeding

Pregnancy data will be collected during this study for all patients and 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.

10.8.3. Extension Period Efficacy Endpoints

The efficacy endpoints related to the Extension Period are:

- Total number and percentage of patients with clinical deteriorations and/or myasthenic crisis during the study
- Total number and percentage of patients needing rescue therapy during the study
- Change from Baseline in the QMG total score regardless of rescue treatment
- Change from Baseline in the MG-ADL total score regardless of rescue treatment
- Change from Baseline in the MGC total score regardless of rescue treatment
- Change from Baseline in EQ-5D-Y regardless of rescue treatment
- Change from Baseline in Neuro-QoL Pediatric Fatigue regardless of rescue treatment
- Change from Baseline in MGFA Post-Interventional Status

These endpoints will be analyzed similarly as described for the secondary endpoints, but based on the FAS population for the entire duration of the study.

10.9. Safety Analyses

The safety endpoints of the study are:

- Frequency of AEs and SAEs
- Frequency of adverse events leading to discontinuation
- Incidence of antidrug antibodies (ADA)
- Physical examination assessments
- Changes from Baseline in vital signs
- Change from Baseline in electrocardiogram parameters
- Change from Baseline in laboratory assessments

Safety analyses will be performed on the Safety Set.

10.9.1. Physical Examinations

The number and percentage of patients with abnormal physical examinations will be summarized by visit.

10.9.2. Vital Signs

Absolute values and change from Baseline in vital signs (including weight and height) will be summarized by visit.

10.9.3. Adverse Events

Treatment-emergent AEs (serious and nonserious) will be defined as all AEs starting on or after the day of first dose of study drug. Pre-treatment SAEs are any SAEs staring prior to the day of first dose of study drug.

All AEs will be coded using the MedDRA version that is current at the time of the analysis.

Adverse events will be summarized for the first 26 weeks and separately for the entire study by System Organ Class (SOC) and Preferred Term (PT) and, in some cases, by PT only.

10.9.4. Clinical Laboratory Tests

Absolute values and change from Baseline over time in clinical chemistry and hematology results will be summarized descriptively. Laboratory data abnormalities (low, normal, high) with respect to the reference range will be summarized using shift analysis compared to the abnormality at Baseline. Listings of patients with abnormal laboratory values will be provided.

10.9.5. Immunogenicity

The number and percentage of patients with positive ADA will be summarized by visit, any time during the first 26 weeks and any time during the study. The proportion of patients ever positive and the proportion of patients always negative may be summarized.

10.10. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic and PD laboratory measurements will be summarized for both Induction and Maintenance Treatment Period. Pharmacokinetic and PD data will be explored using modeling and simulation methods for evaluating the appropriateness of the studied pediatric dose. A separate analysis plan will be written for the PK/PD analyses.

The PK/PD endpoints of the study include:

- Pharmacokinetic/PD parameters including maximum plasma drug concentration (C_{max}), terminal half-life ($t_{½}$), trough (C_{trough}), clearance, free C5, and in vitro hemolytic assay; assessed at Baseline and various time points including 24 hours (Day 2), Week 12, and Week 26 during the treatment.

10.11. Other Statistical Issues

10.11.1. Missing or Invalid Data

Missing data will not be imputed unless otherwise noted.

10.12. Interim Analyses

The primary analysis (ie interim analysis) of the study for regulatory submission will be performed after all patients complete the 26-week Primary Evaluation Treatment Period.

10.13. Sample Size Re-Estimation

After 6 patients complete their Week 26 assessments, if the observed standard deviation in change in QMG is 8 or higher, the final sample size will be re-estimated to be at least 14 instead of 12 to preserve adequate power for testing the primary endpoint.

APPENDIX 4. MYASTHENIA GRAVIS COMPOSITE SCALE

Patient ID and Date

MG Composite Scale

Ptosis, upward gaze (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 2	Immediate = 3
Double vision on lateral gaze, left or right (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 3	Immediate = 4
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
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
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
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
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
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

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

Pharmacokinetic and Pharmacodynamic Endpoints:

- Pharmacokinetic/PD parameters including maximum plasma drug concentration (C_{max}), terminal half-life ($t_{½}$), trough (C_{trough}), clearance, free complement protein 5 (C5), and in vitro hemolytic assay; assessed at Baseline and various time points including 24 hours (Day 2), Week 12, and Week 26 during treatment

Study Design and Methodology:

This is an open-label, multicenter study to evaluate the efficacy, safety, PK, and PD of intravenous eculizumab in pediatric patients aged 6 to < 18 years with acetylcholine receptor (AChR)-antibody (Ab) positive refractory gMG. There will be 4 periods in this study: Screening Period (2 to 4 weeks), Primary Evaluation Treatment Period (26 weeks), Extension Period (up to an additional 208 weeks), and Follow-up Period (8 weeks). All patients who complete Week 26 of Study ECU-MG-303 will continue receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks. The 8-week Follow-up Period is required following the last dose of study drug for all patients upon withdrawal or discontinuation from the study or upon completion of the study when the patient is not continuing to receive eculizumab treatment.

Patients may continue use of acetylcholinesterase inhibitors (AChI), intravenous immunoglobulin (IVIg), and supportive immunosuppressive therapies (ISTs) during the study where applicable under certain restrictions.

Screening Period (2 to 4 weeks):

Patients will be screened for study eligibility only after obtaining the informed assent of the patient and informed permission of the parent or other legal guardian.

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. Patients must remain within the current national vaccination guidelines or local practice for vaccination use with complement-inhibitors. In addition to meningococcal vaccination, patients must be vaccinated against *Haemophilus influenzae* (*H influenzae*) and *Streptococcus pneumoniae* (*S pneumoniae*), and strictly adhere to the national vaccination recommendations for each age group.

The site must notify the Sponsor if any patient experiences signs and symptoms of MG worsening that require rescue or foreseeable imminent change to the background medication, during the Screening Period. Patients whose MG is unstable (as determined by the Investigator) during the Screening Period may be rescreened based on discussion and agreement between the Investigator and the Alexion Medical Monitor.

Primary Evaluation Treatment Period (26 weeks):

All patients will receive eculizumab by intravenous (IV) infusion during the open-label Primary Evaluation Treatment Period. Dosing will be initiated with a weekly weight-based induction regimen and, thereafter, will be every 2 weeks.

Extension Period (up to 208 weeks):

After completing the 26-week Primary Evaluation Treatment Period, patients will continue receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks.

Follow-up Period:

- Safety Follow-up (8 weeks)

Patients who do not enter the Extension Period from the Primary Evaluation Treatment Period, who withdraw from the study at any time, or who do not continue to receive eculizumab treatment upon study completion will be followed for at least 8 weeks from their last dose of eculizumab. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete an 8-week follow-up visit.

2. INTRODUCTION

Myasthenia gravis (MG) is a rare, chronic, autoimmune disease of neuromuscular transmission that manifests clinically in both children and adults as fluctuating weakness in voluntary muscles that is exacerbated during periods of activity and improves after periods of rest (Barnett, 2014; Sieb, 2014). The pathological hallmark of both juvenile and adult forms of MG is production of antibodies (Abs) against the components of the postsynaptic membrane at the neuromuscular junction (NMJ), predominantly the acetylcholine receptor (AChR). Although adults and juveniles with MG share aspects of presentation and pathophysiology, there are differences in epidemiology and prognosis. Additionally, the ongoing development of children and adolescents complicate therapeutic decision making in young patients with MG.

2.1. Epidemiology

Myasthenia gravis in children and adolescents is uncommon and comprises approximately 10% to 20% of all MG cases (Snead, 1980; Szorbor, 1988-1989). The annual incidence of MG in children and adolescents has been reported as approximately 1.1 per million in North America and 1 to 5 per million in Europe (Phillips, 1992; Andrews, 2004; McGrogan, 2010; Della Marina, 2014), with incidence and prevalence varying geographically. Ten percent of patients with MG have disease limited to ocular muscles, while the remaining 90% have generalized MG (gMG), with muscle weakness involving neck, head, spine, bulbar, respiratory, or limb muscles.

Clinically, gMG in children and adolescents presents as fluctuating and fatigable skeletal muscle weakness, which improves with rest, similar to manifestations of the disease in adults. Clinical features may include predominantly ocular symptoms with ptosis, ophthalmoplegia, and/or diplopia. Bulbar symptoms of dysphagia and/or dysphonia may be present, as well as generalized symptoms of exercise intolerance and weakness. As with adults, respiratory muscle weakness may be a feature of MG in children and adolescents and may lead to respiratory distress or even respiratory failure, particularly if left untreated. In children and adolescents with MG, prepubertal patients tend to be more clinically distinct compared to adults with MG, as compared with the pubertal/postpubertal group who share more features with adult-onset MG.

2.2. Unmet Medical Need

While there is no cure for MG, there are a variety of therapies that reduce muscle weakness and improve neuromuscular function. Currently available treatments for MG aim to modulate neuromuscular transmission, inhibit the production or effects of pathogenic antibodies, or inhibit inflammatory cytokines (Kim, 2011). There is currently no specific treatment that targets the underlying pathophysiology of NMJ injury specifically: anti-AChR Ab-AChR interactions resulting in complement activation via the classical pathway and inflammation, with the resultant destruction of the NMJ. With current standard of care, which combines cholinesterase inhibitors, corticosteroids and immunosuppressive therapies (ISTs; most commonly azathioprine [AZA], cyclosporine, and mycophenolate mofetil [MMF]), the majority of MG patients have their disease reasonably well controlled. For the cohort of refractory patients who do not respond adequately to ISTs or cannot tolerate ISTs and those who require repeated treatments with plasma exchange (PE) and/or intravenous immunoglobulin (IVIg) to maintain clinical stability (Conti-Fine, 2006), there is a medical need for alternative treatment strategies targeting different

4.1.7. Unscheduled Visits

Additional (Unscheduled) visits outside the specified visits for study procedures, tests, and assessments may be performed at the request of the Investigator or Sponsor. If an Unscheduled Visit is performed, any tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the electronic case report forms (eCRFs).

4.1.8. Study Completion

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 Extension Period, or
- In the event the study is completed early, the patient has completed all applicable periods of the study including the ET/End of Study visit, or,
- The patient completes the study early (and completes an ET visit) because the study drug has become registered or approved (in accordance with country-specific regulations)

4.2. Study Flow Diagram and Schedule of Assessments

The flow diagram for the study design is illustrated in Figure 1. The Schedule of Assessments during the study for patients in weight cohorts ≥ 40 kg, 30 to < 40 kg and 20 to < 30 kg are summarized in Table 4 and Table 5. The Schedule of Assessments for patients in weight cohort 10 to < 20 kg are summarized in Table 6 and Table 7.Weight cohort may change for an individual patient during the study, and dose regimen will be based on the current visit's recorded body weight. If site/institution policies prohibit study drug to be prepared day-of visit, the weight from the most recent study visit should be used.

Table 4: Schedule of Assessments Part I: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Period /Phase	**Screening**	**Primary Evaluation Treatment Period**																		
Visit Location[a]	**In Clinic**	**In Clinic**																**In Clinic**		
Study Visit[b]	**Screening Visit (1)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Week	**-2 to -4 weeks**	**D1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**			**+W8**
Window (Days)			**±2**																	**±2**
Informed Consent	X																			
Medical History	X																			
MG History	X																			
MGFA Clinical Classification	X																			
Weight[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[g]	X	X								X							X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X									X							X		X	
12-Lead ECG	X	X								X							X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[h]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[i,j]	X[k]	X	X	X	X	X		X		X		X		X			X	X	X	X
QMG[i,k,l]	X[k]	X	X	X	X	X		X		X		X		X			X	X	X	X
MGC[i,l]	X[k]	X	X	X	X	X		X		X		X		X			X	X	X	X
Neuro-QoL Pediatric Fatigue / PROMIS Proxy		X				X		X		X		X		X			X		X	
EQ-5D-Y / Proxy		X				X		X		X		X		X			X		X	
MGFA-PIS[i]						X				X							X		X	X
MGFA-Therapy Status	X	X								X							X			
AChR Ab	X																			

b. History of positive anticholinesterase test (eg, edrophonium chloride or neostigmine test), or
c. Patient demonstrated improvement in MG signs on oral AChIs, as assessed by the Investigator.

7. Presence of refractory gMG, defined as patients with gMG who have one or more of the following:
    a. Failed treatment ≥ 1 year with at least 1 IST, defined as:
        i. Persistent weakness with impairment of activities of daily living, or
        ii. Myasthenia gravis exacerbation and/or crisis while on treatment, or
        iii. Intolerance to ISTs due to side effect or comorbid condition(s).

    Immunosuppressants include, but are not limited to, corticosteroids, AZA, MMF, methotrexate (MTX), cyclosporine, tacrolimus, or cyclophosphamide.

    b. Require maintenance plasma exchange (PE) or IVIg to control symptoms (ie, patients who require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over the last 12 months prior to Screening).
    c. In the opinion of the Investigator, MG poses a significant functional burden despite current MG treatment.
8. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of Class II to IV at Screening.
9. In patients aged 12 to 18 years, QMG total score ≥ 12 at Screening; in patients aged 6 to 11 years, no minimum QMG is required for inclusion; however, patients must have documented limb weakness in at least one limb.
10. All MG-specific treatment has been administered at a stable dosing regimen of adequate duration prior to Screening as follows:
    a. If patients who enter the study are receiving AZA, they must have been on AZA for ≥ 6 months and have been on a stable dose for ≥ 2 months prior to Screening.
    b. If patients who enter the study are receiving other ISTs (ie, MMF, MTX, cyclosporine, tacrolimus, or cyclophosphamide), they must have been on the IST for ≥ 3 months and have been on a stable dose for ≥ 4 weeks prior to Screening.
    c. If patients who enter the study are receiving maintenance IVIg at Screening, they must have been on maintenance IVIg for at least 12 months and on a stable dose for ≥ 3 months prior to Screening, with the frequency and dose expected to remain stable during Screening and for 12 weeks following the first dose of study drug. All other patients must not have received maintenance IVIg within 3 months of Screening.
    d. If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks prior to Screening.
    e. If patients who enter the study are receiving a cholinesterase inhibitor, they must have been on a stable dose for ≥ 2 weeks prior to Screening.
11. Female patients of childbearing potential (ie, have achieved menarche) and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 5 months after the last dose of study drug. For additional details on contraception guidance, please refer to Section 11.9.
12. Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male

For all Alexion products, both in development or post-approval, 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 GDS via fax or email (Section 9.6.9.2). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. 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") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile (Section 9.6.8).

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.

9.8. Safety Monitoring

The Alexion medical monitor, GDS physician, or both will monitor safety data throughout the course of the study.

Alexion will review all information pertaining to the SAEs within the time frames mandated by company procedures. The Alexion medical monitor will, as appropriate, consult with the GDS safety physician, to review trends in safety data.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor or its designee will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or the Sponsor's designee or its representatives. This will be documented in a Clinical Study Agreement between Alexion Pharmaceuticals, Inc. or its designee and the Investigator.

During the study, a monitor from the Sponsor or its designee or representative will have regular contacts with the investigational site, to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or its designee.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor or its designee and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

11.2. Audits and Inspections

Authorized representatives of the Sponsor or the Sponsor's designee, a regulatory authority, and an IEC or an IRB may visit the sites to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor or the Sponsor's designee immediately if contacted by a regulatory agency about an inspection.

APPENDIX 5. EUROPEAN QUALITY OF LIFE 5-DIMENSION – YOUTH VERSION

Sample Health Questionnaire (English version for the UK) to be used for patients 8-18 years of age

EQ-5D-Y

Describing your health TODAY

Please check the ONE box that best describes your health TODAY.

Mobility *(walking around)*

I have no problems walking around ❑
I have some problems walking around ❑
I have a lot of problems walking around ❑

Taking care of myself

I have no problems taking a bath or shower by myself or getting dressed by myself ❑
I have some problems taking a bath or shower by myself or getting dressed by myself ❑
I have a lot of problems taking a bath or shower by myself or getting dressed by myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑
I have some problems doing my usual activities ❑
I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑
I have some pain or discomfort ❑
I have a lot of pain or discomfort ❑

Feeling worried, sad, or unhappy

I am not worried, sad, or unhappy ❑
I am a little worried, sad, or unhappy ❑
I am very worried, sad, or unhappy ❑