ECULIZUMAB

ECU-MG-303

AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ECULIZUMAB IN PEDIATRIC PATIENTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS

IND 101,219

EudraCT Number: 2016-001384-37

Sponsor: Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston MA 02210
USA

Sponsor Contact: [redacted]
Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard, Suite 400
Boston, MA 02210 USA
Telephone: [redacted]
E-mail: [redacted]

Medical Monitor: [redacted]
Alexion Pharmaceuticals Inc.
121 Seaport Boulevard, Suite 400
Boston, MA 02210, USA
Telephone: [redacted]
E-mail: [redacted]

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SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Eculizumab in Pediatric Patients with Refractory Generalized Myasthenia Gravis

PROTOCOL NUMBER: ECU-MG-303 (Amendment 3)

[redacted]

Medical Monitor
Alexion Pharmaceuticals, Inc.

09/30/2020

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for eculizumab. I have read the ECU-MG-303 (Amendment 3) 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 GCP, 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

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Study Role	Name	Address and Telephone Number
Clinical Project Lead	[redacted]	Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard, Suite 400 Boston, MA 02210, USA Telephone : [redacted] E-mail: [redacted]
Medical Monitor	[redacted]	Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard, Suite 400 Boston, MA 02210, USA Telephone: [redacted] E-mail: [redacted]
Serious Adverse Event Reporting	Alexion Pharmaceuticals, Inc.	Email: [redacted] Fax: [redacted]
Investigational Product Supply	Endpoint Clinical, Inc.	Telephone: [redacted] (toll-free) (direct dial) From outside the United States: [redacted] (direct dial)
24-Hour Emergency Contact	24-Hour Telephone Number	Telephone: [redacted]

1. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: Eculizumab	
Name of Active Ingredient: h5G1.1-mAb	
Title of Study: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Eculizumab in Pediatric Patients with Refractory Generalized Myasthenia Gravis	
Study Centers: Global (North America, Europe, and Asia)	
Study Duration: Estimated date first patient enrolled/randomized: Oct 2018 Estimated date last patient completed: Jun 2025	**Phase of Development**: 3
Planned Duration of Study: up to 246 weeks (approximately 4.7 years) Screening Period: 2 to 4 weeks Primary Evaluation Treatment Period: 26 weeks Extension Period: up to 208 weeks Follow-up Period: 8 weeks following the last dose of eculizumab	

Objectives:

The primary objective of this study is to evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized myasthenia gravis (gMG) based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG
- Evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the following measures:
  - Myasthenia Gravis Activities of Daily Living profile (MG-ADL)
  - Myasthenia Gravis Composite score (MGC)
- Evaluate the effect of eculizumab on the following quality of life measures:
  - European Quality of Life 5-Dimension Youth (EQ-5D-Y) Questionnaire – EQ-5D-Y Proxy version for patients < 8 years of age or EQ-5D-Y version for patients ≥ 8 years of age
  - Neurological Quality of Life Pediatric Fatigue (Neuro-QoL Pediatric Fatigue) Questionnaire for patients ≥ 8 years of age
  - PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a for patients < 8 years of age
- Evaluate MGFA Post-Interventional Status over time
- Describe the total number and percentage of patients with clinical deteriorations, myasthenic crises, and rescue therapy use over time
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab treatment in pediatric refractory gMG patients to confirm the pediatric dosing regimen selected through modeling and simulation following 26 weeks of eculizumab treatment

The Extension Period objectives are to:

- Characterize long-term safety beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG
- Characterize long-term efficacy beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG

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

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.

- 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)/early termination (ET) visit.

Clinical Deterioration and Rescue Therapies

Allowed rescue therapy for clinical deterioration includes but is not limited to high-dose corticosteroids, plasma exchange (PE), or IVIg and is at the discretion of the treating physician.

Number of Patients (Planned): At Least 12

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.

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.

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). There is no cap on patients 6 to < 12 years of age.

Diagnosis and Main Criteria for Inclusion/Exclusion:

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
    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, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclosporine, tacrolimus, or cyclophosphamide.

b. Require maintenance 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, 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.

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 condom plus appropriate barrier method for the female partner) while on treatment and for at least 5 months after the last dose of study drug.

Exclusion Criteria:

1. Parent or legal guardian is an Alexion employee.

2. Any active or untreated thymoma. History of thymic carcinoma or thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before Screening.

3. History of thymectomy within 12 months prior to Screening.

4. Weakness only affecting ocular or periocular muscles (MGFA Class I).

5. Myasthenia Gravis crisis or impending crisis at or during Screening (MGFA Class V).
6. Are pregnant or lactating.
7. Any unresolved acute, or chronic, systemic bacterial or other infection, which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics.
8. Unresolved meningococcal infection.
9. For patients who are not receiving a stable maintenance dose of IVIg, as described in the Inclusion Criteria, use of IVIg (eg, as rescue therapy) within 4 weeks prior to first dose.
10. Use of PE within 4 weeks prior to first dose.
11. Use of rituximab within 6 months prior to first dose.
12. Patients who are under 15 kg and are receiving maintenance IVIg.
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 that investigational product, whichever is greater.
14. Have previously received treatment with eculizumab or other complement inhibitors.
15. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
16. Any medical or psychological condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses any added risk for the patient, or confounds the assessment of the patient.
17. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.

Investigational Product, Dosage, and Mode of Administration:

The bodyweight-categorized dosing regimens are provided in Table 1.

Table 1: Weight-based Dosing Regimen of Eculizumab

Weight Cohort[a,b]	Induction Phase	Maintenance Phase
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Week 4; then every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Week 2; then every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Week 2; then every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Week 1; then every 2 weeks

[a] 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.
[b] During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort, the Alexion medical monitor must be contacted prior to dosing.

Supplemental Doses

For patients who enter the study on maintenance IVIg treatment, a series of supplemental doses of eculizumab will be administered to account for the anticipated approximately 50% increase in eculizumab clearance according to Table 2.

Table 2: Supplemental Dosing Regimen of Eculizumab in Patients Receiving Maintenance IVIg

Weight Cohort[a,b]	Induction Phase Supplemental Dose	Induction Phase Total Dose	Maintenance Phase Supplemental Dose	Maintenance Phase Total Dose
≥ 40 kg	600 mg	1500 mg	600 mg	1800 mg
30 to < 40 kg	300 mg	900 mg	600 mg	1500 mg
20 to < 30 kg	300 mg	900 mg	300 mg	900 mg
10 to < 20 kg[c]	300 mg	900 mg	300 mg	600 mg

[a] 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.
[b] During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort, the Alexion medical monitor must be contacted prior to dosing.
[c] Only patients in 15-20 kg weight category to be included in this group.
Notes: The timing of supplemental eculizumab dosing varies by IVIg frequency and is provided below:

- If a patient continues to receive IVIg treatment at a dose cycle interval equal to or more frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered at the same time that each scheduled dose of eculizumab is administered.
- If a patient receives IVIg treatment at a dose cycle interval less frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered following the last dose of the IVIg infusion cycle at the next scheduled eculizumab dose.
- If a patient receives IVIg treatment within 4 weeks prior to receiving the first dose of eculizumab, a supplemental dose of eculizumab will be administered at the same time that the first dose of eculizumab is administered (ie, the total dose is the supplemental dose plus the first scheduled dose).

When IVIg is administered as acute rescue therapy for clinical deterioration, no supplemental dose of eculizumab should be administered. However, if a patient receives more than 1 dose cycle of IVIg as rescue therapy within a 12-week period, supplemental eculizumab should be administered after the last dose of the second IVIg cycle and at the end of each subsequent IVIg dose cycle within the 12-week period in accordance with Table 2.

For patients who undergo PE, plasmapheresis (PP), or receive fresh frozen plasma (FFP), supplemental eculizumab dosing should be administered as shown in Table 3. In addition, patients are to continue study drug infusion according to the protocol-specified dosing regimen. If the PE/PP/FFP is on the day of a scheduled

study drug infusion, the scheduled dose of study drug (instead of the supplemental dose) should be administered.

Table 3: Supplemental Dosing Regimen of Eculizumab after Plasma Exchange/Plasma Infusion Intervention

Type of Intervention	Most Recent Eculizumab Dose	Supplemental Eculizumab Dose With Each Plasma Exchange/Plasma Infusion Intervention	Timing of Supplemental Eculizumab dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 1 to 2 hours after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per infusion of fresh frozen plasma	Approximately 60 minutes[a] prior to each infusion of fresh frozen plasma

[a] Supplemental dosing of eculizumab should occur 60 ± 15 minutes prior to each infusion of fresh frozen plasma.

Statistical Methods:

When the target number of patients has been achieved that have completed the 26-week Primary Evaluation Treatment Period, all patients including patients who discontinued prior to 26 weeks will be analyzed for efficacy, safety, and PK/PD. The planned statistical methods and analyses will be detailed in the statistical analysis plan (SAP). Additional interim analyses during the Extension Period may be performed at the discretion of the Sponsor.

Summary statistics for continuous variables will minimally include the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate. All statistical analyses will be performed based on a 2-sided Type I error of 5% unless noted otherwise. Missing data will not be imputed.

Efficacy:

Efficacy analyses will be performed on the Full Analysis Set (FAS), which consists of all patients who received at least 1 dose of eculizumab. Analyses of the primary efficacy endpoint and secondary efficacy endpoints will be performed on a modified FAS (mFAS), which consists of FAS patients 12 to <18 years of age.

For all patients in the mFAS, the primary endpoint and the secondary endpoints that involve changes from Baseline will be analyzed at a particular visit based on a Repeated-Measures model with effects for the particular baseline covariate and visit. Confidence intervals and p-values will be presented by visit. Graphical displays over time will be produced by visit. Missing efficacy endpoint assessments will not be imputed.

For all patients in the mFAS, the proportion of patients with at least a 3-point reduction in the MG-ADL total score from Baseline will be summarized by visit over time. Confidence intervals and p-values will be presented. Similar analyses will be performed for at least a 5-point reduction in the QMG total score from Baseline. These analyses will be done with no rescue and regardless of rescue.

Descriptive analysis will be used for patients from 6 to < 12 years of age.

Safety:

Safety analyses will be performed on the Safety Set, which includes all patients who have received at least 1 dose of eculizumab. All safety data will be provided in patient listings.

Physical Examinations and Vital Signs:

The number and percentage of patients with abnormal physical examinations will be summarized by visit. Absolute values and change from Baseline in vital signs (including weight and height) will be summarized by visit.

Listings of physical examinations and vital signs will be produced.

Clinical Laboratory Tests:

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

Adverse Events:

Pretreatment SAEs, defined as any SAE that starts after signing the informed consent form (ICF) but before the first dose of study drug, will be summarized in a listing.

Treatment-emergent AEs (TEAEs), defined as any AE that starts during or after the first dose of study drug, will be summarized as serious and nonserious events.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term, seriousness, severity, and relationship to treatment. All AEs will be coded using MedDRA version current at the time of the analysis.

Immunogenicity:

Immunogenicity findings, including the incidence of positive ADAs to eculizumab will be summarized by visit.

Pharmacokinetics/Pharmacodynamics:

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 studied pediatric dose.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and Terms	Definitions
Ab, Abs	antibody, antibodies
AChR	acetylcholine receptor
AChI	acetylcholinesterase inhibitor
ADA	antidrug antibody
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AZA	azathioprine
C5	complement protein 5
C_{max}	maximum plasma drug concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	end-of-study
EQ-5D-Y	European Quality of Life 5-Dimension Youth version
ET	early termination
EU	European Union
FAS	Full Analysis Set
FFP	fresh frozen plasma
FVC	forced vital capacity
GCP	Good Clinical Practices
GDS	Global Drug Safety
gMG	generalized myasthenia gravis
H influenzae	*Haemophilus influenzae*
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization
IEC	Institutional (or Independent) Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	immunosuppressant therapy
IV	intravenous
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living profile
MGC	Myasthenia Gravis Composite Scale
MGFA	Myasthenia Gravis Foundation of America
MMF	mycophenolate mofetil
MMT	manual muscle test
MTX	methotrexate
N meningitidis	*Neisseria meningitidis*
Neuro-QoL Fatigue	Neurological Quality of Life-Fatigue questionnaire
NMJ	neuromuscular junction
PD	pharmacodynamics
PDCO	Paediatric Committee of the European Medicines Agency
PE	plasma exchange
PI	Principal Investigator
PIS	post-intervention status
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria

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

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

pathophysiological aspects of the disease. There are currently no approved therapies specific for the treatment of refractory gMG in pediatric patients. Since complement activation plays a pivotal role in the pathophysiology of MG (Vincent, 2002; Conti-Fine, 2006), eculizumab, a terminal complement inhibitor, may benefit patients who continue to have generalized weakness and bulbar signs and symptoms despite current standard of care.

2.3. Eculizumab Clinical Program in Refractory Generalized Myasthenia Gravis

Alexion has completed 2 clinical studies in adults with refractory gMG, with a Phase 3 extension study currently ongoing.

The totality of the eculizumab clinical data from the pivotal Study ECU-MG-301 and the consistency of the eculizumab treatment effect observed over a multitude of independent but complementary MG-specific outcome measures have established substantial evidence of effectiveness of eculizumab in the treatment of adults with refractory gMG. The safety profile of eculizumab observed in adult refractory gMG patients was consistent with the well-established safety profile of the drug with over 10 years of clinical and postmarketing use. The data observed in the ongoing Study ECU-MG-302 support the long-term safety and maintenance of clinical response of eculizumab in adults with refractory gMG.

Based on the data from these 3 studies, eculizumab was approved for AChR Ab-positive adults with refractory gMG in the EU (14 August 2017), gMG in the US (23 October 2017), and gMG with symptoms that are difficult to control with high-dose IVIg therapy or PE in Japan (25 December 2017).

Refer to the current Investigator's Brochure (IB) for further information on the safety and efficacy data of eculizumab.

2.4. Eculizumab Dose in Pediatric Refractory gMG Patients

The safety and efficacy of the 900 mg/1200 mg dose regimen was previously established in adults with refractory gMG in Study ECU-MG-301. The categorical dose regimen selected for this pediatric study (Study ECU-MG-303) is based on the body weight of the pediatric patient, thus allowing for the accommodation of weight changes during the development and maturation of the patient. For pediatric gMG patients on stable, maintenance IVIg treatment, a series of supplemental doses of eculizumab must be administered. If a patient undergoes plasmapheresis (PP)/PE/fresh frozen plasma (FFP) for clinical deterioration during the study, a supplemental dose of study drug must be administered. The proposed pediatric dose regimen is supported by PK/PD modeling and simulation using data from the MG adult studies, and is identical to that approved for pediatric patients with aHUS, except for the supplemental dose with IVIg administration.

2.5. Rationale for Eculizumab Refractory gMG Pediatric Study

The pathophysiology of MG involves auto-Ab-driven uncontrolled terminal complement activation with membrane attack complex dependent lysis and activation, which causes inflammation at the NMJ, AChR loss, and failure of neuromuscular transmission. Eculizumab binds specifically to the human terminal complement component 5 (C5), inhibiting C5 enzymatic

cleavage and thereby preventing terminal complement activation. The mechanism of action of eculizumab as a potent and selective terminal complement inhibitor supports its use in the management of refractory gMG mediated by complement-activating Abs directed against the NMJ in both adults and children/adolescents.

The favorable benefit-risk for eculizumab in the treatment of adult patients with refractory gMG that was established in the adult clinical program provides the basis for studying eculizumab in the pediatric patient population.

The clinical development program in adults with refractory gMG has informed the methodology of the study design and investigational plan for this first clinical study in pediatric refractory gMG patients.

2.6. Benefit and Risk Assessment

2.6.1. Potential Benefits

Given that MG is a chronic disease, pediatric patients with refractory gMG are at risk of substantial morbidity and mortality, including profound weakness, slurred speech, dysarthria, choking, the inability to swallow hard and/or soft foods, disorienting vision, shortness of breath (both with activity and at rest), significant upper and lower extremity weakness, substantially impaired mobility, marked reductions in ability to perform activities of daily living, extreme fatigue, and episodes of pulmonary failure requiring mechanical ventilation, all of which can have a dramatic impact on quality of life. As there is currently no approved therapy for refractory gMG in the pediatric population, the benefit of sustained terminal complement inhibition and the consistency of the eculizumab treatment effect observed in the adult population support the potential clinical benefit of eculizumab in pediatric refractory gMG patients.

2.6.2. Identified and Potential Risks

2.6.2.1. Meningococcal Infection and Other Encapsulated Bacterial Infections

Eculizumab blocks terminal complement; therefore, patients may have increased susceptibility to encapsulated bacterial infections, in particular *Neisseria meningitidis* (*N meningitidis*). Specific risk mitigation measures in place are described in Section 6.3.4.

2.6.2.2. Immunogenicity

As with any humanized monoclonal Ab, administration of eculizumab may be associated with the development of anti-drug antibodies. Monitoring of immunogenicity is planned, as described in Section 4.2 and Section 9.5.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

3.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG
- Evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the following measures:
  - Myasthenia Gravis Activities of Daily Living profile (MG-ADL)
  - Myasthenia Gravis Composite score (MGC)
- Evaluate the effect of eculizumab on the following quality of life measures:
  - European Quality of Life 5-Dimension Youth (EQ-5D-Y) Questionnaire – EQ-5D-Y Proxy version for patients < 8 years of age or EQ-5D-Y version for patients ≥ 8 years of age
  - Neurological Quality of Life Pediatric Fatigue (Neuro-QoL Pediatric Fatigue) Questionnaire for patients ≥ 8 years of age
  - PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a for patients < 8 years of age
- Evaluate MGFA Post-Interventional Status over time
- Describe total number and percentage of patients with clinical deteriorations, myasthenic crises, and rescue therapy use over time
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab treatment in pediatric refractory gMG patients to confirm the pediatric dosing selected through modeling and simulation following 26 weeks of eculizumab treatment

3.3. Extension Period Objectives

The Extension Period objectives are to:

- Characterize long-term safety beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG
- Characterize long-term efficacy beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG

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.

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

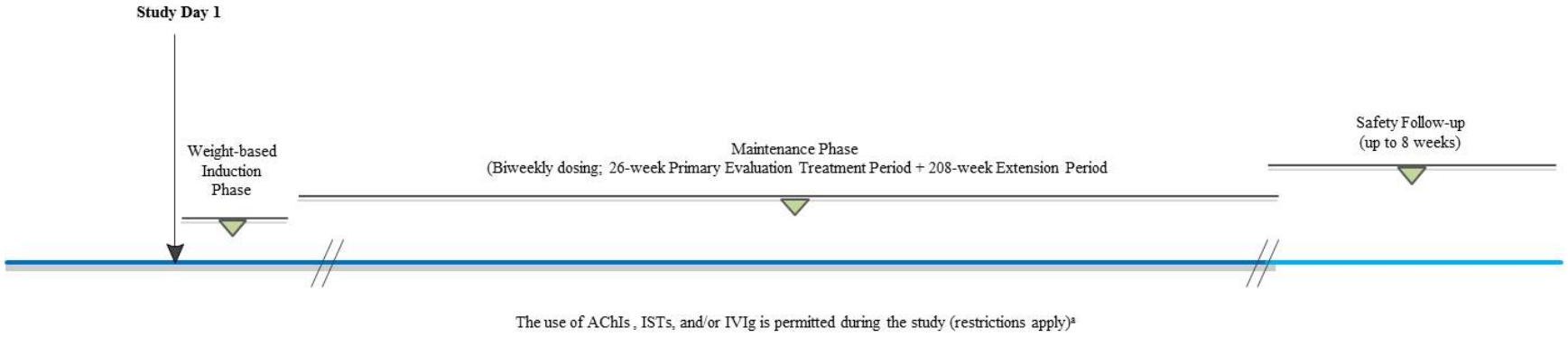
A patient is considered to have completed the study if:

- 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.

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

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																			

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

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**
Clinical Laboratory Tests	X	X								X							X	X	X	
Serum Pregnancy Test[m]	X																X		X	
Urine Pregnancy Test[n]		X				X		X		X		X		X		X				X
PK, Hemolysis, Free C5[o]		B/P 24h	T/P			T/P				T/P							T/P	X	X	
ADA[o]		B								T							T	T	T	
Medically Indicated Tests[p]																		X		
N meningitidis Vaccination[q]	X																			
H influenzae Vaccination[r]	X																			
S pneumonia Vaccination[r]	X																			
Check for Revaccination Status[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

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
Study Drug Infusion ≥40 kg[f,u,v]		900 mg	900 mg	900 mg	900 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[w]	
Study Drug Infusion 30 to <40 kg[f,u,v]		600 mg	600 mg	900 mg	N/A	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[w]	
Study Drug Infusion 20 to <30 kg[f,u,v]		600 mg	600 mg	600 mg	N/A	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[w]	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

c. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

d. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

e. Collect weight with minimal clothing.

f. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort, the Alexion medical monitor must be contacted prior to dosing.

g. Collect height with no shoes or footwear.

h. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.

i. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.

j. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days

k. Recommendation to perform QMG assessment first to confirm eligibility. MG-ADL and MGC assessments only necessary once QMG eligibility is confirmed.
l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.
m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests at 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample. For further details refer to Section 8.2.
p. Any test(s) medically indicated may be performed at the discretion of the Investigator.
q. 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).
r. Vaccinate patients against *H influenzae* and *S pneumoniae*, if not already vaccinated, prior to receiving the first eculizumab infusion.
s. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.
t. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.
u. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
v. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.
w. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.

Abbreviations: AChR Ab = acetylcholine receptor antibody; ADA = anti-drug antibodies; B = baseline sample; C5 = complement protein 5; CD = clinical deterioration; D = day; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of Life 5-Dimension Youth; ET = Early Termination; F/U = Follow-up; 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; N/A = not applicable; Neuro-QoL = Quality of Life in Neurological Disorders; P = peak sample; PK = pharmacokinetics; SCR = Screening; QMG = Quantitative Myasthenia Gravis score for disease severity; T = trough sample; W = week.

Table 5: Schedule of Assessments Part II: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Period /Phase	**Extension Period (Year 1)**															
Visit Location[a]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**	**In Clinic**		
Study Visit[b]	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Weeks	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**			**+W8**
Window (Days)	**±2**															**±2**
Weight[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[g]							X						X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam													X		X	
12-Lead ECG													X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[i,j]							X						X	X	X	X
QMG[i,k,l]							X						X	X	X	X
MGC[i,k]							X						X	X	X	X
Neuro-QoL Pediatric Fatigue/PROMIS Proxy							X						X		X	
EQ-5D-Y/Proxy							X						X		X	
MGFA-PIS[i]							X						X		X	X
Clinical Laboratory Tests							X						X	X	X	
Serum Pregnancy Test[l]															X	
Urine Pregnancy Test[m]	X		X		X		X		X		X		X			X
PK, Hemolysis, Free C5[n]														X	X	
ADA[m]														T	T	
Medically Indicated Tests[o]														X		

Table 5: Schedule of Assessments Part II: Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg (Continued)

Period /Phase	**Extension Period (Year 1)**															
Visit Location[a]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**	**In Clinic**		
Study Visit[b]	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Weeks	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**			**+W8**
Window (Days)	**±2**															**±2**
Check for Revaccination Status[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion ≥40 kg[f,r,s]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[t]	
Study Drug Infusion 30 to <40 kg[f,r,s]	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[t]	
Study Drug Infusion 20 to <30 kg[f,r,s]	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[t]	
Transition follow-up call[u]															X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Unscheduled visits and procedures will be performed at the Investigator's discretion and results will be recorded in the eCRF.

c. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

d. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

e. Collect weight with minimal clothing.

f. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. Dose 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

g. Collect height with no shoes or footwear.

h. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.
i. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.
j. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.
k. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.
l. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
m. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
n. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.
o. Any test(s) medically indicated may be performed at the discretion of the Investigator.
p. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.
q. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.
r. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
s. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.
t. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.
u. 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 as feasible.

Abbreviations: ADA = anti-drug antibodies; B = Baseline sample; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of Life 5-Dimension Youth; ET = Early Termination; F/U = Follow-up; 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; Neuro-QoL = Quality of Life in Neurological Disorders; P = peak sample; PK = pharmacokinetics; SCR = Screening; QMG = Quantitative Myasthenia Gravis score for disease severity; T = trough sample; W = week.

Table 6: Schedule of Assessments Part I: Weight Cohort 10 to < 20 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**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Weeks	**-2 to -4 weeks**	**D1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**W25**	**W27**			**+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
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
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
Adverse Event[h]	X[h]	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
QMG[i,k,l]	X[k]	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
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																		
Clinical Laboratory Tests	X	X						X							X		X	X	
Serum Pregnancy Test[m]	X															X		X	
Urine Pregnancy Test[n]		X			X		X		X		X		X		X				X
PK, Hemolysis, Free C5[o]		B/P/24h	T/P			T/P			T/P							T/P	X	X	

Table 6: Schedule of Assessments Part I: Weight Cohort 10 to < 20 kg (Continued)

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**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Weeks	**-2 to -4 weeks**	**D1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**W25**	**W27**			**+W8**
Window (Days)			**±2**																**±2**
ADA[o]		B							T							T	T	T	
Medically Indicated Tests[p]																	X		
N meningitidis Vaccination[q]	X																		
H influenzae Vaccination[r]	X																		
S pneumonia Vaccination[r]	X																		
Check for Revaccination Status[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion 10 to < 20 kg[f,u,v,w]		600 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg		300 mg[x]	
Study Drug Infusion 20 to <30 kg[f,u,v,w]	N/A	N/A	600 mg	N/A	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[x]	
Study Drug Infusion 30 to <40 kg[f,u,v,w]	N/A	N/A	600 mg	N/A	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[x]	
Study Drug Infusion ≥40 kg[f,u,v,w]	N/A	N/A	900 mg	900 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[x]	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Unscheduled visits and procedures will be performed at the Investigator's discretion and results will be recorded in the eCRF.

c. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.
d. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.
e. Collect weight with minimal clothing.
f. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.
g. Collect height with no shoes or footwear.
h. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.
i. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.
j. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days
k. Recommendation to perform QMG assessment first to confirm eligibility. MG-ADL and MGC assessments only necessary once QMG eligibility is confirmed.
l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.
m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample. For further details refer to Section 8.2.
p. Any test(s) medically indicated may be performed at the discretion of the Investigator.
q. 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).
r. Vaccinate patients against *H influenzae* and *S pneumoniae*, if not already vaccinated, prior to receiving the first eculizumab infusion.
s. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.
t. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.
u. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
v. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.

[w] Should the patient's weight increase ≥ 20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patients current weight. Refer to Table 15 for additional details on weight-based treatment regimens.

[x] Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.

Abbreviations: AChR Ab = acetylcholine receptor antibody; ADA = anti-drug antibodies; B = Baseline sample; C5 = complement protein 5; CD = clinical deterioration; D = day; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of Life 5-Dimension Youth; ET = Early Termination; F/U = Follow-up; 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; N/A = not applicable; Neuro-QoL = Quality of Life in Neurological Disorders; P = peak sample; PK = pharmacokinetics; SCR = Screening; QMG = Quantitative Myasthenia Gravis score for disease severity; T = trough sample; W = week.

Table 7: Schedule of Assessments Part II: Weight Cohort 10 to < 20 kg

Period /Phase	**Extension Period (Year 1)**															
Visit Location[a]	**In Clinic/Remote**						**In Clinic**	**In Clinic/Remote**					**In Clinic**	**In Clinic**		
Study Visit[b]	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**CD[c]**	**ET / EOS**	**F/U[d]**
Study Weeks	**W29**	**W31**	**W33**	**W35**	**W37**	**W39**	**W41**	**W43**	**W45**	**W47**	**W49**	**W51**	**W53**			**+W8**
Window (Days)	**±2**															**±2**
Weight[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[g]							X						X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam													X		X	
12-Lead ECG															X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[i,j]							X						X	X	X	X
QMG[i,k]							X						X	X	X	X
MGC[i,k]							X						X	X	X	X
Neuro-QoL Pediatric Fatigue/PROMIS Proxy							X						X		X	
EQ-5D-Y/Proxy							X						X		X	
MGFA-PIS[i]							X						X		X	X
Clinical Laboratory Tests							X						X	X	X	
Serum Pregnancy Test[l]															X	
Urine Pregnancy Test[m]		X		X		X		X		X		X				X
PK, Hemolysis, Free C5[n]														X	X	
ADA[n]														T	T	
Medically Indicated Tests[o]														X		
Check for Revaccination Status[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion 10 to < 20 kg [f,r,s,t]	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg		300 mg[u]	

Table 7: Schedule of Assessments Part II: Weight Cohort 10 to < 20 kg (Continued)

Period /Phase	Extension Period (Year 1)															
Visit Location[a]	In Clinic/Remote						In Clinic	In Clinic/Remote					In Clinic	In Clinic		
Study Visit[b]	17	18	19	20	21	22	23	24	25	26	27	28	29	CD[c]	ET / EOS	F/U[d]
Study Weeks	W29	W31	W33	W35	W37	W39	W41	W43	W45	W47	W49	W51	W53			+W8
Window (Days)	±2															±2
Study Drug Infusion 20 to <30 kg [f,r,s,t]	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[u]	
Study Drug Infusion 30 to <40 kg [f,r,s,t]	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[u]	
Study Drug Infusion ≥40 kg [f,r,s,t]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[u]	
Transition follow-up call[v]															X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

c. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

d. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

e. Collect weight with minimal clothing.

f. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. When possible, dose regimen should 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

g. Collect height with no shoes or footwear.

h. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.

i. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.

j. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.
k. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.
l. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
m. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
n. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.
o. Any test(s) medically indicated may be performed at the discretion of the Investigator.
p. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.
q. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.
r. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
s. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.
t. Should the patient's weight increase ≥ 20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patient's current weight. Refer to Table 15 for additional details on weight-based treatment regimens.
u. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.
v. 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 as feasible.

Abbreviations: AChR Ab = acetylcholine receptor antibody; ADA = anti-drug antibodies; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of Life 5-Dimension Youth; ET = Early Termination; F/U = Follow-up; 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; Neuro-QoL = Quality of Life in Neurological Disorders; PK = pharmacokinetics; SCR = Screening; QMG = Quantitative Myasthenia Gravis score for disease severity; T = trough sample; W = week.

Table 8: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**					**In Clinic**	**In Clinic/Remote**		**In Clinic**		
Year 2 Visit/Week[b,c]	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V83/W158 (V82/W159)**	**V84/W160 (V83/W161)**	**V85/W162 (V84/W163)**	**V86/W164 (V85/W165)**	**V87/W166 (V86/W167)**	**V88/W168 (V87/W169)**	**V89/W170 (V88/W171)**	**V90/W172 (V89/W173)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V109/W210 (V108/W211)**	**V110/W212 (V109/W213)**	**V111/W214 (V110/W215)**	**V112/W216 (V111/W217)**	**V113/W218 (V112/W219)**	**V114/W220 (V113/W221)**	**V115/W222 (V114/W223)**	**V116/W224 (V115/W225)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Weight[f,g]	X	X	X	X	X	X	X	X	X	X	X
Height[h]						X				X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Physical Exam										X	
12-Lead ECG										X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[i]	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[j,k]						X			X	X	X
QMG[j,l]						X			X	X	X
MGC[j,l]						X			X	X	X
Neuro-QoL Pediatric Fatigue/PROMIS Proxy						X				X	

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**					**In Clinic**	**In Clinic/Remote**		**In Clinic**		
Year 2 Visit/Week[b,c]	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V83/W158 (V82/W159)**	**V84/W160 (V83/W161)**	**V85/W162 (V84/W163)**	**V86/W164 (V85/W165)**	**V87/W166 (V86/W167)**	**V88/W168 (V87/W169)**	**V89/W170 (V88/W171)**	**V90/W172 (V89/W173)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V109/W210 (V108/W211)**	**V110/W212 (V109/W213)**	**V111/W214 (V110/W215)**	**V112/W216 (V111/W217)**	**V113/W218 (V112/W219)**	**V114/W220 (V113/W221)**	**V115/W222 (V114/W223)**	**V116/W224 (V115/W225)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
EQ-5D-Y/Proxy						X				X	
MGFA-PIS[j]										X	X
Clinical Laboratory Tests[x]									X	X	
Serum Pregnancy Test[m]										X	

Table 8: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**					**In Clinic**	**In Clinic/Remote**		**In Clinic**		
Year 2 Visit/Week[b,c]	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V83/W158 (V82/W159)**	**V84/W160 (V83/W161)**	**V85/W162 (V84/W163)**	**V86/W164 (V85/W165)**	**V87/W166 (V86/W167)**	**V88/W168 (V87/W169)**	**V89/W170 (V88/W171)**	**V90/W172 (V89/W173)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V109/W210 (V108/W211)**	**V110/W212 (V109/W213)**	**V111/W214 (V110/W215)**	**V112/W216 (V111/W217)**	**V113/W218 (V112/W219)**	**V114/W220 (V113/W221)**	**V115/W222 (V114/W223)**	**V116/W224 (V115/W225)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Urine Pregnancy Test[n]		X		X		X		X			X
PK, Hemolysis, Free C5[o]						T			X	X	
ADA[o]						T			T	T	
Medically Indicated Tests[p]									X		
Check for Revaccination Status[q]	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[r]	X	X	X	X	X	X	X	X	X	X	X

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**					**In Clinic**	**In Clinic/Remote**		**In Clinic**		
Year 2 Visit/Week[b,c]	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V83/W158 (V82/W159)**	**V84/W160 (V83/W161)**	**V85/W162 (V84/W163)**	**V86/W164 (V85/W165)**	**V87/W166 (V86/W167)**	**V88/W168 (V87/W169)**	**V89/W170 (V88/W171)**	**V90/W172 (V89/W173)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V109/W210 (V108/W211)**	**V110/W212 (V109/W213)**	**V111/W214 (V110/W215)**	**V112/W216 (V111/W217)**	**V113/W218 (V112/W219)**	**V114/W220 (V113/W221)**	**V115/W222 (V114/W223)**	**V116/W224 (V115/W225)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Study Drug Infusion 10 to < 20 kg [g,s,t,u]	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg		300 mg[v]	
Study Drug Infusion 20 to <30 kg[g,s,t,u]	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[v]	

Table 8: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**					**In Clinic**	**In Clinic/Remote**		**In Clinic**		
Year 2 Visit/Week[b,c]	**V31/W54 (V30/W55)**	**V32/W56 (V31/W57)**	**V33/W58 (V32/W59)**	**V34/W60 (V33/W61)**	**V35/W62 (V34/W63)**	**V36/W64 (V35/W65)**	**V37/W66 (V36/W67)**	**V38/W68 (V37/W69)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V57/W106 (V56/W107)**	**V58/W108 (V57/W109)**	**V59/W110 (V58/W111)**	**V60/W112 (V59/W113)**	**V61/W114 (V60/W115)**	**V62/W116 (V61/W117)**	**V63/W118 (V62/W119)**	**V64/W120 (V63/W121)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V83/W158 (V82/W159)**	**V84/W160 (V83/W161)**	**V85/W162 (V84/W163)**	**V86/W164 (V85/W165)**	**V87/W166 (V86/W167)**	**V88/W168 (V87/W169)**	**V89/W170 (V88/W171)**	**V90/W172 (V89/W173)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V109/W210 (V108/W211)**	**V110/W212 (V109/W213)**	**V111/W214 (V110/W215)**	**V112/W216 (V111/W217)**	**V113/W218 (V112/W219)**	**V114/W220 (V113/W221)**	**V115/W222 (V114/W223)**	**V116/W224 (V115/W225)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Study Drug Infusion 30 to <40 kg[g,s,t,u]	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[v]	
Study Drug Infusion ≥40 kg[g,s,t,u]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[v]	
Transition follow-up call[w]										X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Shown as visit/week for Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg (10 to < 20 kg).

c. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

d. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

e. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

f. Collect weight with minimal clothing.

g. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. When possible, dose regimen should 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

h. Collect height with no shoes or footwear.

i. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.

j. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.

k. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.

l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.

m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.

p. Any test(s) medically indicated may be performed at the discretion of the Investigator.

q. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.

r. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.

s. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.

t. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.

u. Should the patient's weight increase ≥20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patients current weight. Refer to Table 15 for additional details on weight-based treatment regimens.

v. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.

w. 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 as feasible.

x. Clinical laboratory tests are to be performed every 6 months during the extension period.

Abbreviations: ADA = antidrug antibodies; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of life 5 Dimension Youth; ET = early termination; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Interventional Status; Neuro-QoL = Quality of Life in Neurological Disorders; PI = Principal Investigator; PK = pharmacokinetics; QMG = Quantitative Myasthenia Gravis Score for Disease Severity; T = trough sample; V = visit; W = week

Table 9: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**				**In-Clinic**	**In Clinic/Remote**			**In Clinic**		
Year 2 Visit/Week[b,c]	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**	**V42/W76 (V41/W77)**	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V65/W122 (V64/W123)**	**V66/W124 (V65/W125)**	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V91/W174 (V90/W175)**	**V92/W176 (V91/W177)**	**V93/W178 (V92/W179)**	**V94/W180 (V93/W181)**	**V95/W182 (V94/W183)**	**V96/W184 (V95/W185)**	**V97/W186 (V96/W187)**	**V98/W188 (V97/W189)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V117/W226 (V116/W227)**	**V118/W228 (V117/W229)**	**V119/W230 (V118/W231)**	**V120/W232 (V119/W233)**	***(Refer to EOS)***	**NA**	**NA**	**NA**	**CD[d]**	**ET/EOS/ V121/ W234 (V120/ W235)**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Weight[f,g]	X	X	X	X	X	X	X	X	X	X	X
Height[h]					X					X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Physical Exam										X	
12-Lead ECG										X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[i]	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[j,k]					X				X	X	X
QMG[j,l]					X				X	X	X
MGC[j,l]					X				X	X	X

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**				**In-Clinic**	**In Clinic/Remote**			**In Clinic**		
Year 2 Visit/Week[b, c]	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**	**V42/W76 (V41/W77)**	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b, c]	**V65/W122 (V64/W123)**	**V66/W124 (V65/W125)**	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b, c]	**V91/W174 (V90/W175)**	**V92/W176 (V91/W177)**	**V93/W178 (V92/W179)**	**V94/W180 (V93/W181)**	**V95/W182 (V94/W183)**	**V96/W184 (V95/W185)**	**V97/W186 (V96/W187)**	**V98/W188 (V97/W189)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b, c]	**V117/W226 (V116/W227)**	**V118/W228 (V117/W229)**	**V119/W230 (V118/W231)**	**V120/W232 (V119/W233)**	***(Refer to EOS)***	**NA**	**NA**	**NA**	**CD[d]**	**ET/EOS/ V121/ W234 (V120/ W235)**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Neuro-QoL Pediatric Fatigue/PROMIS Proxy					X					X	
EQ-5D-Y/Proxy					X					X	
MGFA-PIS[j]										X	X

Table 9: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**				**In-Clinic**	**In Clinic/Remote**			**In Clinic**		
Year 2 Visit/Week[b,c]	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**	**V42/W76 (V41/W77)**	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V65/W122 (V64/W123)**	**V66/W124 (V65/W125)**	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V91/W174 (V90/W175)**	**V92/W176 (V91/W177)**	**V93/W178 (V92/W179)**	**V94/W180 (V93/W181)**	**V95/W182 (V94/W183)**	**V96/W184 (V95/W185)**	**V97/W186 (V96/W187)**	**V98/W188 (V97/W189)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V117/W226 (V116/W227)**	**V118/W228 (V117/W229)**	**V119/W230 (V118/W231)**	**V120/W232 (V119/W233)**	***(Refer to EOS)***	**NA**	**NA**	**NA**	**CD[d]**	**ET/EOS/ V121/ W234 (V120/ W235)**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Clinical Laboratory Tests[x]					X				X	X	
Serum Pregnancy Test[m]										X	
Urine Pregnancy Test[n]		X		X		X		X			X
PK, Hemolysis, Free C5[o]					T				X	X	
ADA[o]					T				T	T	
Medically Indicated Tests[p]									X		

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**				**In-Clinic**	**In Clinic/Remote**			**In Clinic**		
Year 2 Visit/Week[b,c]	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**	**V42/W76 (V41/W77)**	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V65/W122 (V64/W123)**	**V66/W124 (V65/W125)**	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V91/W174 (V90/W175)**	**V92/W176 (V91/W177)**	**V93/W178 (V92/W179)**	**V94/W180 (V93/W181)**	**V95/W182 (V94/W183)**	**V96/W184 (V95/W185)**	**V97/W186 (V96/W187)**	**V98/W188 (V97/W189)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V117/W226 (V116/W227)**	**V118/W228 (V117/W229)**	**V119/W230 (V118/W231)**	**V120/W232 (V119/W233)**	***(Refer to EOS)***	**NA**	**NA**	**NA**	**CD[d]**	**ET/EOS/ V121/ W234 (V120/ W235)**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Check for Revaccination Status[q]	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[r]	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion 10 to < 20 kg [g,s,t,u]	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg		300 mg[v]	

Table 9: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**				**In-Clinic**	**In Clinic/Remote**			**In Clinic**		
Year 2 Visit/Week[b,c]	**V39/W70 (V38/W71)**	**V40/W72 (V39/W73)**	**V41/W74 (V40/W75)**	**V42/W76 (V41/W77)**	**V43/W78 (V42/W79)**	**V44/W80 (V43/W81)**	**V45/W82 (V44/W83)**	**V46/W84 (V45/W85)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V65/W122 (V64/W123)**	**V66/W124 (V65/W125)**	**V67/W126 (V66/W127)**	**V68/W128 (V67/W129)**	**V69/W130 (V68/W131)**	**V70/W132 (V69/W133)**	**V71/W134 (V70/W135)**	**V72/W136 (V71/W137)**	**CD[d]**	**ET/EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V91/W174 (V90/W175)**	**V92/W176 (V91/W177)**	**V93/W178 (V92/W179)**	**V94/W180 (V93/W181)**	**V95/W182 (V94/W183)**	**V96/W184 (V95/W185)**	**V97/W186 (V96/W187)**	**V98/W188 (V97/W189)**	**CD[d]**	**ET /EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**V117/W226 (V116/W227)**	**V118/W228 (V117/W229)**	**V119/W230 (V118/W231)**	**V120/W232 (V119/W233)**	***(Refer to EOS)***	**NA**	**NA**	**NA**	**CD[d]**	**ET/EOS/ V121/ W234 (V120/ W235)**	**F/U[e] (+W8)**
Window (Days)	**±2**										**(±2)**
Study Drug Infusion 20 to <30 kg[g,s,t,u]	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[v]	
Study Drug Infusion 30 to <40 kg[g,s,t,u]	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[v]	
Study Drug Infusion ≥40 kg[g,s,t,u]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[v]	
Transition follow-up call[w]										X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Shown as visit/week for Weight Cohorts ≥40 kg, 30 to <40 kg, and 20 to <30 kg (10 to <20 kg).

c. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

d. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

e. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

f. Collect weight with minimal clothing.

g. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. When possible, dose regimen should 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

h. Collect height with no shoes or footwear.

i. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.

j. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.

k. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.

l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.

m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.

p. Any test(s) medically indicated may be performed at the discretion of the Investigator.

q. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.

r. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.

s. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.

[t.] For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.

[u.] Should the patient's weight increase ≥20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patients current weight. Refer to Table 15 for additional details on weight-based treatment regimens.

[v.] Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.

[w.] 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 as feasible.

[x.] Clinical laboratory tests are to be performed every 6 months during the extension period.

Abbreviations: ADA = antidrug antibodies; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-Y = European Quality of life 5 Dimension Youth; ET = early termination; F/U = Follow-up; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Interventional Status; NA = not applicable; Neuro-QoL = Quality of Life in Neurological Disorders; PI = Principal Investigator; PK = pharmacokinetics; QMG = Quantitative Myasthenia Gravis Score for Disease Severity; T = trough sample; V = visit; W = week

Table 10: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**		**In Clinic/**	**In Clinic/Remote**					**In-Clinic**		
Year 2 Visit/Week[b,c]	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**	**V54/W100 (V53/W101)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**	**V78/W148 (V77/W149)**	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V99/W190 (V98/W191)**	**V100/W192 (V99/W193)**	**V101/W194 (V100/W195)**	**V102/W196 (V101/W197)**	**V103/W198 (V102/W199)**	**V104/W200 (V103/W201)**	**V105/W202 (V104/W203)**	**V106/W204 (V105/W205)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**										**(±2)**
Weight[f,g]	X	X	X	X	X	X	X	X	X	X	X
Height[h]			X							X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Physical Exam										X	
12-Lead ECG										X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Event[i]	X	X	X	X	X	X	X	X	X	X	X
MG-ADL[j,k]			X						X	X	X
QMG[j,l]			X						X	X	X
MGC[j,l]			X						X	X	X
Neuro-QoL Pediatric Fatigue/PROMIS Proxy			X							X	
EQ-5D-Y/Proxy			X							X	

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**		**In Clinic/**	**In Clinic/Remote**					**In-Clinic**		
Year 2 Visit/Week[b,c]	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**	**V54/W100 (V53/W101)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**	**V78/W148 (V77/W149)**	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V99/W190 (V98/W191)**	**V100/W192 (V99/W193)**	**V101/W194 (V100/W195)**	**V102/W196 (V101/W197)**	**V103/W198 (V102/W199)**	**V104/W200 (V103/W201)**	**V105/W202 (V104/W203)**	**V106/W204 (V105/W205)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**										**(±2)**
MGFA-PIS[j]										X	X
Clinical Laboratory Tests[x]									X	X	

Table 10: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**		**In Clinic/**	**In Clinic/Remote**					**In-Clinic**		
Year 2 Visit/Week[b,c]	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**	**V54/W100 (V53/W101)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**	**V78/W148 (V77/W149)**	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V99/W190 (V98/W191)**	**V100/W192 (V99/W193)**	**V101/W194 (V100/W195)**	**V102/W196 (V101/W197)**	**V103/W198 (V102/W199)**	**V104/W200 (V103/W201)**	**V105/W202 (V104/W203)**	**V106/W204 (V105/W205)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**										**(±2)**
Serum Pregnancy Test[m]										X	
Urine Pregnancy Test[n]		X		X		X		X			X
PK, Hemolysis, Free C5[o]			T						X	X	
ADA[o]			T						T	T	
Medically Indicated Tests[p]									X		
Check for Revaccination Status[q]	X	X	X	X	X	X	X	X	X	X	X
Patient Safety Information Card[r]	X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion 10 to < 20 kg [g,s,t,u]	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg		300 mg[v]	

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**		**In Clinic/**	**In Clinic/Remote**					**In-Clinic**		
Year 2 Visit/Week[b,c]	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**	**V54/W100 (V53/W101)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**	**V78/W148 (V77/W149)**	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V99/W190 (V98/W191)**	**V100/W192 (V99/W193)**	**V101/W194 (V100/W195)**	**V102/W196 (V101/W197)**	**V103/W198 (V102/W199)**	**V104/W200 (V103/W201)**	**V105/W202 (V104/W203)**	**V106/W204 (V105/W205)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**										**(±2)**
Study Drug Infusion 20 to <30 kg[g,s,t,u]	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg		600 mg[v]	

Table 10: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**										
Visit Location[a]	**In Clinic/Remote**		**In Clinic/**	**In Clinic/Remote**					**In-Clinic**		
Year 2 Visit/Week[b,c]	**V47/W86 (V46/W87)**	**V48/W88 (V47/W89)**	**V49/W90 (V48/W91)**	**V50/W92 (V49/W93)**	**V51/W94 (V50/W95)**	**V52/W96 (V51/W97)**	**V53/W98 (V52/W99)**	**V54/W100 (V53/W101)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V73/W138 (V72/W139)**	**V74/W140 (V73/W141)**	**V75/W142 (V74/W143)**	**V76/W144 (V75/W145)**	**V77/W146 (V76/W147)**	**V78/W148 (V77/W149)**	**V79/W150 (V78/W151)**	**V80/W152 (V79/W153)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V99/W190 (V98/W191)**	**V100/W192 (V99/W193)**	**V101/W194 (V100/W195)**	**V102/W196 (V101/W197)**	**V103/W198 (V102/W199)**	**V104/W200 (V103/W201)**	**V105/W202 (V104/W203)**	**V106/W204 (V105/W205)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**										**(±2)**
Study Drug Infusion 30 to <40 kg[g,s,t,u]	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg		900 mg[v]	
Study Drug Infusion ≥40 kg[g,s,t,u]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg		1200 mg[v]	
Transition follow-up call[w]										X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Shown as visit/week for Weight Cohorts ≥40 kg, 30 to <40 kg, and 20 to <30 kg (10 to <20 kg).

c. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

d. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

e. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

f. Collect weight with minimal clothing.

g. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. When possible, dose regimen should 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

h. Collect height with no shoes or footwear.

i. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.

j. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.

k. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.

l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.

m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.

o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.

p. Any test(s) medically indicated may be performed at the discretion of the Investigator.

q. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.

r. Review the Patient Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.

s. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.

t. For supplemental weight-based eculizumab dosing, refer to Table 16 and Table 17.

u. Should the patient's weight increase ≥20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patients current weight. Refer to Table 15 for additional details on weight-based treatment regimens.

v. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.

w. 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 as feasible.

x. Clinical laboratory tests are to be performed every 6 months during the extension period.

Abbreviations: ADA = antidrug antibodies; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of life 5 Dimension Youth; ET = early termination; F/U = Follow-up; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Interventional Status; Neuro-QoL = Quality of Life in Neurological Disorders; PI = Principal Investigator; PK = pharmacokinetics; QMG = Quantitative Myasthenia Gravis Score for Disease Severity; T = trough sample; V = visit; W = week

Table 11: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts)

Phase	**Extension Period**				
Visit Location[a]	**In Clinic/Remote**	**In-Clinic**	**In Clinic**		
Year 2 Visit/Week[b,c]	**V55/W102 (V54/W103)**	**V56/W104 (V55/W105)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V81/W154 (V80/W155)**	**V82/W156 (V81/W157)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V107/W206 (V106/W207)**	**V108/W208 (V107/W209)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**				**±2**
Weight[f,g]	X	X	X	X	X
Height[h]		X		X	
Vital Signs	X	X	X	X	X
Physical Exam				X	
12-Lead ECG				X	
Concomitant Medication	X	X	X	X	X
Adverse Event[i]	X	X	X	X	X
MG-ADL[j,k]		X	X	X	X
QMG[j,l]		X	X	X	X
MGC[j,l]		X	X	X	X
Neuro-QoL Pediatric Fatigue/PROMIS Proxy		X		X	
EQ-5D-Y/Proxy		X		X	
MGFA-PIS[j]				X	X
Clinical Laboratory Tests[x]		X	X	X	
Serum Pregnancy Test[m]				X	
Urine Pregnancy Test[n]		X			X
PK, Hemolysis, Free C5[o]		T	X	X	
ADA[o]		T	T	T	

Table 11: Schedule of Assessments (Extension Period): Year 2 through Year 5 (All Weight Cohorts) (Continued)

Phase	**Extension Period**				
Visit Location[a]	**In Clinic/Remote**	**In-Clinic**	**In Clinic**		
Year 2 Visit/Week[b,c]	**V55/W102 (V54/W103)**	**V56/W104 (V55/W105)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 3 Visit/Week[b,c]	**V81/W154 (V80/W155)**	**V82/W156 (V81/W157)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 4 Visit/Week[b,c]	**V107/W206 (V106/W207)**	**V108/W208 (V107/W209)**	**CD[d]**	**ET / EOS**	**F/U[e] (+W8)**
Year 5 Visit/Week[b,c]	**NA**	**NA**	**NA**	**NA**	**NA**
Window (Days)	**±2**				**±2**
Medically Indicated Tests[p]			X		
Check for Revaccination Status[q]	X	X	X	X	X
Patient Safety Information Card[r]	X	X	X	X	X
Study Drug Infusion 10 to < 20 kg [g,s,t,u]	300 mg	300 mg		300 mg[v]	
Study Drug Infusion 20 to <30 kg[g,s,t,u]	600 mg	600 mg		600 mg[v]	
Study Drug Infusion 30 to <40 kg[g,s,t,u]	900 mg	900 mg		900 mg[v]	
Study Drug Infusion ≥40 kg[g,s,t,u]	1200 mg	1200 mg		1200 mg[v]	
Transition follow-up call[w]				X	

a. In Clinic – visits must be conducted at the investigational sites; Remote – visits may be conducted remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

b. Shown as visit/week for Weight Cohorts ≥40 kg, 30 to <40 kg, and 20 to <30 kg (10 to <20 kg).

c. Unscheduled visits and procedures will be performed at the Investigator's discretion, and results will be recorded in the eCRF.

d. Perform an evaluation visit for CD as soon as possible within 48 hours of notification of symptom onset. The PI may schedule additional evaluation visits at their discretion.

e. Patients who complete the study and transition to uninterrupted treatment with commercially available eculizumab will not be required to complete a follow-up visit.

f. Collect weight with minimal clothing.

g. Weight changes during the development and maturation of pediatric patients impact the dosing profile of eculizumab and should be adjusted to accommodate any growth changes in patients. 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. For additional details on weight-based treatment regimens, refer to Table 15 for scheduled doses of eculizumab and Table 16 and Table 17 for supplemental doses of eculizumab. During the initial

induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort the Alexion medical monitor must be contacted prior to dosing.

h. Collect height with no shoes or footwear.
i. All AEs (serious and nonserious) will be collected from the signing of the informed consent form.
j. Prior to study drug infusion, perform the MG-ADL, QMG, and MGC using a properly trained evaluator, preferably the same evaluator at approximately the same time of day throughout the study; MGFA-PIS must be performed by the PI or suitably-trained neurologist, preferably the same evaluator throughout the study.
k. The recall period for the MG-ADL is the preceding 7 days, or since the last visit if the visit interval is < 7 days.
l. Withhold acetylcholinesterase inhibitors for at least 10 hours prior to the QMG and MGC tests.
m. Perform serum pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
n. Perform urine pregnancy tests on all female patients of childbearing potential at the specified time points. Additional pregnancy tests (serum or urine) may also be performed at any visit at the PI's discretion.
o. Obtain Baseline and trough blood samples for PK, hemolysis, free C5, and ADA tests 5 – 90 minutes before study drug infusion. Obtain peak blood samples for PK, hemolysis, and free C5 tests 60-120 minutes after the completion of study drug infusion. Obtain 24 hour post dose blood samples for PK, hemolysis, and free C5 after study drug infusion at Visit 2 (Day 1). For the sample collected at 24 hours, there will be a window of ±1 hour for collecting the sample.
p. Any test(s) medically indicated may be performed at the discretion of the Investigator.
q. Patients must be revaccinated for *N meningitidis*, *H influenzae*, and *S pneumoniae* to provide active coverage according to current medical/country guidelines.
r. Review the Participant Safety Information Card with the patient and caregiver to discuss the importance of carrying the safety card at all times.
s. Administer study drug after completion of all other tests and procedures, excluding the peak blood sampling for PK, hemolysis, and free C5 assay.
t. For supplemental weight-based eculizumab dosing please refer to Table 16 and Table 17.
u. Should the patient's weight increase ≥20kg during the study, dosing should be based on the most recently recorded body weight at a prior dosing visit and adjusted accordingly to ensure the proper dosing regimen per patients current weight. Refer to Table 15 for additional details on weight-based treatment regimens.
v. Study drug infusion will occur at the EOS visit only. Study drug will not be administered at an ET visit.
w. 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 as feasible.
x. Clinical laboratory tests are to be performed every 6 months during the extension period.

Abbreviations: ADA = antidrug antibodies; C5 = complement protein 5; CD = clinical deterioration; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; EQ-5D-Y = European Quality of life 5 Dimension Youth; ET = early termination; F/U = Follow-up; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Interventional Status; Neuro-QoL = Quality of Life in Neurological Disorders; PI = Principal Investigator; PK = pharmacokinetics; QMG = Quantitative Myasthenia Gravis Score for Disease Severity; T = trough sample; V = visit; W = week.

4.3. Protocol Definitions

4.3.1. Clinical Deterioration and Rescue Therapy

On-study rescue therapy (eg, high dose corticosteroid, plasma exchange [PE], or intravenous immunoglobulin [IVIg]) will be allowed when 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. Every effort should be made to notify the Sponsor within 24 hours should a patient require rescue therapy.

For this protocol, clinical deterioration warranting the use of on-study rescue therapy is defined as follows:

- Patients who experience an MG crisis, which is defined as weakness due to MG that is severe enough to necessitate intubation or to delay extubation following surgery; or,
- Significant symptomatic worsening that requires rescue medication in the opinion of the Investigator; or,
- Patients for whom the Investigator believes that the patients' health is in jeopardy if rescue therapy is not given.

4.3.2. Clinical Evaluator

Clinical Evaluators are study staff that have been trained and certified in administering the QMG, MG-ADL, and MGC. The Clinical Evaluator may be a neurologist, physical therapist, or other study team member delegated by the Investigator. Clinical Evaluator training and certification for this protocol will take place either at the Investigator's meeting or via the Sponsor's designated online training portal or other mechanism.

4.3.3. Responsibilities for Myasthenia Gravis Assessments

Responsibilities for MG assessments are summarized in Table 12. Throughout the study, MG assessments for an individual patient should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator.

Table 12: Responsibilities for MG Assessments

Assessment	Evaluator
MG-ADL	Clinical Evaluator
QMG including FVC	Clinical Evaluator
MGC (non-MMT Components)	Clinical Evaluator
MGC (MMT Components: neck flexion or extension, shoulder abduction, and hip flexion)	PI or Neurologist
MGFA-PIS	PI or Neurologist
MGFA Classification	PI or Neurologist

Abbreviations: FVC = forced vital capacity; MG-ADL = Myasthenia Gravis Activities of Daily Living Profile; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MMT = manual muscle test; PI = Principal Investigator; QMG = Quantitative Myasthenia Gravis.

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

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

condom plus appropriate barrier method for the female partner) while on treatment and for at least 5 months after the last dose of study drug. For additional details on contraception guidance, please refer to Section 11.9.

5.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

1. Parent or legal guardian is an Alexion employee.
2. Any active or untreated thymoma. History of thymic carcinoma or thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before Screening
3. History of thymectomy within 12 months prior to Screening.
4. Weakness only affecting ocular or periocular muscles (MGFA Class I).
5. Myasthenia Gravis crisis or impending crisis at or during Screening (MGFA Class V).
6. Are pregnant or lactating.
7. Any unresolved acute, or chronic, systemic bacterial or other infection, which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics.
8. Unresolved meningococcal infection.
9. For patients who are not receiving a stable maintenance dose of IVIg, as described in the Inclusion Criteria, use of IVIg (eg, as rescue therapy) within 4 weeks prior to first dose.
10. Use of PE within 4 weeks prior to first dose.
11. Use of rituximab within 6 months prior to first dose.
12. Patients who are under 15 kg and are receiving maintenance IVIg.
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 that investigational product, whichever is greater.
14. Have previously received treatment with eculizumab or other complement inhibitors.
15. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
16. Any medical or psychological condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses any added risk for the patient, or confounds the assessment of the patient.
17. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening

5.3. Rationale for Inclusion or Exclusion

Study ECU-MG-301 established the efficacy and safety of eculizumab in AChR-Ab positive refractory gMG patients aged ≥ 18 years. The inclusion/exclusion criteria in Study ECU-MG-303 have been selected to characterize a pediatric population comparable to that of patients aged

≥ 18 years assessed in Study ECU-MG-301, with allowances for differences in disease presentation and treatment practice.

Efficacy, safety, and PK/PD data obtained from this study, combined with data from the refractory gMG clinical program in patients aged ≥ 18 years and data from other indications in which eculizumab has been developed and for which pediatric data are available, is designed to inform the dose regimen and efficacy and safety profile of eculizumab in pediatric refractory gMG patients.

5.4. Discontinuations

5.4.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigational site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified. If the Sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigational site will be notified. A discussion must occur between the Sponsor and the Investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Sponsor agrees with the Investigator that it is medically appropriate for that patient. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled patient to continue in the study with or without study drug.

Patients will be permanently discontinued from the study in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Any of the following occur during the study:
  - Serious hypersensitive reactions (eg, anaphylaxis, bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, clinical syndrome suggestive of serum sickness, vasculitis)
  - Severe uncontrolled infection
  - Pregnancy or planned pregnancy
- Adverse Event
  - If the Investigator decides that the patient should be withdrawn because of a serious adverse event (SAE) or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately. Refer to Section 9.
- Investigator Decision [Physician Decision]
  - The Investigator decides that the patient should be discontinued from the study in the best interest of the patient.
- Patient Decision [Withdrawal by Patient or Withdrawal by Parent/Guardian]

  - The patient or the patient's legal representative (ie, parents or legal guardian) requests to be withdrawn from the study

- Sponsor Decision
  - The Sponsor or Health Authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:
    - Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
    - Sponsor decision to suspend or discontinue testing, evaluation, or development of the study drug
    - Failure of the Investigator to comply with the approved protocol, pertinent guideline and/or regulations
    - Submission of knowingly false information from the Investigator to the Sponsor and/or regulatory authorities
    - The Sponsor medical monitor deems it is in the best interest of the patient

Should the study be terminated early, the Sponsor will notify the national competent authority and the IRB or IEC according to local requirements.

Patients who discontinue the study early will have an ET visit at the time of withdrawal and a Follow-up Visit at 8 weeks following the last eculizumab dose performed, as shown in the Schedule of Assessments (Table 4 through Table 11). If a female patient is permanently discontinued from eculizumab treatment due to pregnancy, the Investigator will attempt to follow-up with the patient until the outcome of the pregnancy is established.

5.4.2. Discontinuation of Study Sites/Site Terminated

Study site participation may be discontinued if the Sponsor or its designee, the Investigator, or the IRB or IEC of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practices (GCP).

5.4.3. Discontinuation of the Study/Study Terminated

The study will be discontinued if the Sponsor or its designee or any regulatory authority judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

6.1.1. Study Drug Labeling

The study drug, eculizumab, will be manufactured and supplied by Alexion or a contract manufacturing organization in single 30 mL vials as a solution concentration of 10 mg/mL. Each vial contains 300 mg of eculizumab for intravenous (IV) administration. Eculizumab will be individually packaged in kits. Both vials and kits will be labeled according to the protocol and local regulatory requirements.

Study drug orders will be released to each site upon receipt of all required documents based upon applicable regulations. Details are provided in the Pharmacy Manual.

Table 13: Study Drug

Product Name	Eculizumab
Dosage Form	Concentrate for solution for infusion
Unit Dose	300 mg
Route of Administration	Intravenous infusion
Physical Description	30 mL vial
Manufacturer	Alexion or a contract manufacturing organization

6.1.2. Study Drug Storage

Upon arrival at the center, the study drug should be promptly removed from the shipping cooler and stored in refrigerated conditions between 2°C to 8°C. The study drug must be stored in a secure, limited-access storage area, and temperature must be monitored daily. On-site storage temperature excursions must be reported to the Sponsor in a timely manner.

Diluted solutions of study drug (dosing solutions) may be stored between 2°C to 8°C (36°F to 46°F) and at room temperature for a maximum of 24 hours. The 24-hour expiration includes preparation time, storage time, warming time, and infusion time. The solution should be allowed to warm to 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.

Refer to the Pharmacy Manual for additional instructions.

6.1.3. Study Drug Preparation

Infusions of study drug should be prepared using aseptic technique. Each vial of study drug contains 300 mg of active ingredient in 30 mL of product solution. Withdraw the required amount of study drug from the vials. Transfer the recommended dose to an infusion bag. Dilute the study drug to a final concentration of 5 mg/mL by addition to the infusion bag of the appropriate amount (equal volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP. The final volume of a 5 mg/mL diluted study drug solution is 60 mL for 300 mg doses (1 vial), 120 mL for 600 mg doses (2 vials), 180 mL for 900 mg doses (3 vials), and 240 mL for 1200 mg doses (4 vials) as shown in Table 14.

Table 14: Study Drug Reconstitution

Study Drug	Volume of Study Drug	Volume of Diluent[a]	Total Volume of Administration
300 mg (1 vial)	30 mL	30 mL	60 mL
600 mg (2 vials)	60 mL	60 mL	120 mL
900 mg (3 vials)	90 mL	90 mL	180 mL
1200 mg (4 vials)	120 mL	120 mL	240 mL

[a] Choose one of the following diluents: 1) 0.9% sodium chloride; 2) 0.45% sodium chloride; 3) 5% dextrose in water; 4) Ringer's injection.

Gently invert the infusion bag containing the diluted study drug solution to ensure thorough mixing of the product and diluents. Discard any unused portion left in a vial, as the product contains no preservatives. The diluted solution should be allowed to warm to room temperature by exposure to ambient air prior to administration.

6.1.4. Study Drug Administration

Study drug should only be administered via IV infusion, using a weight-based schedule (Section 6.2). **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.**

Prior to study drug administration, the diluted solution should be allowed to warm to room temperature by exposure to ambient air. The diluted solution must not be heated in a microwave or with any heat source other than ambient air temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

The diluted study drug should be intravenously administered over 1 to 4 hours in pediatric patients. For those patients who reach ≥ 18 years of age during the study, the study drug should be administered intravenously over 35 (± 10) minutes. It is not necessary to protect the infusion bags from light while study drug is being administered to the patient. The patient should be monitored for at least 1 hour following infusion.

If an AE occurs during administration of the study drug, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event; however, the overall duration should not exceed 2 hours from the start of the infusion in patients aged ≥ 18 years and 4 hours from the start of infusion in pediatric patients. In patients aged ≥ 18 years on maintenance IVIg, the overall duration should not exceed 4 hours from the start of the infusion. The AE must be captured in the patient's source document and eCRF.

The actual start and stop times of all dose administrations will be recorded in the patient's source documents and eCRF. Refer to the Pharmacy Manual for additional directions on study drug administration.

Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion, and for at least 1 hour after patients have completed their infusion.

6.1.5. Study Drug Accountability

When a study 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 study monitor. Additionally, reception of study drug (as well as reception conditions)

must be reported to the Interactive Response Technology (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 (SOPs) 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 CRA that the site has correctly entered the appropriate status for all IP. The pharmacist or designee must maintain accurate records demonstrating dates and amount of IP received, to whom dispensed (subject-by-subject accounting), and accounts of any IP 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.

6.1.6. Study Drug 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 eculizumab 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.

6.2. Dosing Regimen

6.2.1. Rationale for Selection of Doses in the Study

The doses of eculizumab to be administered in this study have been selected to produce eculizumab trough concentration coverage comparable to that observed in Study ECU-MG-301, in which the efficacy and safety of eculizumab in adult patients (18 years of age or older) with refractory AChR-Ab positive gMG was established. A modeling and simulation study was completed to support the planned bodyweight-categorized dose regimens, which is described in further detail below.

Demonstrating PK bridging between aHUS and refractory gMG patients aged ≥ 18 years was critical to select dose regimens for pediatric patients with refractory gMG, as substantial pediatric data has been generated for pediatric patients with aHUS, and no prior PK data from

pediatric patients with refractory gMG exists. The successful PK bridging enables extrapolation of the aHUS pediatric data and corresponding PK model to pediatric patients with refractory gMG. Simulations using the aHUS PK model and gMG PK model, respectively, demonstrated the comparability of eculizumab serum concentration time profiles between patients with aHUS and patients with refractory gMG for body weight ≥ 40 kg.

Demonstrating PD bridging between aHUS/paroxysmal nocturnal hemoglobinuria (PNH) and patients aged ≥ 18 years with refractory gMG was also important. Using PK and PD data from patients aged ≥ 18 years and pediatric patients with aHUS and patients aged ≥ 18 years and pediatric patients with PNH, the PK/PD (hemolysis) analysis identified an eculizumab threshold concentration range of 50-100 µg/mL to achieve complete inhibition of hemolysis.

Using PK and PD data from patients aged ≥ 18 years with refractory gMG from Studies C08-001 and ECU-MG-301, the PK/PD analysis of hemolysis or free C5 identified an eculizumab threshold serum concentration of 85 µg/mL to achieve complete inhibition of hemolysis, which is within the range of 50-100 µg/mL identified above in aHUS.

Therefore, the PD bridging was successfully demonstrated between the 2 indications.

In both aHUS and gMG PK models, body weight was identified as the only important covariate and, therefore, body weight categorical-based dosing is recommended in the pediatric population. The body weight exponent for the aHUS PK model was used, because the aHUS PK model leveraged the prior pediatric PK data within the weight range of interest.

The aHUS PK model was used to simulate eculizumab concentration time profiles for the pediatric patients with refractory gMG. The simulation results showed that overall the proposed dosing regimens across the body weight categories essentially maintained therapeutic levels of eculizumab. Hence, the proposed bodyweight-categorized dosing regimens are expected to achieve immediate, sustained, and complete inhibition of terminal complement in pediatric patients with refractory gMG.

Complete and sustained inhibition of complement activity will be confirmed with PK/ PD data derived from this study.

6.2.2. Dosing Regimen Preparation and Administration

Eculizumab will be administered weekly during the initial induction phase and every 2 weeks during the maintenance phase. The dosing regimen will be based on the pediatric patient's body weight (Table 15).

Table 15: Weight-based Dosing Regimen of Eculizumab

Weight Cohort[ab]	Induction Phase	Maintenance Phase
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Week 4; then every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Week 2; then every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Week 2; then every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Week 1; then every 2 weeks

[a] 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
[b] During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort, the Alexion medical monitor must be contacted prior to dosing.

Eculizumab 300 mg, 600 mg, 900 mg, or 1200 mg will be administered via IV infusion based on the patient's most recently recorded body weight at a prior dosing visit, as presented in Table 15. Doses of study drug must only be prepared and dispensed by qualified study personnel. Study drug is to be dispensed only to enrolled patients who are confirmed eligible for participation in this study. Once study drug is prepared for a patient, it can only be administered to that patient. Vials of study drug are for one-time use only, and any drug product remaining in the vial should not be used for another patient. Any drug remaining in the infusion tubing or infusion bag should not be used for another patient.

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

6.2.3. Supplemental Eculizumab Doses in Patients Receiving Maintenance IVIg Treatment

Maintenance IVIg treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies and, thus, may decrease serum eculizumab concentrations (Jin, 2005; Wang, 2008; Fitzpatrick, 2011). Fitzpatrick et al reported that, in adult multifocal motor neuropathy, patients receiving cycles of IVIg 1 g/kg over 1 to 5 days and repeated on average at 4-weekly intervals, eculizumab treatment resulted in a significantly lower median eculizumab exposure (78.7 µg/mL, interquartile range [IQR] 55–108) compared to exposure in patients not receiving IVIg (119.7 µg/mL, IQR 95–147), which translates to an approximate median increase of 50% in the clearance of eculizumab under IVIg co-administration (Fitzpatrick, 2011).

Therefore, for pediatric gMG patients receiving maintenance IVIg treatment, a series of supplemental doses of eculizumab will be administered to account for the anticipated approximately 50% increase in eculizumab clearance. For further details on supplemental dosing, please refer to Table 16. In addition, patients are to continue eculizumab infusion according to the protocol-specified dosing regimen.

Table 16: Supplemental Dosing Regimen of Eculizumab in Patients Receiving Maintenance IVIg

Weight Cohort[a,b]	Induction Phase Supplemental Dose	Induction Phase Total Dose	Maintenance Phase Supplemental Dose	Maintenance Phase Total Dose
≥ 40 kg	600 mg	1500 mg	600 mg	1800 mg
30 to < 40 kg	300 mg	900 mg	600 mg	1500 mg
20 to < 30 kg	300 mg	900 mg	300 mg	900 mg
10 to < 20 kg[c]	300 mg	900 mg	300 mg	600 mg

[a] 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

[b] During the initial induction phase, if a patient's weight increases or decreases resulting in a change in weight cohort, the Alexion medical monitor must be contacted prior to dosing

[c] Only patients in 15-20 kg weight category to be included in this group.

Notes: The timing of supplemental eculizumab dosing varies by IVIg frequency and is provided below:

- If a patient continues to receive IVIg treatment at a dose cycle interval equal to or more frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered at the same time that each scheduled dose of eculizumab is administered.
- If a patient receives IVIg treatment at a dose cycle interval less frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered following the last dose of the IVIg infusion cycle at the next scheduled eculizumab dose.

If a patient receives IVIg treatment within 4 weeks prior to receiving the first dose of eculizumab, a supplemental dose of eculizumab will be administered at the same time that the first dose of eculizumab is administered (ie, the total dose is the supplemental dose plus the first scheduled dose).

For patients who enter the study on a stable IVIg maintenance dose regimen, PK/PD samples will be analyzed after the first 4 weeks of eculizumab administration for the evaluation of eculizumab exposure. If the PK concentration values are greater than 1790 µg/mL (Alexion Internal Report: ECU-MG-Adult PK-PD Modeling Report, Addendum ECU-MG-302), the maximum concentration value observed in Studies ECU-MG-301 and ECU-MG-302 in patients with refractory gMG, the supplemental dose of eculizumab may be adjusted downward or waived, as appropriate, so that the predicted maximum PK concentration is below 1790 µg/mL.

6.2.4. Supplemental Eculizumab Doses Following Rescue Therapy

When IVIg is administered as acute rescue therapy for clinical deterioration, no supplemental dose of eculizumab should be administered. However, if a patient receives more than 1 dose cycle of IVIg as rescue therapy within a 12-week period, supplemental eculizumab should be administered after the last dose of the second IVIg cycle and at the end of each subsequent IVIg dose cycle within the 12-week period in accordance with Table 16.

If a patient undergoes PP/PE/FFP for clinical deterioration during the study, a supplemental dose of study drug must be administered within 1 to 2 hours after each PP/PE/FFP session unless the PP/PE/FFP session is on the day of a scheduled study drug infusion. If FFP has been administered, a supplemental dose of study drug must be administered 1 hour prior to each

infusion of FFP. If the PP/PE/FFP is on the day of a scheduled study drug infusion, the scheduled dose of study drug (instead of the supplemental dose) should be administered within 1 to 2 hours after the completion of PP/PE/FFP session. For further details on supplemental dosing please refer to Table 17. In addition, patients are to continue eculizumab infusion according to the protocol specified dosing regimen.

Table 17: Supplemental Dosing Regimen of Eculizumab for Plasma Exchange/Plasma Infusion

Type of Intervention	Most Recent Eculizumab Dose	Supplemental Eculizumab Dose With Each Plasma Exchange/Plasma Infusion Intervention	Timing of Supplemental Eculizumab dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 1 to 2 hours after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per infusion of fresh frozen plasma	Approximately 60 minutes[a] prior to each infusion of fresh frozen plasma

[a] Supplemental dosing of eculizumab should occur 60 ± 15 minutes prior to each infusion of fresh frozen plasma.

6.3. Concomitant Medications

6.3.1. Allowed Medications

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

Changes in concomitant medications and/or nondrug therapies and procedures will be recorded in the eCRF.

The following additional restrictions apply:

- Acetylcholinesterase inhibitors
  - Acetylcholinesterase inhibitor treatment must be withheld for at least 10 hours prior to administration of the QMG and MGC tests.
- Immunosuppressive therapies:

  - The following ISTs are allowed during the study: corticosteroid, AZA, MMF, MTX, tacrolimus, cyclosporine, or cyclophosphamide. The ISTs and the appropriate dose levels to be used for an individual patient will be at the discretion of the treating physician. During the Primary Evaluation Treatment Period, the patient's IST dose may be adjusted on the basis of weight/body-surface/age to account for the child's growth.
  - 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 a rescue therapy for clinical deterioration.

- Intravenous immunoglobulin
  - If a patient enters the study receiving maintenance IVIg, a supplemental dose of study drug will be administered at the first scheduled dose. Subsequent supplemental dosing will be informed as described in Section 6.2.3.
- Plasma Exchange/Plasmapheresis/Fresh Frozen Plasma (PE/PP/FFP)
  - Use of PE/PP/FFP will be allowed as rescue therapy for patients who experience a clinical deterioration as defined by this protocol. The rescue therapy used for an individual patient will be at the discretion of the treating physician. Every effort should be made to notify the Sponsor within 24 hours should a patient require a rescue therapy.
  - If a patient undergoes PE during the study, a supplemental dose of study drug must be administered (Section 6.2.4).

6.3.2. Disallowed Medications

The use of rituximab and SC Ig is prohibited during the study.

6.3.3. Clinical Deterioration and Rescue Therapies

The use of permitted on-study rescue therapy is described in Section 4.3.1.

6.3.4. Vaccination

As with any terminal complement antagonist, the use of eculizumab 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. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement-inhibitors (eg, eculizumab).

Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.

Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 5 months following the last dose of eculizumab.

In addition to meningococcal vaccination, patients must be vaccinated against *H influenzae* and *S pneumoniae*, and strictly adhere to the national vaccination recommendations for each age group.

Due to the length of the Extension Period of this study, patients may be revaccinated for appropriate vaccinations based on adherence to the national vaccination recommendations for each age group to provide active coverage according to current medical/country guidelines. Investigators will assess the need for revaccination, which will be recorded in the source documents and electronic case report form (eCRF).

6.4. Treatment Compliance

The infusion of study drug into patients will be under the supervision of the Investigator or their designee to ensure that the patients received the appropriate dose at the appropriate time-points during the study.

Patients who fail to return for a scheduled visit within the acceptable visit windows (±2 days) must be contacted by the site study staff to determine the reason for missing the appointment. Patients should be strongly encouraged to return to the investigational site for evaluation if clinical deterioration or an AE is suspected to have occurred. In the exceptional circumstance, if a patient cannot or does not come to the study site for examination, the patient will be instructed to see his or her local neurologist or physician. In this event, the investigational site will (or attempt to) obtain relevant medical records as documentation from the local physician's examination, and enter relevant data in the eCRF as appropriate.

As it is vital to obtain information on any patient's missing visit (in-clinic or remote) to assure the missing appointment was not due to a clinical deterioration or an AE, every effort must be made to undertake protocol-specified follow-up procedures (Table 5 and Table 7 based on weight cohort). Follow-up due-diligence documentation will consist of 3 phone calls followed by 1 registered letter to the patient's last known address, and documented in both the source documents and the eCRF.

Patients should be registered in the IXRS as soon as the Study ECU-MG-303 informed consent form (ICF) is signed. The initial shipment of study drug for Study ECU-MG-303 will be triggered by the IXRS.

6.5. Continued Access to Study Drug

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

7. ASSESSMENT OF EFFICACY

Efficacy assessments will be performed as summarized in the Schedules of Assessments (Section 4.2). Preferably, the same parent or guardian is recommended to be available to accompany the child to each visit in order to reduce variability in endpoint reporting.

7.1. 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 (Appendix 1). The range of total QMG score is 0 to 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.

A modified QMG score has been developed for use in patients younger than 12 years of age that will be used for patients aged 6 to 11 years at the time of Screening (Goldstein, 2015; Appendix 2). The modified QMG omits the assessment of grip strength and uses a modified assessment of swallowing (slurp test) compared to the traditional QMG, with total scores ranging from 0 to 21. In this study, patients will continue to be evaluated based on the QMG scale initially completed upon entry into the study. Change in age during the study will not constitute a patient changing the type of survey completed (ie, a patient who enrolls at age 11 will continue being assessed with the modified QMG scale even after he or she reaches 12 years of age). The QMG 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.

7.2. Myasthenia Gravis Activities of Daily Living Score

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in MG patients (Appendix 3). The 8 items of the MG-ADL were derived from symptom-based components of the original 13-item QMG 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 to 24. 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. The MG-ADL 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.

For patients <12 years of age, caregiver assistance can be provided during the MG-ADL assessment.

7.3. Myasthenia Gravis Composite Score

The MGC is a validated assessment tool for measuring clinical status of patients with MG (Burns, 2010). 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 (Appendix 4). The range of total MGC score is 0 to 50. Higher scores indicate more

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.

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.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All summary statistics will be computed and displayed by visit where applicable. Descriptive statistics for continuous variables will minimally include the following: n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate. Unless otherwise stated, all statistical summaries will be displayed by younger (<12 years) and older (12 to < 18 years) age groups separately and/or combined. A two-sided Type I error of 5% will be used for statistical tests unless otherwise stated. The statistical modeling will be performed for the applicable endpoints only for the older age group, as very few patients are anticipated to be enrolled in the younger age group. Study data will be summarized by each age group and overall. All study data collected on the CRF and from other sources will be listed for individual patients. Baseline will be defined as the last non-missing value on or prior to first dose of eculizumab, unless otherwise stated. No imputation will be performed for missing efficacy data.

The statistical analysis plan (SAP) will be developed and finalized prior to the primary analysis and will provide further details. The primary analysis will be conducted when all patients have completed the 26-week Primary Evaluation Treatment Period or discontinued prior to the completion of the Primary Evaluation Treatment Period. This analysis will include all efficacy, safety, and PK/PD study data for regulatory submission purpose. Section 10.12 outlines the plan for subsequent interim analyses and the final analysis. Another SAP will be developed and finalized prior to the completion of the entire study (including the Extension Period).

Analyses will be performed using the SAS® software Version 9.4 or higher.

10.2. Hypotheses

The null and alternative hypotheses related to primary endpoint for this study is described as:

$$H_0: \mu = 0 \; vs. \; H_1: \mu \neq 0,$$

where μ represents the mean improvement in QMG from Baseline over time regardless of rescue under null and alternate hypotheses.

10.3. Determination of Sample Size

The sample size will be determined to ensure adequate power for testing the primary endpoint for this study in the older age group. The assumptions regarding change from Baseline in QMG and MG-ADL scores were based on the subset of a younger patient population treated with eculizumab in Studies ECU-MG-301 and ECU-MG-302.

Based on eleven younger (<25 years) patients from those studies, the mean and SD were calculated at both 12 and 26 weeks of eculizumab exposure (Table 19).

Table 19: Mean [±SD] Change from Baseline in QMG and MG-ADL for Younger Patients (Data from Studies ECU-MG-301 and ECU-MG-302)

	QMG	MG-ADL
Baseline	20.9 (6.32)	8.9 (4.46)
Change at Week 12	-8.9 (6.86)	-5.7 (4.27)
Change at Week 26	-9.0 (5.58)	-6.9 (4.93)

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living profile; QMG = Quantitative Myasthenia Gravis score for disease severity

Based on a two-sided one-sample t-test with a significance level of 0.05 and assuming an improvement in QMG total score at Week 26 with mean (SD) of 9 (7), a total of 10 patients will provide approximately 95% power to detect a statistically significant improvement in QMG total score from Baseline. Similarly, assuming an improvement in MG-ADL total score at Week 26 with mean (SD) of 7 (5), a total of 10 patients will provide approximately 97% power. Likewise, based on a two-sided one-sample t-test with a significance level of 0.05 and assuming an improvement in QMG total score at Week 12 with mean (SD) of 9 (7), a total of 10 patients will provide approximately 95% power to detect a statistically significant improvement in QMG total score from Baseline. Similarly, assuming an improvement in MG-ADL total score at Week 12 with mean (SD) of 6 (5), a total of 10 patients will provide approximately 92% power.

Assuming a loss of 15% of patients due to not meeting evaluability criteria, a total of at least 12 patients will be planned to be enrolled in the older age group for the primary analysis to enroll at least 10 evaluable patients. There will be no statistical considerations to determine the number of patients to be enrolled in the younger age group. Section 10.3.1 provides additional information about sample size re-estimation.

In addition, a maximum of 6 patients on maintenance IVIg aged 12 to < 18 years are eligible to be enrolled in the study. 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 is no cap on patients 6 to < 12 years of age.

10.3.1. Interim Monitoring of Variability and Sample Size Re-assessment

Since the estimates provided in Table 19 are based on a small number of patients and it is unknown whether the variability in change in QMG in this study population is consistent with patients aged ≥ 18 years, an interim monitoring of the variability in change in QMG from Baseline will be performed. After 6 patients complete the Week 26 assessments, if the observed standard deviation in QMG change from Baseline is approximately 8 or higher, the final sample size will be re-estimated to be at least 14 patients instead of 12 patients to preserve adequate power for testing the primary and endpoint.

10.4. Analysis Sets

10.4.1. Full Analysis Set

Efficacy analyses will be performed on the Full Analysis Set (FAS), which consists of all patients who received at least 1 dose of eculizumab. A subset of the FAS that includes older

patients (12 to < 18 years of age) only will be used for analyses of the primary and secondary endpoints and will be defined as the modified FAS (mFAS). The FAS will be used for other efficacy results summaries by including younger patients (< 12 years of age), if any are enrolled.

10.4.2. Safety Set

Safety analyses will be performed on the Safety Set, which consists of all patients who received at least 1 dose of eculizumab.

10.4.3. Other Analysis Set

Pharmacokinetic/PD analyses will be performed on the PK/PD Analysis Set. The PK/PD Analysis Set will include patients who have PK/PD data assessments during this study.

10.5. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized for the Safety Set. Summary statistics will be presented. No formal hypothesis testing will be performed.

10.6. Patient Disposition

The number of patients screened and the number of patients in different analysis sets will be summarized. The number and percentage of patients discontinued will be summarized along with reasons for discontinuation in the Safety Set.

10.7. Prior and Concomitant Medications

Prior and concomitant medications will be summarized for all patients in the Safety Set. Medications will be coded using the World Health Organization Drug Dictionary (WHODrug; the most current version available at the time of the analyses).

10.8. Efficacy Analyses

10.8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline in the QMG total score over time regardless of rescue treatment. The primary efficacy analysis for the change from Baseline in the QMG total score will be conducted at Week 12 in order to assess the effect of eculizumab treatment during the Primary Evaluation Treatment Period after the 12 weeks during which MG medications (ie, ISTs, IVIg) are continued at a stable dose. The Paediatric Committee of the European Medicines Agency (PDCO)-specific primary efficacy analysis will be conducted at Week 26. The primary efficacy analysis will be performed on the mFAS. A Repeated-Measures model will be used to analyze observed change in QMG with baseline QMG score and visits as covariates. The least-squares mean at Week 12 will be used to test the primary hypothesis at a significance level of 5%. The least-squares mean at Week 26 will be used to test the PDCO-specific primary hypothesis at a significance level of 5%. The standard error of the mean and 95% confidence interval will be produced. Missing primary endpoints at post-baseline visits will not be imputed.

10.8.1.1. Analysis of Primary Endpoint based on Evaluable Patients

The analysis of the primary efficacy endpoint will be performed on the mFAS (evaluable) set.

10.8.2. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- 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 from Baseline over time with no rescue treatment
- Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from Baseline over time regardless of rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time with no rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline 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

For all patients in the mFAS, the secondary endpoints that involve change from Baseline will be analyzed at a particular visit based on the repeated-measures models with effects for the particular baseline covariate and visit. Confidence intervals and p-values will be presented by visit. Graphical displays over time will be produced by visit. Missing secondary endpoint assessments will not be imputed.

For all patients in the mFAS, the secondary endpoints that involve proportion of patients with a pre-specified response will be summarized at a particular visit. Confidence intervals and p-values will be presented by visit.

The number and percentage of patients with at least one on-study clinical deterioration and/or MG crisis during first 26 weeks will be summarized. Use of rescue therapy during the first 26 weeks will also be summarized.

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.

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.

11.3. Institutional Review Board / Independent Ethics Committee

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC protocol approval, and all materials that have been submitted and approved by the IRB or IEC for this study including the patient ICF and recruitment materials must be maintained by the PI and made available for inspection.

11.4. Quality Control and Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its designee may conduct quality assurance audits as described in Section 11.2.

11.5. Ethics

11.5.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit a copy of the written approval to the Sponsor or its designee before enrolling any patients into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and reviewed annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug, as required. Alexion Pharmaceuticals, Inc. or designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

11.5.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

11.6. Informed Consent and Assent

The PI(s) at each center will ensure that each patient and/or parental guardian are given full and adequate verbal and written information about the nature, purpose, possible risk, and benefit of the study. Patients and/or parental guardian must also be notified that they are free to refuse to join the study and may discontinue from the study at any time. The patient and/or parental guardian should be given the opportunity to ask questions and allowed adequate time to consider the information provided.

The Investigator is responsible for ensuring that informed consent is given by each patient or the patient’s legal representative. This includes obtaining the appropriate signatures and dates on the

ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

The PI(s) must maintain the original, signed ICF. If the ICF is amended, the original signed, amended version must also be retained. A copy of the signed ICF must be given to the patient and/or parental guardian.

The same parent or guardian is recommended to be available to accompany the child to each study visit, in order to reduce subjective variability in assessments.

As used in this protocol, the term "informed consent" includes all informed assent given by patients, informed permission by parent or legal guardian, or, as applicable, informed consent by the patient during study participation.

11.7. Data Protection

The following measures will be implemented for the protection of patients' personal data:

- Each patient will be assigned a unique identifier. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names or any information that would make a patient identifiable will not be transferred.
- The patient and/or parental guardian must be informed that the patient's personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the patient and/or parental guardian, as well as a notice of the collection, use, and storage of the personal data through the informed consent or other privacy notice in accordance with local data protection law.
- The patient and/or parental guardian must be informed that the patient's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.8. Changes or Deviations to Protocol

The Investigator may need to deviate from the protocol to eliminate an immediate hazard to a study subject without prior notification of the IRB/IEC. Any deviations from the protocol must be fully documented. The deviation and the reasons for it should be submitted to the IRB/IEC, Sponsor, and appropriate regulatory authority if required (ICH GCP E6 [R1] 4.5.4). After the commencement of the clinical study, the Sponsor may make changes to the protocol. If those changes are significant, the regulatory authority and applicable IRB/IEC will be notified.

11.9. Data Handling and Recordkeeping

11.9.1. Inspection of Records

The Sponsor or the Sponsor's designee will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, study

drug accountability records, patient charts and study source documents, and other records relative to study conduct.

11.9.2. Retention of Records

The PI must maintain all documentation relating to the study according to local regulations or a minimum period of 2 years after the last marketing application approval worldwide or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or its designee or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

The PI must maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents.

11.10. Contraceptive Guidance

Female patients of childbearing potential and male patients with female partners of childbearing potential, pregnant, or breastfeeding, must use effective methods of contraception (as defined below), starting at Screening and continuing for at least 5 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 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 a 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.

11.11. Publication Policy

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

12. LIST OF REFERENCES

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APPENDIX 1. QUANTITATIVE MYASTHENIA GRAVIS SCORE FOR DISEASE SEVERITY

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 :		

APPENDIX 2. MODIFIED QUANTITATIVE MYASTHENIA GRAVIS SCORE FOR DISEASE SEVERITY

Test Item	None	Mild	Moderate	Severe
Grade	0	1	2	3
Subjective double vision	None	Occasional	Frequent	Constant
Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz water (slurp test)	<10 seconds	10-15 seconds	>15 seconds	Cannot swallow (test not attempted)
Speech (nasal phonation)	None	Occasional	Frequent	Constant
Right arm outstretched (90 degree sitting), seconds	240	90-239	10-89	0-9
Left arm outstretched (90 degree sitting), seconds	240	90-239	10-89	0-9

Source: Goldstein, 2015

APPENDIX 3. MYASTHENIA GRAVIS ACTIVITIES OF DAILY LIVING (MG-ADL) PROFILE

Items	Grade 0	Grade 1	Grade 2	Grade 3	Score (0,1,2,3)
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	

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.

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

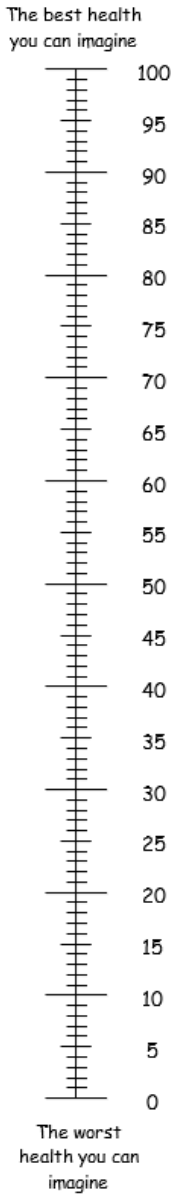
I have no pain or discomfort ❑
I have some pain or discomfort ❑
I have a lot of pain or discomfort ❑

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 ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line to show how good or bad your health is TODAY.



APPENDIX 6. EUROPEAN QUALITY OF LIFE 5-DIMENSION – YOUTH VERSION (PROXY)

To be used for patients < 8 years of age.

EQ-5D-Y

Describing the child's health TODAY

Under each heading, please check the ONE box that **you think** best describes the child's health **TODAY**.

Mobility *(walking around)*

He/she has no problems walking around ❑

He/she has some problems walking around ❑

He/she has a lot of problems walking around ❑

Taking care of him/herself

He/she has no problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

He/she has some problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

He/she has a lot of problems taking a bath or shower by him/herself or getting dressed by him/herself ❑

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

He/she has no problems doing his/her usual activities ❑

He/she has some problems doing his/her usual activities ❑

He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑

He/she has some pain or discomfort ❑

He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑

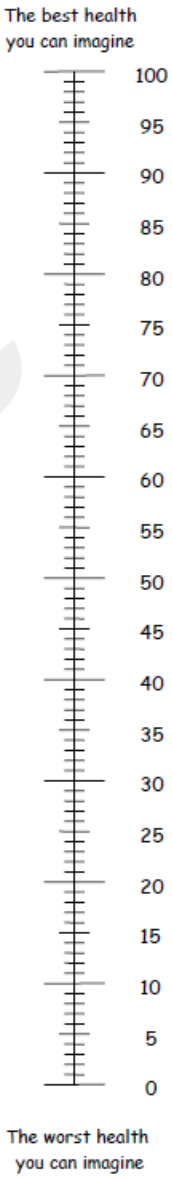
He/she is a little worried, sad or unhappy ❑

He/she is very worried, sad or unhappy ❑

2

The child's health TODAY

- We would like to know how good or bad you think the child's health is TODAY.
- This line is numbered 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line to show how good or bad **you think** the child's health is **TODAY**.



3

APPENDIX 7. NEUROLOGICAL QUALITY OF LIFE PEDIATRIC FATIGUE

To be used for patients ≥ 8-17 years of age.

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

	In the past 7 days…	None of the time	A little bit of time	Some of the time	Most of the time	All of the time
NQFTGped01	I felt tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped04	I had trouble starting things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped05	I had trouble finishing things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped06	I needed to sleep during the day……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped08	Being tired made it hard to play or go out with my friends as much as I would like...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped11r1	I was too tired to eat……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped12	Being tired makes me sad……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped13	Being tired makes me mad……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped07	I got upset by being too tired to do things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped09	I needed help doing my usual things at home……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTGped10	I felt weak……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX 8. PROMIS PARENT PROXY ITEM BANK V2.0 – FATIGUE – SHORT FORM 10A

To be used in patients < 8 years of age.

PROMIS Parent Proxy Item Bank v2.0 – Fatigue – Short Form 10a

Parent Proxy Fatigue – Short Form 10a

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

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
PAFatigue12r	Being tired made it hard for my child to play or go out with friends as much as he/she would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAFatigue6r	My child felt weak	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAFatigue2r	My child got tired easily	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue8r	Being tired made it hard for my child to keep up with schoolwork	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue4r	My child had trouble finishing things because he/she was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue7r	My child had trouble starting things because he/she was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue12r	My child was so tired it was hard for him/her to pay attention	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue9r	My child was too tired to do sports or exercise	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PCFatigue5r	My child was too tired to do things outside	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAFatigue4r	My child was too tired to enjoy the things he/she likes to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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APPENDIX 9. MYASTHENIA GRAVIS FOUNDATION OF AMERICA CLINICAL CLASSIFICATION

Class	Clinical signs
I	Any ocular muscle weakness. May have weakness of eye closure. All other muscle strength is normal.
II	Mild weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIa	Predominantly affecting limb or axial muscles or both. May also have lesser involvement of oropharyngeal muscles.
IIb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIIa	Predominantly affecting limb or axial muscles or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IVa	Predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles.
IVb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
V	Defined by 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.

APPENDIX 10. MYASTHENIA GRAVIS FOUNDATION OF AMERICA THERAPY STATUS

NT	No therapy
SPT	Status postthymectomy (record type of resection)
CH	Cholinesterase inhibitors
PR	Prednisone
IM	Immunosuppression therapy other than prednisone (define)
PE(a)	Plasma exchange therapy, acute (for exacerbations or preoperatively)
PE(c)	Plasma exchange therapy, chronic (used on a regular basis)
IG(a)	IVIg therapy, acute (for exacerbations or preoperatively)
IG(c)	IVIg therapy, chronic (used on a regular basis)
OT	Other forms of therapy (define)

APPENDIX 11. MYASTHENIA GRAVIS FOUNDATION OF AMERICA POST-INTERVENTIONAL STATUS

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.
Pharmacological 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 data).

APPENDIX 12. SUMMARY OF LABORATORY PANELS AND TESTS

Chemistry Panel	**Complete Blood Count and Differential**
Sodium	White blood cell count
Potassium	White blood cell differential
Chloride	Red blood cell count (RBC)
Bicarbonate	RBC mean corpuscular volume
Blood urea nitrogen	RBC distribution width
Creatinine	Hemoglobin
Glucose	Hematocrit
Alkaline phosphatase	Platelet count
Alanine amino transferase	
Aspartate amino transferase	**Other**
Total bilirubin	Human chorionic gonadotropin (urine pregnancy test)
Albumin	Anti-acetylcholine receptor (AChR) antibody
Total protein	Pharmacokinetics
Uric acid	Pharmacodynamics
	Free complement component 5
	Anti-drug antibody

APPENDIX 13. COLLECTION OF FOLLOW-UP INFORMATION FROM PATIENTS WHO WITHDRAW FROM THE STUDY

To gain understanding of the patient's post-treatment disease status, the Sponsor may request additional Post-Treatment Follow-up information from patients who discontinue prematurely for up to 1 year following discontinuation. An ICF (and/or an ICF Addendum) will be provided to all patients and/or the parent or other legal guardian (as applicable) describing the reason for collecting follow-up information, the information that will be collected, and how the information will be used. The ICF (and/or ICF Addendum) will clearly state that the patient and/or the parent or legal guardian has the option to accept or reject, and that either decision will have no impact on their medical benefits. Prior to collecting any follow-up information, the ICF (and/or ICF Addendum) must be signed.

The Sponsor may obtain patient post-treatment data by querying the patient's medical records, through the study physician or the patient's current treating physician. The follow-up data to be collected from the physician may include the following:

- How has the patient's MG status changed since they left Study ECU-MG-303 (better/worse/unchanged); if better or worse, what are the changes?
- What are the patient's current MG medications and the doses, and MG medication history since leaving Study ECU-MG-303?
- Has the patient experienced any exacerbations (clinical deteriorations) of MG, or any myasthenic crises since leaving Study ECU-MG-303; if so how many times?
- Has the patient experienced any MG-related hospitalizations since leaving Study ECU-MG-303; if so how many times
- Has the patient required rescue treatment with IV acetylcholinesterase inhibitors, corticosteroids, plasma exchange or IVIg since leaving Study ECU-MG-303; if so how many times
- Has the patient had any assessments using the MG-ADL, QMG, MGC, Neuro-QoL Fatigue or EQ-5D-Y scale; if so, what are the results, and was it administered by the same person who did the assessment during the clinical study
- Have there been any changes in non-drug therapy.

This information will not be entered into the trial Electronic Data Capture systems and will not be part of any safety or efficacy analysis that will be included in the ECU-MG-303 clinical study report.