

**A Phase III, Open-Label, Extension Trial of ECU-MG-301
to Evaluate the Safety and Efficacy of Eculizumab in
Subjects with Refractory Generalized Myasthenia Gravis
(gMG)**

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ECULIZUMAB
ECU-MG-302
A PHASE III, OPEN-LABEL, EXTENSION TRIAL OF
ECU-MG-301 TO EVALUATE THE SAFETY AND
EFFICACY OF ECULIZUMAB IN SUBJECTS WITH
REFRACTORY GENERALIZED MYASTHENIA GRAVIS
(gMG)
IND 101,219

EudraCT NUMBER: 2013-002191-41

Sponsor: Alexion Pharmaceuticals, Inc.
100 College Street
New Haven, CT 06510, USA

Sponsor Contact: PPD
Alexion Pharmaceuticals, Inc.
100 College Street, New Haven, CT 06510, USA
Telephone: PPD Facsimile: PPD

Medical Monitor: PPD
PPD
Alexion Pharmaceuticals, Inc.
100 College Street, New Haven, CT 06510, USA
Telephone: PPD Facsimile PPD

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PROTOCOL TITLE: A Phase III, Open-Label Extension Trial of ECU-MG-301 to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG)

PROTOCOL NUMBER: ECU-MG-302 (Amendment 2)

PPD



Alexion Pharmaceuticals, Inc.

100 College Street
New Haven, CT 06510
USA

Telephone: PPD

Facsimile: PPD

20 Dec 2016

Date

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase III, Open-Label, Extension Trial of ECU-MG-301 to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG)

PROTOCOL NUMBER: ECU-MG-302 (Amendment 2)

I have received and read the ECU-MG-302 study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to conduct the trial in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

Printed Name of Investigator

Signature of Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Trial	Name	Address and Telephone number
Clinical Project Leader	PPD [REDACTED]	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510, USA Tel: PPD [REDACTED] Mobile: PPD [REDACTED] Fax: PPD [REDACTED] Email: PPD [REDACTED]
Responsible Physician (Medical Monitor)	PPD [REDACTED]	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510, USA Tel: PPD [REDACTED] Mobile: PPD [REDACTED] Fax: PPD [REDACTED] Email: PPD [REDACTED]
After-Hour Emergency Contact	24 Hour Emergency Contact	24 hour Telephone Number USA: Tel: PPD [REDACTED] Europe: Tel: PPD [REDACTED] Australia: Tel: PPD [REDACTED]
Serious Adverse Event Reporting	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510, USA Email: PPD [REDACTED] Fax: PPD [REDACTED]
Clinical Supplies	Almac Clinical Services	4204 Technology Drive Durham NC 27704 USA Tel: PPD [REDACTED] Fax: PPD [REDACTED] 9 Charlestown Road Seagoe Industrial Estate Craigavon BT63 5PW United Kingdom Tel: PPD [REDACTED]
Bioanalytical Analysis (PK/PD and C5 Assays and Report Writing)	MPI	MPI Research 54943 North Main Street Mattawan, MI 49071 USA Tel: PPD [REDACTED]
Interactive Voice/Web Response System	Almac Clinical Technologies	Almac Clinical Technologies 25 Fretz Road Souderton, PA 18964 USA Tel: PPD [REDACTED]

Table 1: Emergency Contact Information

Role in Trial	Name	Address and Telephone number
Clinical Laboratory	Q2 Solutions (formerly QLab)	<p>North America: Q2 Solutions Central Laboratory 27027 Tourney Road Valencia, CA 91355 USA Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p> <p>Europe: Quintiles Laboratories Europe The Alba Campus Rosebank Livingston West Lothian EH54 7EG United Kingdom Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p> <p>Japan: Quintiles Laboratories Japan 2-18-17 Nishi-ochiai Shinjuku-ku Tokyo, 161-0031 Japan Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p> <p>Argentina: Coordination Center - Latin America (QLAT) Centro de Coordinación de Q2 Solutions QSquared Solutions Argentina Av. Triunvirato 3030 C1427AAQ CABA – Buenos Aires Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p> <p>Brazil: Latin America (QLAT) Diagnósticos da América Av. Juruá 434 Alphaville – São Paulo 06455-010 Tel: PPD [REDACTED] Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p> <p>Singapore: Q Squared Solutions Pte. Ltd 79 Science Park Drive, #06-08, Cintech IV Singapore Science Park I, 118264 Tel: PPD [REDACTED] Fax: PPD [REDACTED]</p>

Table 1: Emergency Contact Information

Role in Trial	Name	Address and Telephone number
Site Management and Monitoring	Quintiles IMS	4820 Emperor Boulevard Durham, NC 27703 USA Tel: PPD

2. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: Eculizumab	
Name of Active Ingredient: h5G1.1-mAb	
Title of Study: A Phase III, open-label extension trial of ECU-MG-301 to evaluate the safety and efficacy of eculizumab in subjects with refractory generalized Myasthenia Gravis (gMG)	
Study Rationale: Trial ECU-MG-301, a Phase 3 clinical trial, has been initiated to evaluate the safety and efficacy of eculizumab in the treatment of refractory gMG. This extension trial is designed to provide the subjects who have participated in the ECU-MG-301 trial an opportunity to receive eculizumab and to collect clinical data that will provide long-term safety and efficacy information on eculizumab in patients with refractory gMG.	
Study Center(s): Approximately 100 centers in North America, South America, Europe, Asia-Pacific, and Middle East	
Principal Investigator: PPD	
Investigators: A list containing all Investigators will be provided with the final study report.	
Study period (years): 4 years Estimated date first subject enrolled: 2014 Estimated date last subject completed: 2018 The end of trial is defined as last subject's last visit.	Phase of development: 3
Objectives: <i>Primary:</i> <ul style="list-style-type: none"> To evaluate the long-term safety of eculizumab in subjects with refractory gMG <i>Secondary:</i> <ul style="list-style-type: none"> To evaluate the long-term efficacy of eculizumab in subjects with refractory gMG as measured by the improvement or maintenance of the MG-specific Activities of Daily Living profile (MG-ADL) To evaluate the long-term efficacy of eculizumab by additional efficacy measures including: <ul style="list-style-type: none"> Quantitative Myasthenia Gravis (QMG) score; Myasthenia Gravis Composite (MGC) score, and Improvement or maintenance in primary symptoms that are most clinically meaningful to the subjects To characterize the effect of eculizumab on quality of life measures To describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in subjects with gMG. 	
Methodology: This is an open-label trial. All subjects who have completed the ECU-MG-301 trial may be eligible to participate in this extension trial. Prior to initiating any extension trial procedures, informed consent form must be signed and inclusion/exclusion criteria must be evaluated and met. Subjects will enter this extension trial within 2 weeks after completing Visit 17 (Week 26) in the ECU-MG-301 trial. Blind Induction Phase (Visits 1-4, Day 1 and Weeks 1-3): To preserve the blinded nature of the ECU-MG-301 trial, all subjects must undergo a blind induction phase prior	

to entering the open-label maintenance phase of this trial (ie, all subjects will receive blinded Investigational Product [IP] weekly for 4 doses). Patients who were randomized to the placebo arm in the ECU-MG-301 trial will receive 4 vials IP (3 vials/900 mg eculizumab plus 1 vial placebo) at Visits 1 to 4. Patients who were randomized to the eculizumab arm in the ECU-MG-301 trial will continue to receive 4 vials IP (1200 mg eculizumab) every two weeks at Visits 1 and 3 and placebo at Visits 2 and 4. All patients will receive 4 vials/1200 mg eculizumab open-label at Visit 5 and onward throughout the trial.

Open-Label Maintenance Phase (Visit 5 and onward):

All subjects will receive open-label eculizumab (4 vials/1200 mg) every 2 weeks during the maintenance phase. All subjects must be present at the trial site for Visits 1 to 16, 23, 29, 42, 55, 68, 81, 94, and 107 for visit-specific procedures and assessments (including IP administration). For other visits, subjects may have the opportunity to receive IP administration remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Principal Investigator (PI) in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a qualified staff member from the medical facility near the subject's home or by home care health professionals. The trial medication will be prepared at the Investigator's pharmacy, at the designated homecare pharmacy, or at the subject's home, and transported under controlled conditions to the subject's home or to the medical facility for administration. During a remote dosing visit, information on adverse events (AEs), concomitant medications, and signs or symptoms of Clinical Deterioration in MG will be collected and sent by the qualified staff that performs the remote infusion to the Investigator's site for evaluation on the day of the visit. Subjects must go to the trial site for evaluation if the subject reports any signs or symptoms that suggest a serious AE (SAE) or Clinical Deterioration.

Supportive immunosuppressive therapy (IST) is allowed during the extension trial at the Investigator's discretion. Change in IST or its dose/schedule will be allowed if due to intolerance or if medically indicated, at the discretion of the Investigator. However, use of rituximab is prohibited during the trial. Subjects may continue participation in this study and receive the IP until the product is registered and available to treat subjects diagnosed with refractory gMG (in accordance with country specific regulations) or for maximum of 4 years, whichever occurs first. In Denmark, patient participation may continue for a maximum of 48 months.

Subjects must be informed of the potential signs and symptoms of MG crisis and instructed to contact the Investigator site as soon as possible after the onset of symptoms. Every effort should be made to evaluate the subject reporting Clinical Deterioration as soon as possible and within 48 hours of notification of the Investigator site of symptom onset. At the evaluation visit, the Investigator or his/her designee will perform the assessments as specified by this protocol. The Investigator will determine whether or not the subject meets the Clinical Deterioration as defined by this protocol and treat the subject accordingly (reference below "On-Trial Rescue Therapies").

On-Trial Rescue Therapies:

On-Trial Rescue Therapy (for example, high dose corticosteroid, plasma exchange [PE] or intravenous immunoglobulin [IVIg]) will be allowed when a subject's health is in jeopardy if rescue therapy is not administered (eg, emergency, and/or emergent but not life-threatening situations), or if a subject experiences Clinical Deterioration as defined in this protocol. The rescue therapy used for a particular subject will be at the discretion of the Investigator. Every effort should be made to notify the Sponsor within 24 hours should a subject require a rescue therapy.

For this protocol, Clinical Deterioration warranting use of On-Trial Rescue Therapy is as follows:

- Subjects 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. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some subjects); or,
- Significant symptomatic worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items other than double vision or eyelid droop or,
- Subjects for whom the Investigator believes that the subjects' health is in jeopardy if rescue therapy is not given (eg, emergency, and/or emergent but not life-threatening situations).

Follow-up Period:

Safety Follow-up (8 weeks): If a subject withdraws from the extension trial or discontinues eculizumab treatment at any time and for any reason after receiving any amount of IP, the subject will be required to complete an Early

Termination (ET) Visit at the time of the withdrawal and a Follow-up Visit 8 weeks following the last dose of IP administration. If a subject is discontinued due to an AE, the event will be followed until it is resolved or, in the opinion of the PI, is determined medically stable. Subjects who withdraw from the extension trial and transition to treatment with the commercially available eculizumab will not be required to complete a 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 (refer to [Section 7.1.3.2](#), [Section 7.3.6](#), and [Appendix 11](#)).

Number of Patients (Planned): Approximately 92.

This is an extension trial to the ECU-MG-301 trial. Approximately 92 patients with gMG will be enrolled in the ECU-MG-301 trial. Patients who complete the 26-week treatment period (Visit 17) in the ECU-MG-301 trial may potentially enter this extension trial.

Study Endpoints:

Primary Endpoint:

- Safety and tolerability of eculizumab

Primary Efficacy Endpoint:

- Change from baseline in the MG-ADL total score

Secondary Efficacy Endpoints:

- Change from baseline in QMG total score
- Proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline and with no rescue therapy
- Proportion of subjects with at least a 5-point reduction in the QMG total score from baseline and with no rescue therapy
- Change from baseline in the MGC scale total score
- Change from baseline in MG-QOL-15

Tertiary Efficacy Endpoints:

- Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from baseline)
- Change from baseline in Neuro-QOL Fatigue
- Change from baseline in EQ-5D
- Change from baseline in the MG-ADL individual items and sub-categories for the bulbar (items 1, 2, and 3), respiratory (item 4), limb (items 5 and 6) and ocular (items 7 and 8) in subjects with abnormal baseline scores for the particular item or sub-categories

Pharmacokinetics and Pharmacodynamics (PK/PD):

PK and PD parameters during blinded induction phase and open-label maintenance phase of treatment

Inclusion Criteria:

1. Subject has completed the ECU-MG-301 trial.
2. Subject has given written informed consent.
3. Subject is willing and able to comply with the protocol requirements for the duration of the trial.
4. Female subjects of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). All subjects must practice an effective, reliable, and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment.

Exclusion Criteria:

1. Subjects who withdrew from the ECU-MG-301 trial as a result of an AE related to trial drug.
2. Female subjects who are pregnant, breastfeeding or intend to conceive during the course of the trial.
3. Unresolved meningococcal infection
4. Hypersensitivity to murine proteins or to one of the excipients of eculizumab

5. Any medical condition or circumstances that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, pose any added risk for the subject, or confound the assessment of the subjects.

Investigational product, dosage, and mode of administration: Investigational Product (eculizumab and/or placebo [placebo used only during the blind-induction phase]), will be administered intravenously according to the following regimen:

Blind Induction Phase:

To maintain the blind of the ECU-MG-301 trial, all subjects will undergo a blind induction phase (Visits 1 to 4, Day 1, and Weeks 1 to 3). Investigational product (eculizumab, placebo or eculizumab plus placebo) will be administered weekly during the induction phase according to the following schedule:

Treatment Group	Ecuzumab Amount during Blind Induction Phase	Equivalent Ecuzumab Dose	Visits
Subjects from the ECU-MG-301 Trial Ecuzumab arm	4 vials of ecuzumab (300 mg/vial)	1200 mg	1 and 3
	4 vials of placebo	0 mg	2 and 4
Subjects from the ECU-MG-301 Trial Placebo arm	3 vials of ecuzumab (300 mg/vial) plus 1 vial of placebo	900 mg	1 through 4

Open-Label Maintenance Phase:

All subjects will receive 4 vials of ecuzumab (1200 mg) every 2 weeks starting with Visit 5 and throughout the remainder of the trial.

Supplemental Dose:

If a subject undergoes plasmapheresis or PE for Clinical Deterioration during the Study Period, a supplemental dose of 2 vials of IP (600 mg of ecuzumab) must be administered within 1 to 2 hours after each PE session unless the PE session is on the day of a scheduled IP infusion. If the PE is on the day of a scheduled IP infusion, the scheduled dose of IP (instead of the supplemental dose) should be administered within 1 to 2 hours after the completion of PE session. In addition, subjects are to continue ecuzumab infusion according to the protocol specified dosing regimen.

Duration of treatment: Approximately 4 years

The duration for an individual subject may vary depending on when the subject enters the trial, the maximum time being 4 years.

Reference therapy, dosage and mode of administration: Not Applicable

Criteria for evaluation:

Efficacy:

Duration of treatment commences with the first IP (ecuzumab) infusion during the Induction Phase.

- The MG-ADL focuses on relevant symptoms and performance of ADL in subjects with MG. The MG-ADL consists of 8 items, 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 the effects of 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. In this trial, the recall period for MG-ADL is the last 7 days. If the number of days since the last visit is less than 7, the recall period is since the last visit. MG-ADL will be performed by a trained evaluator at the protocol specified time points and preferably by the same evaluator each time throughout the study.
- The QMG scoring system is considered to be an objective evaluation of MG therapy and is based on a quantitative testing of muscle strength and endurance/fatigability of sentinel muscle groups. The QMG 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. The range of total QMG score is 0 – 39. The QMG will be administered at approximately the same time of day throughout the study by a trained evaluator at the protocol specified time points and preferably by the same evaluator each time.
- The MGC assesses 10 important functional areas most frequently affected by MG: ocular (2 items),

facial (1 item), bulbar (3 items), respiratory (1 item), axial (1 item) and gross motor (2 items). The scales are weighted for clinical significance that incorporates subject-reported outcomes. Higher scores indicate more functional impairment. The range of total MGC score is 0 – 50. MGC will be administered at the approximately same time of day throughout the study by a well-trained evaluator at the protocol specified time points, and preferably by the same evaluator each time.

Safety:

The safety of eculizumab will be assessed based on:

- The AEs, SAEs, and changes from baseline through trial completion in vital signs, electrocardiogram (ECG), routine clinical laboratory tests (chemistry, hematology), Columbia-Suicide Severity Rating Scale (C-SSRS), and pregnancy tests for female subjects of childbearing potential.
- Immunogenicity: blood samples will be collected for evaluation for anti-drug antibody (ADA) at specified time points to describe the presence or absence of an immune response to eculizumab and to evaluate, if antibodies are detected, whether the antibodies neutralize the activity of eculizumab (ability of eculizumab to inhibit C5 cleavage by C5 convertase).

Pharmacokinetics:

Blood samples will be collected at specified time points to study the concentration of eculizumab versus time. PK parameters such as maximum concentration, trough and peak eculizumab concentration during the blinded induction and open-label maintenance phases will be reported. Clearance and terminal half-life will be estimated.

Pharmacodynamics:

Blood samples for PD analyses will be collected at specified time points to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration also may be monitored.

Biomarkers:

Blood samples for acetylcholine receptor antibody (AChR Ab) will be collected at protocol specified time points.

Quality of Life:

The MG-QOL15, Neuro-QOL Fatigue, and EQ-5D will be used.

Statistical methods:

Analyses will be produced using data from this trial alone (Extension Trial) as well as combined analyses that will include data from the ECU-MG-301 trial (Combined Trial Analyses). The analyses will include safety, efficacy and PK/PD analyses. The Statistical Analysis Plan (SAP) will cover both the standalone trial analyses and the combined ECU-MG-301 and ECU-MG-302 trial analyses.

Treatment groups will be indicated by eculizumab/eculizumab for the subjects originally randomized to the eculizumab arm in the ECU-MG-301 trial and placebo/eculizumab for the subjects originally randomized to the placebo arm in the ECU-MG-301 trial. The Extension Trial analyses will be presented by treatment group. The Combined Trial Analyses, where the data are aligned based on the subject's first dose date of eculizumab, will only be presented as 1 combined eculizumab treatment group since all subjects will have received eculizumab.

Interim statistical analyses for safety and the primary and secondary efficacy endpoints may be performed at the discretion of the Sponsor. All analyses will be prospectively defined in the statistical analysis plan. The final statistical analyses will be performed after the study ends and the database has been locked.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
Ab	Antibody
AChR	Acetylcholine Receptor
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse Event
AZA	Azathioprine
BP	Blood Pressure
C5	Complement Protein 5
CBC	Complete Blood Count
eCRF	Electronic Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
EIU	Exposure <i>in-utero</i>
EOI	Event of Interest
EOS	End of Study
EQ-5D	EuroQOL
EQ VAS	EuroQOL Visual Analog Scale
ET	Early Termination
FAS	Full Analysis Set
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
gMG	Generalized Myasthenia Gravis
HCG	Human Chorionic Gonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IST	Immunosuppressant Therapy
IV	Intravenous
IVIg	Intravenous Immunoglobulin
IXRS	Interactive Voice or Web Response System
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activity of Daily Living profile
MGFA-PIS	Myasthenia Gravis Foundation of America Post Interventional Status
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MM	Minimal Manifestation
MMF	Mycophenolate Mofetil
MTX	Methotrexate

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NIF	Negative Inspiratory Force
NMJ	Neuromuscular Junction
PD	Pharmacodynamics
PE	Plasmapheresis or Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol Population
PR	Pharmacological Remission
QOL	Quality of Life
QMG	Quantitative Myasthenia Gravis
RR	Respiration Rate
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
US	United States
WHO Drug	World Health Organization Drug Dictionary

5. INTRODUCTION

Myasthenia Gravis (MG) is a rare, debilitating, acquired autoimmune disease of the neuromuscular junction (NMJ), caused by the failure of neuromuscular transmission, which results from the binding of auto-antibodies (Abs) to proteins involved in signaling at the NMJ (Conti-Fine 2006). Myasthenia Gravis is clinically characterized by weakness and fatigability of skeletal muscles; however, in the MG patient population there is a wide range of disease severity. Although many patients with MG can be managed with anticholinesterase inhibitor therapy and immunosuppressant therapy (IST), there is a cohort of patients who continue to have marked generalized weakness and bulbar signs and symptoms of the disease despite adequate dosing of IST (Conti-Fine 2006). For these patients, there is a medical need for alternative treatment strategies targeting different pathophysiological aspects of the disease. Since complement activation plays a pivotal role in the pathophysiology of MG (Conti-Fine 2006, Vincent 2002), eculizumab, a terminal complement inhibitor, may benefit patients who continue to have generalized weakness and bulbar signs and symptoms despite current standard of care. Following the completion of a Phase 2 pilot trial in subjects with refractory generalized Myasthenia Gravis (gMG), Alexion has initiated a Phase 3 trial, Study ECU-MG-301, to evaluate the safety and efficacy of eculizumab in the same subject population. This extension trial is designed to provide the subjects that completed the ECU-MG-301 trial with the opportunity to receive eculizumab, and to collect clinical data that will provide long term safety and efficacy information on eculizumab in subjects with refractory gMG. Since this is an extension trial of the ECU-MG-301 trial, the same maintenance dose of eculizumab will be used.

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

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this trial is to evaluate the long-term safety of eculizumab in subjects with refractory gMG.

6.2. Secondary Objectives

The secondary objectives of this trial are:

- To evaluate the long-term efficacy of eculizumab in subjects with refractory gMG as measured by the improvement or maintenance of the MG-specific Activities of Daily Living profile (MG-ADL)
- To evaluate the long-term efficacy of eculizumab by additional efficacy measures including:
 - Quantitative Myasthenia Gravis (QMG) score;
 - Myasthenia Gravis Composite (MGC) score, and
 - Improvement or maintenance in primary symptoms that are most clinically meaningful to the subject.
- To characterize the effect of eculizumab on quality of life measures
- To describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in subjects with refractory gMG

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This is an open-label, multi-center trial to evaluate the safety and efficacy of eculizumab for the treatment of subjects with refractory gMG. All subjects who have completed the ECU-MG-301 trial may be eligible to participate in this extension trial. Prior to initiating any extension trial procedures, informed consent form (ICF) must be signed and inclusion/exclusion criteria must be evaluated and met.

Subjects will enter this extension trial within 2 weeks after they have completed Visit 17 (Week 26) in the ECU-MG-301 trial. There will be 2 phases in this trial: Blind Induction Phase and Open-Label Maintenance Phase. The schedule of assessments for Visits 1 to 16 (beginning of Year 1) are provided in [Table 4](#). The schedule of assessments for Visits 17 to 29 (end of Year 1) are provided in [Table 5](#). The schedules of assessments for Years 2 through 4 are provided in [Table 6](#) and [Table 7](#). The schedule of assessments for the safety follow-up visit is provided in [Table 9](#).

Subjects may continue participation in this trial and receive the investigational product (IP) until the product is registered and available to treat subjects diagnosed with refractory gMG (in accordance with country specific regulations) or for a maximum of 4 years, whichever occurs first. In Denmark, patient participation may continue for a maximum of 48 months. The end of trial is defined as last subject's last visit.

7.1.1. Blind Induction Phase

To preserve the blinded nature of the ECU-MG-301 trial, all subjects must undergo a Blind Induction Phase prior to entering the Open-Label Maintenance Phase of this trial, ie, all subjects will receive blinded IP weekly for 4 weeks. [Table 10](#) provides details on treatment assignment during the Blind Induction Phase.

7.1.2. Open-Label Maintenance Phase

All subjects will receive open-label eculizumab (4 vials/1200 mg) every 2 weeks during the Open-Label Maintenance Phase starting at Visit 5 and onward. The duration of the trial for an individual subject will vary depending on when the subject enters the trial, the maximum time being up to 4 years.

All subjects must be present at the trial site for Visits 1 to 16, 23, 29, 42, 55, 68, 81, 94, and 107, as applicable, for visit-specific procedures/assessments including IP administration. For other visits, subjects may have an opportunity to receive IP administration remotely at a medical facility that is located near the subject's home or at the subject's home with the permission of the Principal Investigator (PI) in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. These visits will be conducted by a qualified staff member from the medical facility near the subject's home or by home care health professionals. The trial medication will be prepared at the Investigator's pharmacy, at a designated homecare pharmacy, or at the subject's home, and transported under controlled conditions to the subject's home or to the medical facility for administration. During a remote dosing visit, information on adverse

events (AEs), concomitant medications, and signs or symptoms of Clinical Deterioration in MG will be collected by the qualified staff that performs the remote visit, and sent to the Investigator's site for evaluation on the day of the visit. Subjects must go to the trial site for evaluation if the subject reports any signs or symptoms that suggest a serious AE (SAE) or Clinical Deterioration.

Supportive IST is permitted during the extension trial at the Investigator's discretion. Change in IST or its dose/schedule will be allowed if due to intolerance or medically indicated at the discretion of the Investigator. However, use of rituximab is prohibited during the trial.

Subjects must be informed of the potential signs and symptoms of MG crisis and instructed to contact the Investigator as soon as possible after onset of symptoms. Every effort should be made for the subject reporting Clinical Deterioration to be evaluated as soon as possible and within 48 hours of notification of the Investigator of symptom onset. At the evaluation visit, the Investigator or his/her designee will perform the assessments as specified by this protocol (refer to [Table 8](#)). The Investigator will determine whether or not the subject meets the Clinical Deterioration as defined by this protocol and treat the subject accordingly (refer to [Section 7.1.4](#)).

Subjects may continue participation in this trial and receive IP for a maximum of 4 years **or** until the product is registered and commercially available to treat patients diagnosed with gMG (in accordance with country specific regulations), whichever occurs first.

7.1.3. Follow-up Period

7.1.3.1. Safety Follow-up (8 Weeks)

If a subject withdraws from the extension trial or discontinues eculizumab treatment at any time and for any reason after receiving any amount of IP, the subject will be required to complete an Early Termination (ET) Visit at the time of the withdrawal (refer to [Table 7](#) end of study [EOS]/ET) and a Follow-up Visit (refer to [Table 9](#)) 8 weeks following the last dose of IP administration. If a subject is discontinued due to an AE, the event will be followed until it is resolved or, in the opinion of the Investigator, is determined medically stable. Subjects who withdraw from the extension trial and transition to treatment with the commercially available eculizumab will not be required to complete a Follow-up Visit.

7.1.3.2. 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 EOS/ET visit (refer to [Appendix 11](#)).

7.1.4. Clinical Deterioration Definition and Rescue Therapies

On-Trial Rescue Therapy, eg, high dose corticosteroid, plasma exchange (PE), or intravenous immunoglobulin (IVIg), will be allowed when a subject's health is in jeopardy if rescue therapy is not administered (eg, emergency, and/or emergent but not life-threatening situations), or if a subject experiences Clinical Deterioration as defined in this protocol. The rescue therapy used for a particular subject will be at the discretion of the Investigator. Every effort should be made to notify the Sponsor within 24 hours should a subject require a rescue therapy.

For this protocol, Clinical Deterioration warranting the use of On-Trial Rescue Therapy is as follows:

- Subjects 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. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some subjects; or,
- Significant symptomatic worsening to a score of 3 or a 2-point worsening from Baseline (ie, Study ECU-MG-302 Day 1) on any one of the individual MG-ADL items other than double vision or eyelid droop; or,
- Subjects for whom the Investigator believes that the subjects' health is in jeopardy if rescue therapy is not given (eg, emergency, and/or emergent but not life-threatening situations).

7.1.5. Clinical Evaluator

The Clinical Evaluators are study staff that have been trained and certified in administering the MG-ADL, QMG, 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 on-line training portal.

7.1.6. Responsibilities for MG Assessments

Responsibilities for MG assessments are listed in [Table 3](#). Throughout the trial, MG assessments should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator.

Table 3: MG Assessments (Responsibilities)

Assessment	Evaluator
MG-ADL	Clinical Evaluator
QMG including FVC	Clinical Evaluator
NIF	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 Activity 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; NIF = negative inspiratory force; PI = Principal Investigator; QMG = Quantitative MG.

7.1.7. Neisseria meningitidis Re-vaccination

Due to the length of this extension trial, patients must be revaccinated for N. meningitidis to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines. During the first visit (Visit 1 on Day 1), Investigators are to assess

the need for re-vaccination and are to record the anticipated date of re-vaccination in the source documents and electronic case report form (eCRF).

7.2. Study Design and Schedule of Assessments

[Figure 1](#) presents the overall study design and [Table 4](#) through [Table 9](#) present the Schedule of Assessments for the study.

Figure 1: Study Design for Trial ECU-MG-302

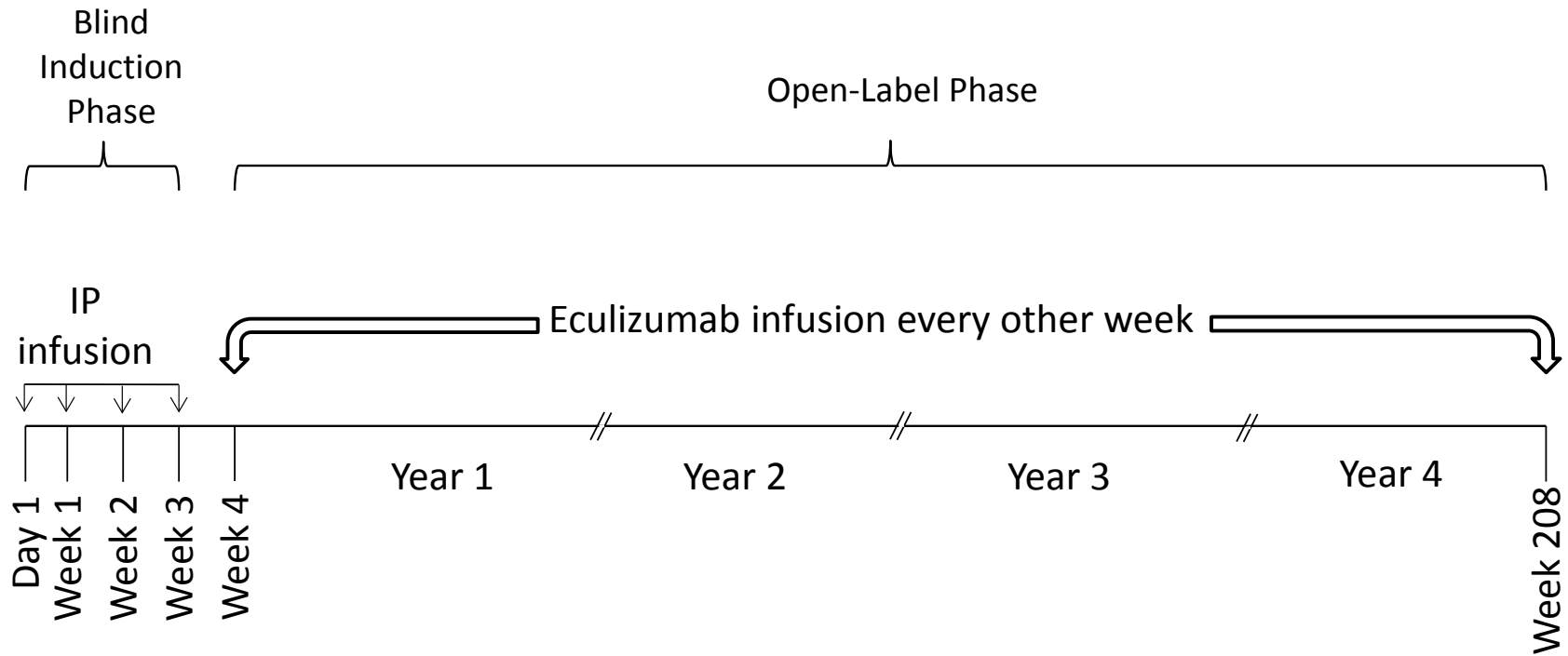


Table 4: Schedule of Assessments: Visits 1 to 16

Phase	Blind Induction				Open-Label Maintenance												
	In Clinic				In Clinic												
Visit Location ¹	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	UNS ²
Trial Visit	Day 1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	
Review Inclusion / Exclusion Criteria	X																
Informed Consent	X																
Weight	X															X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination																X	
12-Lead ECG	X															X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG Therapy Status	X															X	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-QOL15	X				X		X		X		X		X			X	
Neuro-QOL Fatigue	X				X		X		X		X		X			X	
EQ-5D	X				X		X		X		X		X			X	
MG-ADL ³	X	X	X	X	X		X		X		X		X			X	
QMG ³	X	X	X	X	X		X		X		X		X			X	
NIF ³	X	X	X	X	X		X		X		X		X			X	
MGC ³	X	X	X	X	X		X		X		X		X			X	
MGFA-PIS ⁴																X	
C-SSRS	X								X							X	
AChR Abs Test									X							X	
Clinical Laboratory Tests ⁵	X				X		X		X							X	
Pregnancy Test (Serum) ⁶	X															X	
PK/PD/Free C5 (Serum) ⁷	B	T/P			T/P		T/P		T/P				T/P			T/P	
ADA ⁷	B				X				X							X	
Medically Indicated Tests																	

Table 4: Schedule of Assessments: Visits 1 to 16 (Continued)

Phase Visit Location	Blind Induction				Open-Label Maintenance												
	In Clinic				In Clinic												
Trial Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	UNS ²
Trial Day or Week	Day 1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	
Check for <i>N. meningitidis</i> Revaccination ⁸	X						X		X							X	
Patient Safety Information Card ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP Infusion ^{9,10}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AChR Abs = acetylcholine receptor antibodies; B = baseline; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic Case Report Form; EQ-5D = EUROQOL; ADA = anti-drug antibody; IP=Investigational Product; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA-PIS = Myasthenia Gravis Foundation of America Post Interventional Status; MG-QOL15 = 15 item Myasthenia Gravis quality of life; MGC = Myasthenia Gravis Composite; Neuro-QOL = neurological quality of life; NIF = negative inspiratory force; P = peak sample; PK = pharmacokinetics; PD = pharmacodynamics; QMG = Quantitative MG (QMG) Score for Disease Severity; T = trough sample; UNS = unscheduled visit.

If a subject undergoes plasma exchange (PE) for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 1 to 2 hours after the completion of IP infusion.

¹ 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.

² Unscheduled visit and procedures will be performed at the investigator’s discretion and results will be recorded in the eCRF.

³ Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, NIF and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.

⁴ MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.

⁵ Clinical Lab Tests will be performed at the central laboratory. Refer to [Appendix 5](#) for a summary of clinical lab test panels and tests.

⁶ Pregnancy tests must be performed on all women of child bearing potential at the specified time points. Additional pregnancy test (urine or serum) may also be performed at any visit at the PI’s discretion.

⁷ Baseline and trough blood samples for PK, PD and free C5 and all samples for ADA are to be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing are to be taken 60 minutes after the completion of the IP infusion.

If a subject undergoes PE for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 60 minutes after the completion of IP infusion.

⁸ Subjects must be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

⁹ IP will be administered after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay (Refer to [Section 10.5](#)).

¹⁰ If a subject undergoes PE for a Clinical Deterioration (as defined by this protocol) a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Per-protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE.

Table 5: Schedule of Assessments: Visits 17 to 29

Phase	Open-Label Maintenance												
	In Clinic/Remote						In Clinic	In Clinic/Remote					In Clinic
Visit Location ¹	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	EOS /ET/ V29
Trial Visit Year 1	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52
Weight													X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination													X
12-Lead ECG													X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
MG Therapy Status													X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-QOL15							X						X
Neuro-QOL Fatigue							X						X
EQ-5D							X						X
MG-ADL ²							X						X
QMG ²							X						X
MGC ²							X						X
MGFA-PIS ³							X						X
C-SSRS							X						X
AChR Abs Test													X
Clinical Laboratory Tests ⁴								X					X
Pregnancy serum test (serum) ⁵								X					X
PK/PD/Free C ₅ ⁶								T/P					T/P
ADA ⁶								X					X

Table 5: Schedule of Assessments: Visits 17 to 29 (Continued)

Phase	Open-Label Maintenance												
	In Clinic/Remote						In Clinic	In Clinic/Remote					In Clinic
Visit Location	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	EOS / ET / V29
Trial Visit Year 1	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52
Medically indicated tests													
Check for <i>N. meningitidis</i> revaccination ⁷							X						X
Patient Safety Information Card ⁷	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Infusion ^{8,9}	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AChR Abs = acetylcholine receptor antibodies; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D = EUROQOL; EOS = end of study; ADA = anti-drug antibody; IP=Investigational Product; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA-PIS = Myasthenia Gravis Foundation of America Post Interventional Status; MG-QOL15 = 15 item Myasthenia Gravis quality of life; MGC = Myasthenia Gravis composite; Neuro-QOL = neurological quality of life; NIF = negative inspiratory force; P = peak sample; PK = pharmacokinetics; PD = pharmacodynamics; QMG = Quantitative MG (QMG) Score for Disease Severity; T = trough sample.

¹ 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.

² Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.

³ MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.

⁴ Clinical Lab Tests will be performed at the central laboratory. Refer to [Appendix 5](#) for a summary of clinical lab test panels and tests.

⁵ Pregnancy tests must be performed on all women of child bearing potential at the specified time points. Additional pregnancy test (urine or serum) may also be performed at any visit at the PI’s discretion.

⁶ Baseline and trough blood samples for PK, PD and free C5 and all samples for ADA are to be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing are to be taken 60 minutes after the completion of the IP infusion.

If a subject undergoes plasma exchange (PE) for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 60 minutes after the completion of IP infusion.

⁷ Subjects may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines. Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

⁸ IP will be administered after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay (Refer to [Section 10.5](#)).

⁹ If a subject undergoes PE for a Clinical Deterioration (as defined by this protocol) a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Per-protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE.

Table 6: Schedule of Assessments: Year 2 Visits 30 to 42, Year 3 Visits 56 to 68, and Year 4 Visits 82 to 94

Phase	Open-Label Maintenance												
	In Clinic/Remote												In Clinic
Visit Location ¹	V 30 W 54	V 31 W 56	V 32 W 58	V 33 W 60	V 34 W 62	V 35 W 64	V 36 W 66	V 37 W 68	V 38 W 70	V 39 W 72	V 40 W 74	V 41 W 76	V 42 W 78
Year 2 Trial Visit / Week													
Year 3 Trial Visit / Week	V 56 W 106	V 57 W 108	V 58 W 110	V 59 W 112	V 60 W 114	V 61 W 116	V 62 W 118	V 63 W 120	V 64 W 122	V 65 W 124	V 66 W 126	V 67 W 128	V 68 W 130
Year 4 Trial Visit / Week	V 82 W 158	V 83 W 160	V 84 W 162	V 85 W 164	V 86 W 166	V 87 W 168	V 88 W 170	V 89 W 172	V 90 W 174	V 91 W 176	V 92 W 178	V 93 W 180	V 94 W 182
Weight													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination													
12-Lead ECG													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-QOL15													X
Neuro-QOL Fatigue													X
EQ-5D													X
MG-ADL ²													X
QMG ²													X
MGC ²													X
MGFA-PIS ³													X
C-SSRS													X
AChR Abs Test													X
Clinical Laboratory Tests ⁴													X
Pregnancy serum test (serum) ⁵													X
PK/PD/Free C5 ⁶													T/P
ADA ⁶													X
Medically indicated tests													

Table 6: Schedule of Assessments: Year 2 Visits 30 to 42, Year 3 Visits 56 to 68, and Year 4 Visits 82 to 94 (Continued)

Phase	Open-Label Maintenance												
	In Clinic/Remote												In Clinic
Year 2 Trial Visit / Week	V 30 W 54	V 31 W 56	V 32 W 58	V 33 W 60	V 34 W 62	V 35 W 64	V 36 W 66	V 37 W 68	V 38 W 70	V 39 W 72	V 40 W 74	V 41 W 76	V 42 W 78
Year 3 Trial Visit / Week	V 56 W 106	V 57 W 108	V 58 W 110	V 59 W 112	V 60 W 114	V 61 W 116	V 62 W 118	V 63 W 120	V 64 W 122	V 65 W 124	V 66 W 126	V 67 W 128	V 68 W 130
Year 4 Trial Visit / Week	V 82 W 158	V 83 W 160	V 84 W 162	V 85 W 164	V 86 W 166	V 87 W 168	V 88 W 170	V 89 W 172	V 90 W 174	V 91 W 176	V 92 W 178	V 93 W 180	V 94 W 182
Check for <i>N.meningitidis</i> revaccination ⁷						X							X
Patient Safety Information Card ⁷	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Infusion ^{8,9}	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AChR Abs = acetylcholine receptor antibodies; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D = EUROQOL; ADA = anti-drug antibody; IP=Investigational Product; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA-PIS = Myasthenia Gravis Foundation of America Post Interventional Status; MG-QOL15 = 15 item Myasthenia Gravis quality of life; MGC = Myasthenia Gravis composite; Neuro-QOL = neurological quality of life; NIF = negative inspiratory force; P = peak sample; PK = pharmacokinetics; PD = pharmacodynamics; QMG = Quantitative MG (QMG) Score for Disease Severity; T = trough sample.

- ¹ 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.
- ² Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.
- ³ MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- ⁴ Clinical Lab Tests will be performed at the central laboratory. Refer to [Appendix 5](#) for a summary of clinical lab test panels and tests.
- ⁵ Pregnancy tests must be performed on all women of child bearing potential at the specified time points. Additional pregnancy test (urine or serum) may also be performed at any visit at the PI’s discretion.
- ⁶ Baseline and trough blood samples for PK, PD and free C5 and all samples for ADA are to be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing are to be taken 60 minutes after the completion of the IP infusion. If a subject undergoes plasma exchange (PE) for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 60 minutes after the completion of IP infusion.
- ⁷ Subjects may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines. Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.
- ⁸ IP will be administered after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay (Refer to [Section 10.5](#)).
- ⁹ If a subject undergoes PE for a Clinical Deterioration (as defined by this protocol) a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Per protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE.

Table 7: Schedule of Assessments: Year 2 Visits 43 to 55, Year 3 Visits 69 to 81, and Year 4 Visits 95 to 107

Phase	Open-Label Maintenance												
	Visit Location ¹	In Clinic/Remote											In Clinic
Year 2 Trial Visit / Week	V 43 W 80	V 44 W 82	V 45 W 84	V 46 W 86	V 47 W 88	V 48 W 90	V 49 W 92	V 50 W 94	V 51 W 96	V 52 W 98	V 53 W 100	V 54 W 102	EOS / ET ² V 55 / W 104
Year 3 Trial Visit / Week	V 69 W 132	V 70 W 134	V 71 W 136	V 72 W 138	V 73 W 140	V 74 W 142	V 75 W 144	V 76 W 146	V 77 W 148	V 78 W 150	V 79 W 152	V 80 W 154	EOS / ET / V 81 W 156
Year 4 Trial Visit / Week	V 95 W 184	V 96 W 186	V 97 W 188	V 98 W 190	V 99 W 192	V 100 W 194	V 101 W 196	V 102 W 198	V 103 W 200	V 104 W 202	V 105 W 204	V 106 W 206	EOS / ET / V 107 W 208
Weight													X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination													X
12-Lead ECG													X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
MG-QOL15													X
Neuro-QOL Fatigue													X
EQ-5D													X
MG-ADL ³													X
QMG ³													X
MGC ³													X
MGFA-PIS ⁴													X
C-SSRS													X
AChR Abs Test													X
Clinical Laboratory Tests ⁵													X
Pregnancy serum test (serum) ⁶													X
PK/PD/Free C5 ⁷													T/P
ADA ⁷													X
Medically indicated tests													

Table 7: Schedule of Assessments: Year 2 Visits 43 to 55, Year 3 Visits 69 to 81, and Year 4 Visits 95 to 107 (Continued)

Phase	Open-Label Maintenance												
	In Clinic/Remote												In Clinic
Year 2 Trial Visit / Week	V 43 W 80	V 44 W 82	V 45 W 84	V 46 W 86	V 47 W 88	V 48 W 90	V 49 W 92	V 50 W 94	V 51 W 96	V 52 W 98	V 53 W 100	V 54 W 102	EOS / ET V 55 / W 104
Year 3 Trial Visit / Week	V 69 W 132	V 70 W 134	V 71 W 136	V 72 W 138	V 73 W 140	V 74 W 142	V 75 W 144	V 76 W 146	V 77 W 148	V 78 W 150	V 79 W 152	V 80 W 154	EOS / ET / V 81 W 156
Year 4 Trial Visit / Week	V 95 W 184	V 96 W 186	V 97 W 188	V 98 W 190	V 99 W 192	V 100 W 194	V 101 W 196	V 102 W 198	V 103 W 200	V 104 W 202	V 105 W 204	V 106 W 206	EOS / ET / V 107 W 208
Check for <i>N. meningitidis</i> revaccination ⁸							X						X
Patient Safety Information Card ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Infusion ^{9,10}	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AChR Abs = acetylcholine receptor antibodies; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS/ET = end of study/early termination; EQ-5D = EUROQOL; ADA = anti-drug antibody; IP=Investigational Product; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA-PIS = Myasthenia Gravis Foundation of America Post Interventional Status; MG-QOL15 = 15 item Myasthenia Gravis quality of life; MGC = Myasthenia Gravis composite; Neuro-QOL = neurological quality of life; NIF = negative inspiratory force; P = peak sample; PK = pharmacokinetics; PD = pharmacodynamics; QMG = Quantitative MG (QMG) Score for Disease Severity; T = trough sample.

¹ 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.

² If a subject withdraws early from the trial an Early Termination (ET) Visit will be performed. The assessments listed for Visit 55 will be performed at ET Visit.

³ Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.

⁴ MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.

⁵ Clinical Lab Tests will be performed at the central laboratory. Refer to [Appendix 5](#) for a summary of clinical lab test panels and tests.

⁶ Pregnancy tests must be performed on all women of child bearing potential at the specified time points. Additional pregnancy test (urine or serum) may also be performed at any visit at the PI’s discretion.

⁷ Baseline and trough blood samples for PK, PD and free C5 and all samples for ADA are to be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing are to be taken 60 minutes after the completion of the IP infusion.

If a subject undergoes plasma exchange (PE) for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 60 minutes after the completion of IP infusion.

⁸ Subjects may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

⁹ IP will be administered after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay (Refer to [Section 10.5](#)).

¹⁰ If a subject undergoes PE for a Clinical Deterioration (as defined by this protocol) a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Per-protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE.

Table 8: Schedule of Assessments: Evaluation Visit for Clinical Deterioration

Visit Location ¹	In Clinic
Trial Visit	Clinical Deterioration Evaluation Visit ²
Vital Signs	X
Concomitant Medications	X
Adverse Event	X
MG-ADL ³	X
QMG ³	X
NIF ³	X
MGC ³	X
AChR Abs Test	X
Clinical Laboratory Tests ⁴	X
PK/PD/Free C5 ⁵	X
Medically Indicated Tests	X
Patient Safety Information Card ⁶	X
IP Infusion ^{7,8}	X

Abbreviations: AChR Abs = acetylcholine receptor antibodies; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis composite; NIF = negative inspiratory force; PK = pharmacokinetics; PD = pharmacodynamics; QMG = Quantitative MG (QMG) Score for Disease Severity.

¹ 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.

² Evaluation visit for MG Clinical Deterioration must be performed as soon as possible and no later than 48 hours of notification of Investigator of the symptom onset. Additional unscheduled visits can be scheduled at the discretion of the investigator.

³ Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, NIF and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.

⁴ Clinical Lab Tests will be performed at the central laboratory. Refer to [Appendix 5](#) for a summary of clinical lab test panels and tests.

⁵ Baseline and trough blood samples for PK, PD and free C5 and all samples for ADA are to be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing are to be taken 60 minutes after the completion of the IP infusion.

If a subject undergoes plasma exchange (PE) for a Clinical Deterioration, 3 blood samples for PK, PD and free C5 will be collected [1] 5 – 90 minutes prior to PE; [2] after PE and before IP infusion; and [3] at 60 minutes after the completion of IP infusion.

⁶ Subjects may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

⁷ IP will be administered after completion of all other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay (Refer to [Section 10.5](#)).

⁸ If a subject undergoes PE for a Clinical Deterioration (as defined by this protocol) a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Per-protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE.

Table 9: Schedule of Assessments: Safety Follow-up Visit

Safety Follow-up	
Trial Visit	Follow-up
Trial Week	+ Week 8
Vital Signs	X
Concomitant Medications	X
Adverse Events	X
MG-QOL 15	X
MG-ADL ¹	X
QMG ¹	X
MGC ¹	X
MGFA-PIS ²	X
Check for <i>N. meningitidis</i> revaccination ³	X
Patient Safety Information Card ⁴	X

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MG-QOL15 = 15 item Myasthenia Gravis quality of life; MGC = Myasthenia Gravis composite; MGFA-PIS = Myasthenia Gravis Post Interventional Status QMG = Quantitative MG (QMG) Score for Disease Severity.

¹ Throughout the study, it is preferred that the same properly trained evaluator perform the clinical assessments of MG-ADL, QMG, and MGC. Additionally, the clinical assessments of QMG, NIF and MGC shall be performed at approximately the same time of day. If a subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the tests.

² MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.

³ Subjects may be revaccinated for *N. meningitidis* to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines. Subjects will be given a Patient Safety Information Card prior to the first dose of trial medication. At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

⁴ At each visit throughout the trial, site staff will ensure that the subject has the Patient Safety Information Card, and document in the source documents.

7.3. Trial Visit Procedures

Visit 1/Day 1 should occur within 2 weeks (14 days \pm 2) of Visit 17 in Trial ECU-MG-301 in order to prevent a lapse in dosing. Visit intervals during Blind Induction Phase (Visits 1 to 4) are weekly (every 7 \pm 2 days after the last visit, based on PK profile). Visit intervals during the Open-Label Maintenance Phase (Visits 5 to 107) are every 2 weeks (every 14 \pm 2 days since the last visit). IP will be administered after completion of all other tests and procedures (excluding the peak blood sampling for PK/PD and free C5 assay) as described in [Section 10.5](#).

Subjects who fail to return for a scheduled visit must be contacted by the site study staff to determine the reason for missing the appointment. Subjects 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 subject cannot or does not come to the study site for examination, then the subject will be instructed to see his or her local neurologist or physician. In this event, the investigational site will 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 subject's missing visit 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 9](#)). Follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the subject's last known address, and documented in both the source documents and the eCRF.

Patients should be registered in the Interactive Voice or Web Response System (IXRS) as soon as the ECU-MG-302 ICF is signed. The initial shipment of study drug for ECU-MG-302 will be triggered by the IXRS when the first patient in the ECU-MG-301 trial is registered as completing the study (Visit 17), and moves to the ECU-MG-302 trial.

7.3.1. Blind Induction Phase

7.3.1.1. Baseline (Visit 1/Day 1)

Once all the eligibility criteria have been confirmed by the Investigator and the subject has signed the ICF, the subject will be assigned to a Blind Induction Phase treatment group based on their treatment assignment in the ECU-MG-301 trial. The following tests and evaluations will be performed at the Baseline Visit (Visit 1/Day 1):

- Review inclusion and exclusion criteria
- Measure body weight
- Perform a 12-lead electrocardiogram (ECG)
- Measure vital signs, including assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR), and heart rate (HR)
- Evaluate and record any new AEs or changes in AEs:
 - Since this an extension to the ECU-MG-301 trial, AEs with an onset date before the Day 1 of this extension trial will be recorded on the ECU-MG-301 eCRF regardless of when the subject signed the ECU-MG-302 ICF.

- Any ongoing AEs at the time of Day 1 of this extension trial will be recorded on both the ECU-MG-301 and ECU-MG-302 CRFs. Since this will be done automatically by the system, sites will not be required to record these data twice.
- AEs with an end date before Day 1 of ECU-MG-302 will be recorded only on the ECU-MG-301 eCRF.
- Record any new concomitant medications or changes to concomitant medications (including non-drug therapies):
 - Since this is an extension to the ECU-MG-301 trial, concomitant medication with an onset date before Day 1 of this extension trial will be recorded on the ECU-MG-301 eCRF regardless of when the subject signed the ECU-MG-302 ICF. Since this will be done automatically by the system, sites will not be required to record these data twice.
 - Any ongoing concomitant medication (including non-drug therapies) at the time of Day 1 of this extension trial will have to be recorded on both ECU-MG-301 and ECU-MG-302 eCRFs.
 - Concomitant medication (including non-drug therapies) with an end date before Day 1 of ECU-MG-302 trial will be recorded only on the ECU-MG-301 eCRF.
- Record MG Therapy Status (refer to [Appendix 6](#))
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, negative inspiratory force (NIF), and MGC; these shall be performed at approximately the same time of day, preferably by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC assessments.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EuroQOL [EQ-5D])
- Perform Columbia-Suicide Severity Rating Scale (C-SSRS; [Appendix 9](#))
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#))
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure). Pregnancy testing (urine or serum) may also be performed at any time during the trial at the Investigator's discretion.
- Determine if the subject needs *Neisseria meningitidis* (*N. meningitidis*) re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

- Provide the Patient Safety Information Card describing the IP and emergency contact information to the subject prior to the first dose of IP.
- Collect baseline blood samples for PK, PD, free Complement protein 5 (C5), and anti-drug antibody (ADA) assays before the infusion of IP.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.1.2. Visit 2 (Week 1)

The following tests and procedures will be completed at Visit 2 (Week1):

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications since the previous visit (including non-drug therapies)
- Evaluate and record AEs since the previous visit
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days. If the number of days since the last visit was less than 7, the recall period is since the last visit.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.1.3. Visits 3 and 4 (Weeks 2 and 3)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications since the previous visit (including non-drug therapies)

- Evaluate and record AEs since the previous visit
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2. Open-Label Maintenance Phase Year 1

7.3.2.1. Visit 5 (Week 4)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications since the previous visit (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.

- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.2. Visits 6, 8, 10, 12, 14, and 15 (Weeks 6, 10, 14, 18, 22, and 24)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.3. Visit 7 (Week 8)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).

- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.4. Visit 9 (Week 12)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the acetylcholine receptor antibodies (AChR Abs) test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.

- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.5. Visit 11 (Week 16)

The following tests and procedures will be completed at Visit 11:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.6. Visit 13 (Week 20)

The following tests and procedures will be completed at Visit 13:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.

- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.7. Visit 16 (Week 26)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Measure body weight.
- Complete physical examination including assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and general neurologic examination.
- Perform a 12-lead ECG.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Record MG Therapy Status (refer to [Appendix 6](#)).
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.

- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.8. Visits 17 to 22 and 24 to 28 (Weeks 28 to 38 and 42 to 50)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.9. Visit 23 (Week 40)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.2.10. Visit 29 (Week 52)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Measure body weight.
- Perform a 12-lead ECG.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Record MG Therapy Status (refer to [Appendix 6](#)).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.

- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3. Open-Label Maintenance Phase Year 2

7.3.3.1. Visits 30-34 and 36-41 (Weeks 54-62 and 66-76)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3.2. Visit 35 (Week 64)

The following tests and procedures will be completed at Visit 35:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3.3. Visit 42 (Week 78)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3.4. Visits 43 to 48 and 50 to 54 (Weeks 80 to 90 and 94 to 102)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3.5. Visit 49 (Week 92)

The following tests and procedures will be completed at Visit 49:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.3.6. Visit 55 (Week 104)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Measure body weight.
- Perform a 12-lead ECG.

- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate CRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4. Open-Label Maintenance Phase Year 3

7.3.4.1. Visits 56 to 60 and 62 to 67 (Weeks 106 to 114 and 118 to 128)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4.2. Visit 61 (Week 116)

The following tests and procedures will be completed at Visit 61:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4.3. Visit 68 (Week 130)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.

- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS, [Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate CRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4.4. Visits 69 to 74 and 76 to 80 (Weeks 132 to 142 and 146 to 154)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4.5. Visit 75 (Week 144)

The following tests and procedures will be completed at Visit 75:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.4.6. Visit 81 (Week 156)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Measure body weight.
- Perform a 12-lead ECG.
- Record any new medications or changes to concomitant medications (including non-drug therapies).

- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion. Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5. Open-Label Maintenance Phase Year 4

7.3.5.1. Visits 82 to 86 and 88 to 93 (Weeks 158 to 166 and 170 to 180)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.

- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5.2. Visit 87 (Week 168)

The following tests and procedures will be completed at Visit 87:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5.3. Visit 94 (Week 182)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.

- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5.4. Visits 95 to 100 and 102 to 106 (Weeks 184 to 194 and 198 to 206)

The following tests and procedures will be completed at these visits:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.

- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5.5. Visit 101 (Week 196)

The following tests and procedures will be completed at Visit 101:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.5.6. Visit 107 (Week 208)

The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Measure body weight.
- Perform a 12-lead ECG.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.

- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays 5 to 90 minutes before the IP infusion. Peak blood samples for PK, PD, and free C5 are to be taken at least 60 minutes after the completion of the IP infusion.
- Collect a blood sample for ADA assay 5 to 90 minutes before the IP infusion.
- Contact the IXRS to obtain the study drug kit assignment.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in [Section 10.5](#) and observe subjects for at least 1 hour after the end of the IP infusion.

7.3.6. End of Study / Early Termination

An EOS visit will be performed before a subject leaves the study for any reason, including study termination. An ET visit will be performed if a subject withdraws early during the study. The tests and procedures for the EOS or ET visit are as follows:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Complete physical examination including assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and general neurologic examination.
- Measure body weight.
- Perform a 12-lead ECG.

- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Record MG Therapy Status (refer to [Appendix 6](#)).
- Evaluate and record AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days or since the last visit whichever occurs earlier.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Administer questionnaires to evaluate quality of life (MG-QOL15, Neuro-QOL Fatigue, and EQ-5D).
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Perform C-SSRS ([Appendix 9](#)).
- Obtain a blood sample for the AChR Abs test.
- Obtain blood samples for clinical laboratory tests (chemistry and hematology; refer to [Appendix 5](#)).
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate eCRF pages (concomitant medication or procedure).
- Collect trough blood samples for PK, PD, and free C5 assays.
- Seek consent from patients to allow the Sponsor to collect information concerning their post-treatment MG status for up to 1 year from the EOS/ET visit (refer to [Section 7.1.3.2](#), [Section 7.3.6](#), and [Appendix 11](#)).

7.3.7. Visits for Evaluation of Clinical Deterioration

The evaluation visit for Clinical Deterioration must be performed as soon as possible, ideally within 48 hours of the Investigator receiving notification of the symptom onset. Additional evaluation visits can be scheduled at the discretion of the Investigator. The following tests and procedures will be completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies), including all treatments for MG.
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days or since the last visit whichever occurs earlier.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Collect blood sample for the AChR Abs test.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- If medically indicated for evaluation of clinical deterioration, additional tests may be performed at the discretion of the Investigator.
- PK/PD sampling at or during crisis or deterioration Visit:
 - Collect 1 blood sample for PK, PD, and free C5 assays if no IP is administered.
 - If IP is administered at the visit for Clinical Deterioration, baseline and trough blood samples for PK, PD, free C5, and all samples for ADA will be taken 5 – 90 minutes before the IP infusion. Peak blood samples for PK, PD and free C5 testing will be taken at least 60 minutes after the completion of the IP infusion.
 - If the subject receives PE at the time of Clinical Deterioration, a supplemental dose of IP will be administered. Collect 3 blood samples for PK, PD, and free C5 at [1] 5 to 90 minutes before PE, [2] after PE and before IP infusion, and [3] at least 1 to 2 hours after completion of the IP infusion.
- IP administration:
 - Subject will continue IP administration in accordance with protocol specified IP administration schedule.
 - If the crisis or Clinical Deterioration Visit coincides with a regular visit per protocol, subject will receive the regular IP administration per protocol schedule.
 - If subjects undergo PE, a supplemental dose (2 vials IP) must be administered within 1 to 2 hours after each PE session unless the PE session is on the day of a scheduled IP infusion. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose instead of the

supplemental dose should be administered within 1 to 2 hours after the end of the PE.

- Contact the IXRS to obtain the study drug kit assignment.

7.3.8. Unscheduled Visit

Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments will be performed at the discretion of the Investigator. If an Unscheduled Visit is performed, any tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the eCRF.

7.3.9. Safety Follow-up Period (Post-Treatment +Week 8)

If a subject withdraws from the trial at any time and for any reason after receiving any amount of IP, a follow-up visit for safety assessment is required at 8 weeks after the last dose of IP.

Subjects who transition to treatment with the commercially available eculizumab directly from the extension trial will not be required to complete a Follow-up Visit. The following tests and procedures will be completed at the follow-up visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR.
- Record any new medications or changes to concomitant medications (including non-drug therapies).
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Determine if the subject needs *N. meningitidis* re-vaccination. Re-vaccinate as needed to provide active coverage as specified by the vaccine manufacturer or according to current medical/country guidelines.
- Administer MG-ADL by a properly trained evaluator and preferably by the same evaluator throughout the trial. The recall period is the preceding 7 days.
- Administer MG-QOL15 questionnaire to evaluate quality of life.
- Assess change from baseline in the MGFA-PIS ([Appendix 8](#)). The MGFA-PIS must be performed by the PI or the same neurologist throughout the trial.
- Administer clinical assessments QMG and MGC; these shall be performed at approximately the same time of day, by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Seek consent from patients to allow the Sponsor to collect information concerning their post-treatment MG status for up to 1 year from the EOS/ET visit (refer to [Section 7.1.3.2](#), [Section 7.3.6](#), and [Appendix 11](#)). An updated ICF (and/or ICF Addendum) will be provided to all patients. The updated ICF (and/or ICF Addendum)

will also be provided to discontinued patients, subject to IRB/IEC approval ([Appendix 11](#)).

If a subject is discontinued due to an AE, the AE will be followed until it is resolved or, in the opinion of the PI, is determined medically stable.

7.3.10. Post-Treatment Follow-up Period (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 EOS/ET visit (refer to [Section 7.1.3.2](#), [Section 7.3.6](#), and [Appendix 11](#)).

7.4. Number of Subjects

This trial is an extension to the ECU-MG-301 trial. Approximately 92 subjects with refractory gMG will be enrolled in the ECU-MG-301 trial at approximately 100 centers. Subjects who complete the ECU-MG-301 trial may potentially enter this extension trial.

7.5. Treatment Assignment

In order to maintain the blind of the ECU-MG-301 trial, all subjects will undergo a 4-week blinded induction treatment period. During this Blind Induction Phase, subjects will receive weekly blinded treatment (eculizumab or placebo or eculizumab plus placebo) for 4 weeks based upon the treatment received in the ECU-MG-301 trial (refer to [Table 10](#) in [Section 9.1](#)).

During the Open-Label Maintenance Phase, all subjects will receive 4 vials (1200 mg) eculizumab every 2 weeks from Visit 5 and onward throughout the trial.

Study drug kit assignments will be provided by the IXRS during the Blind Induction and Open-Label Maintenance Phases.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Subject completed the ECU-MG-301 trial.
2. Subject has given written informed consent.
3. Subject is willing and able to comply with the protocol requirements for the duration of the trial.
4. Female subjects of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). All subjects (female and male) must practice an effective, reliable and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment.

8.2. Subject Exclusion Criteria

1. Subjects who withdrew from the ECU-MG-301 trial as a result of an AE related to trial drug.
2. Female subjects who are pregnant, breastfeeding, or intend to conceive during the course of the trial.
3. Unresolved meningococcal infection.
4. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
5. Any medical condition or circumstances that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, pose any added risk for the subject, or confound the assessment of the subjects.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal of Subjects from the Trial

Subjects may withdraw consent for study participation or assessment of post-treatment MG status at any time. Every effort should be made to ensure subjects are willing to comply with trial participation prior to conducting the screening procedures. The subjects should be fully informed of the restrictions related to the change of concomitant medications during the trial. Investigators may choose to discontinue a subject's treatment because of AEs, as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the subject's safety or well-being. The study staff should notify the Sponsor and their site monitor of all trial withdrawals as soon as possible.

Reproduction and development studies with eculizumab have not been performed; therefore, eculizumab should not be administered to pregnant women. At the time of the last follow-up visit, all subjects of childbearing potential must continue to use adequate contraception for up to 5 months following discontinuation of eculizumab treatment. If a subject becomes pregnant, the IP must be immediately discontinued and the Sponsor must be notified. Each pregnancy will be followed to term and the Sponsor notified regarding the outcome.

8.3.2. Handling of Withdrawals

When a subject withdraws or is withdrawn from the trial, the Investigator shall record the withdrawal reason(s) in the source documents and in the eCRF. Whenever possible, all subjects who prematurely withdraw from the trial will undergo all assessments at the ET visit per the Schedule of Assessments (Table 7).

A follow-up visit for safety assessment is required at 8 weeks (± 2 days) after the last dose of IP administration (Table 9).

If a subject is discontinued due to an AE, the event will be followed until it is resolved or, in the opinion of the Investigator, the subject is determined to be medically stable. Every effort will be made to undertake protocol-specified safety follow-up procedures.

Subjects who fail to return for final assessments will be contacted by the site study staff and reminded of the requirement for follow-up. As it is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE, follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the subject's last known address. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

8.3.3. Sponsor's Termination of Trial

The Sponsor or a regulatory authority may discontinue the trial at any time for any reason including, for example, clinical or administrative reasons.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Product

Eculizumab (900 mg or 1200 mg) or matching placebo (only during the Blind Induction Phase) will be administered intravenously over approximately 35 minutes (range of 25 to 45 minutes).

Blind Induction Phase

To maintain the blind of ECU-MG-301, all subjects will undergo a Blind Induction Phase. During the Blind Induction Phase, IP will be administered weekly (7 days \pm 2) according to the regimen in [Table 10](#):

Table 10: Treatment Assignment during the Blind Induction Phase

Blind Induction Phase	Eculizumab Amount during Blind Induction Phase	Equivalent Eculizumab Dose	Visits
Subjects from ECU-MG-301 Trial Eculizumab arm	4 vials of eculizumab (300 mg/vial)	1200 mg	1 and 3
	4 vials of placebo	0 mg	2 and 4
Subjects from ECU-MG-301 Trial Placebo arm	3 vials of eculizumab (300 mg/vial) plus 1 vial placebo	900 mg	1 through 4

Open-Label Maintenance Phase

During the Open-Label Maintenance Phase, all subjects will receive 4 vials eculizumab (1200 mg) every 2 weeks (14 days \pm 2) starting with Visit 5 and continuing throughout the trial.

Supplemental Doses

If a subject undergoes PE for Clinical Deterioration during the Study Period, a supplemental dose of 2 vials of IP (600 mg of eculizumab) must be administered within 1 to 2 hours after each PE session, unless the PE session is on the day of a scheduled IP infusion. If the PE is on the day of a scheduled IP infusion, the scheduled dose of IP (instead of the supplemental dose) should be administered. In addition, subjects are to continue eculizumab infusion according to the protocol specified dosing regimen.

9.2. Concomitant Medications

9.2.1. Allowed Medications

9.2.1.1. Palliative and Supportive Care

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

The following medications are allowed under certain circumstances and restrictions.

9.2.1.1.1. Cholinesterase Inhibitors

Cholinesterase inhibitor treatment must be withheld for at least 10 hours prior to any efficacy measurements (ie, QMG and MGC). Cholinesterase inhibitor therapy dose/schedule changes will be permitted due to intolerance or if medically indicated, at the discretion of the Investigator. Any changes in cholinesterase inhibitor will be recorded on the concomitant medication eCRF.

9.2.1.1.2. Immunosuppressive Agents

- Immunosuppressive agents, eg, corticosteroid, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), tacrolimus, cyclosporine, or cyclophosphamide at the appropriate dose level to be used for an individual subject will be permitted at the discretion of the Investigator.

Immunosuppressant therapy dose/schedule changes will be permitted due to intolerance or if medically indicated, at the discretion of the Investigator. Reductions in IST dosing should be performed slowly, and preferably only after the subject has been in the extension study for at least 12 weeks. Any changes in IST will be recorded on the concomitant medication eCRF.

- High dose steroid as an On-Trial Rescue Therapy should be reserved for subjects that experience Clinical Deterioration as defined by this protocol. The rescue therapy used for a particular subject will be at the discretion of the Investigator. Every effort should be made to notify the Sponsor within 24 hours should a subject require a rescue therapy.

9.2.1.1.3. Plasma Exchange / Plasmapheresis / IVIg

- Plasma Exchange or IVIg will be allowed as On-Trial Rescue Therapy for subjects that experience a Clinical Deterioration as defined by this protocol. The rescue therapy used for a particular subject will be at the discretion of the Investigator.
- Every effort should be made to notify the Sponsor within 24 hours should a subject require a rescue therapy. Routine use of Plasma Exchange or IVIg as maintenance therapy to control MG symptoms outside of rescue is not permitted.
- If PE is administered, supplemental IP (2 vials) will be administered within 1 to 2 hours after the end of each PE session unless the PE session is on the day of a scheduled IP infusion. Routine (per protocol schedule) IP administration will be continued per the specified dose-administration schedule for the subject (refer to appropriate Schedule of Assessments in [Section 7.1](#)). If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose (instead of the supplemental dose) should be administered within 1 to 2 hours after the end of the PE session.

9.2.2. Disallowed Medications

The use of rituximab is prohibited during the trial.

9.3. Treatment Compliance

The infusion of IP into subjects will be under the supervision of the Investigator or their designee to ensure that the subject received the appropriate dose at the appropriate time-points during the trial.

Subjects who fail to return for a scheduled visit within the acceptable intervals must be contacted by the site study staff to determine the reason for missing the appointment. Instructions for handling of missing visits are provided in [Section 7.3](#).

9.4. Randomization

To preserve the blinded nature of the ECU-MG-301 trial, all subjects must undergo a 4-week Blind Induction Phase prior to entering the open-label phase of this trial. Subjects who had been randomized to the placebo arm in the ECU-MG-301 trial will receive 4 vials of IP (3 vials/900 mg eculizumab plus 1 vial placebo) every week at Visits 1 through 4. Subjects who were randomized to the eculizumab arm in the ECU-MG-301 trial will receive 4 vials IP (1200 mg eculizumab) every 2 weeks at Visits 1 and 3 and placebo at Visits 2 and 4.

During the Open-Label Maintenance Phase, all subjects will receive open-label eculizumab (4 vials/1200 mg) every other week starting with Visit 5 and continuing throughout the trial.

The patient identification number and study drug kits assignment will be provided by the IXRS.

9.5. Blinding and Unblinding

All patients will receive eculizumab in this study, including during the 4-week Blind Induction Phase (Visits 1 to 4), and during the Open-Label Maintenance Phase (Visits 5 to 107).

During the Blind Induction Phase, all patients, investigational site personnel, Sponsor staff, Sponsor designees, and all staff directly associated with the conduct of the trial will be blinded to the subject treatment assignments. The double-blind will be maintained by using identical IP kits and labels for eculizumab and placebo. The placebo will have an identical appearance to that of eculizumab.

There is no antidote to reverse the effects of eculizumab; therefore unblinding would not be helpful in the planning of patient treatment for a given event. Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the patient's treatment allocation using IXRS. The Investigator must note the date, time and reason for unblinding.

The Investigator should inform the Sponsor that the patient was unblinded, however they are not required to reveal to the Sponsor the patients' treatment allocation.

When an AE is an unexpected related SAE, the blind will be broken by the Sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees, and/or IRBs.

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

After the Blind Induction Phase, the remainder of the study is open-label; therefore, unblinding is not applicable.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Each vial of IP contains eculizumab 300 mg or matching placebo (used only during Blind Induction Phase) for IV administration.

10.2. Investigational Product Packaging and Labeling

The active IP, eculizumab, is manufactured and supplied by Alexion in single 30 mL vials as a solution concentration of 10 mg/mL. The placebo is manufactured by Alexion Pharmaceuticals, Inc. as a matching sterile, clear, colorless solution in an identical 30-mL vial and without active ingredient but with the same buffer components as eculizumab.

All IP will be prepared in vials, packaged in kits, and labeled at Almac Clinical Services in an identical manner. Almac Clinical Services or its affiliate will ship the IP and release to each participating trial center upon receipt of all required essential documents based upon federal, state, and local regulations.

Table 11 provides detailed information for both eculizumab and the placebo. For additional information on eculizumab, refer to the current IB.

Table 11: Investigational Product

	Investigational Product	
Product Name	Eculizumab	Placebo
Dosage Form	Concentrated solution for infusion	Solution for infusion
Unit Dose	300 mg	0 mg
Route of Administration	Intravenous infusion	Intravenous infusion
Physical Description	30 mL vial	30 mL vial
Manufacturer	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.

10.3. Investigational Product Storage

IP will be released to the site upon receipt of all required essential documents based upon federal, state, and local regulations. Each kit will have a 1-panel label describing the contents and a place for the pharmacist to record the subject number and initials.

Upon arrival at the center, the IP should be promptly removed from the shipping cooler and stored in refrigerated conditions at 2 to 8°C in the original package in order to protect from light. The pharmacist should immediately record the reception of the IP in IXRS and notify the distributor and Sponsor if vials are damaged and/or if temperature excursions have occurred during transportation (please refer to the Pharmacy Manual for detailed instructions). IP must be stored in a secure, limited-access storage area with controlled temperature. Temperature must be recorded on a daily basis.

Diluted solutions of IP are stable for 24 hours at 2 to 8°C (36 to 46°F) and at room temperature. The 24 hours start from the time of IP preparation until the end of infusion.

10.4. Investigational Product Preparation

Infusions of IP should be prepared using aseptic technique. Each vial of IP contains 300 mg of active ingredient in 30 mL of product solution or matching placebo.

Withdraw the required volume of IP from the vials. Transfer the recommended dose to an infusion bag. Dilute the IP by addition to the infusion bag of the appropriate amount (equal volume) of 1 of the following: 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 diluted IP solution is 240 mL for 900 mg doses (3 vials eculizumab plus 1 vial placebo) and 1200 mg doses (4 vials eculizumab), and 120 mL for 600 mg doses (2 vials eculizumab) (Table 12).

Table 12: Investigational Product Reconstitution

Trial Phase	IP	Volume of IP	Volume of Diluent ¹	Total Volume of Administration
Blind Induction Phase	900 mg (3 vials) eculizumab plus 1 vial placebo	90 mL 30 mL	90 mL 30 mL	240 mL
	1200 mg (4 vials) eculizumab	120 mL	120 mL	240 mL
Maintenance Phase	1200 mg (4 vials) eculizumab	120 mL	120 mL	240 mL
Supplemental Dose²	600 mg (2 vials) eculizumab	60 mL	60 mL	120 mL

¹ Use one of the following diluents: (a) 0.9% sodium chloride; (b) 0.45% sodium chloride; (c) 5% dextrose in water; (d) Ringer's injection.

² Supplemental dose that is not administered on a scheduled visit.

Gently agitate the infusion bag containing the diluted IP 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.

Refer to the Pharmacy Manual for additional information.

10.5. Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION

IP should only be administered via IV infusion; the infusion will be administered after completion of all other tests and procedures (excluding the peak blood sampling for PK/PD and free C5 assay). Prior to 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 IP should be intravenously administered over approximately 35 minutes (range of 25 to 45 minutes). It is not necessary to protect the infusion bags from light while IP is being administered to the subject. At the site's discretion, the diluted IP may be administered via gravity feed, a syringe-type pump, or an infusion pump. The subjects will be monitored for at least 1 hour following infusion.

If an AE occurs during the administration of the IP, 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. The AE must be captured in the subject's source document and eCRF.

10.6. Investigational Product Accountability

When an IP 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 trial monitor. A signed copy should be faxed to the contact provided on the packing list and the duplicate copy kept in the pharmacy binder. Additionally, reception of IP (as well as reception conditions) must be reported to the IXRS system to allow drug randomization, resupply, estimations, and drug expiration control.

Accountability logs and Inventory logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the IP. During the trial, the following information must be noted in the accountability log: the subject number(s), initials of subject(s) to whom drug is dispensed, kit number, the date(s) and time that the IP is prepared and dispensed, and the initials of the pharmacist or designee who prepared the IP. Sites should keep a running total of their drug supply. Empty vials and vials with residual materials should be kept for inspection and accountability by the trial monitor prior to their destruction and handled per local site pharmacy standard operating procedures for clinical IPs. Destruction of used and unused vials, either locally or centrally, must be properly documented.

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

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

Refer to the Pharmacy Manual for additional information.

10.7. Investigational Product Handling and Disposal

At the completion of the trial, in order to satisfy regulatory requirements regarding IP accountability, all remaining IP inventory will be reconciled and retained, returned, or destroyed according to applicable provincial and federal regulations.

11. ASSESSMENT OF EFFICACY

This extension trial is designed to provide the subjects who have participated in the ECU-MG-301 trial with an opportunity to receive eculizumab and to collect clinical data that will provide long term safety and tolerability information on eculizumab. Efficacy is a secondary objective of this trial. The long-term efficacy of eculizumab in subjects with refractory gMG will be measured by the improvement in the MG-ADL total score. Duration of treatment commences with the first infusion of IP (eculizumab). The Schedule of Assessments (refer to [Section 7.2](#)) defines the 4-year trial time period and assessments for the study efficacy endpoints. Efficacy will be assessed comparing eculizumab outcomes to placebo outcomes in the protocol ECU-MG-301. Statistical analyses of the efficacy endpoints are summarized in [Section 15](#) and described in more detail in the Statistical Analysis Plan (SAP). For all scales noted below except the EuroQOL Visual Analog Scale (EQ-VAS) and MGFA PIS, the higher the score the greater the impairment.

11.1. Efficacy Endpoints

The primary efficacy endpoint is the change from baseline in the MG-ADL total score. The secondary efficacy endpoints include:

1. Change from baseline in QMG total score
2. Proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline and with no rescue therapy
3. Proportion of subjects with at least a 5-point reduction in the QMG total score from baseline and with no rescue therapy
4. Change from baseline in the Myasthenia Gravis Composite (MGC) scale total score
5. Change from baseline in MG-QOL-15

The tertiary efficacy endpoints for this trial include:

1. Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from baseline)
2. Change from baseline in Neuro- QOL Fatigue
3. Change from baseline in EQ-5D
4. Change from baseline in the MG-ADL individual items and sub-categories for the bulbar (items 1, 2, and 3), respiratory (item 4), limb (items 5 and 6) and ocular (items 7 and 8) in subjects with abnormal baseline scores for the particular item or sub-categories

11.2. MG Activities of Daily Living Profile (MG-ADL)

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of ADL in MG subjects (refer to [Appendix 2](#)). 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. MG-ADL will be performed by a properly trained evaluator at the protocol specified time points and preferably by the same evaluator each time throughout the study.

11.3. QMG Scoring System

The current 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 (refer to [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 (Benatar 2012). The QMG shall be administered at approximately the same time of day throughout the study by a properly trained evaluator at the protocol specified time points and preferably by the same evaluator each time throughout the study.

11.4. MGC Score

The MGC is a validated assessment tool for measuring clinical status of subjects with MG (Burns 2011). The MGC assesses 10 important functional areas most frequently affected by MG: ocular (2 items), facial (1 item), bulbar (3 items), respiratory (1 item), axial (1 item), and gross motor (2 items) (refer to [Appendix 7](#)). The scales are weighted for clinical significance that incorporates subject-reported outcomes. Higher scores indicate more functional impairment. The range of total MGC score is 0 to 50. The MGC shall be administered at approximately the same time of day throughout the study by a properly trained evaluator at the protocol specified time points and preferably by the same evaluator each time throughout the study.

11.5. Quality of Life Assessments

11.5.1. MG-QOL 15

The 15-item Myasthenia Gravis Quality of Life scale (MG-QOL 15; refer to [Appendix 3](#)) is a health-related quality of life evaluative instrument specific to subjects with MG. MG-QOL 15 was designed to provide information about subjects' perception of impairment and disability and the degree to which disease manifestations are tolerated and to be easy to administer and interpret (Burns 2011). The MG-QOL 15 will be completed by the subject. Higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction.

11.5.2. Neuro-QOL Fatigue

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue, completed by the subject (Cella 2010). Higher scores indicate greater fatigue and greater impact of MG on activities (refer to [Appendix 4](#)).

11.5.3. EUROQOL

The EQ-5D is a reliable and validated survey of health status in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, completed by the subject (Szende 2004) .

Each area has 3 levels: Level 1 (no problems), Level 2 (some problems), and Level 3 (extreme problems; refer to [Appendix 10](#)). The EQ VAS records the subject's self-rated health on a vertical, 20 cm visual analogue scale where the endpoints are labeled "best imaginable health state," marked as 100 and "worst imaginable health state," marked as 0.

11.6. Other Efficacy Assessments

11.6.1. Negative Inspiratory Force (NIF) and Forced Vital Capacity (FVC)

Subjects with increasingly severe MG can suffer from potentially fatal respiratory complications including profound respiratory muscle weakness. Respiratory function is monitored closely for evidence of respiratory failure in MG subjects and ventilator support is recommended in the event of consistent declines in serial measurements of FVC or NIF, loss of upper airway integrity (difficulty handling oral secretions, swallowing, or speaking) or in the setting of emerging respiratory failure. FVC as one of the test items in QMG will be performed when QMG is performed. NIF is to be performed using the NIF Meter.

11.6.2. MGFA 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 Minimal Manifestation (MM) and Pharmacological Remission (PR) will be assessed and recorded by the PI or the same neurologist skilled in the evaluation of MG subjects throughout the trial. The sub-scores of MM (ie, MM-0, MM-1, and MM-3) will not be used in this protocol. For the purposes of assessing MGFA-PIS status in this study, Baseline is defined as the pre-treatment baseline of ECU-MG-301.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Vital Signs

Vital signs will be measured at every visit and will include assessments of systolic and diastolic BP, temperature, RR, and HR. Vital signs will be obtained after the subject has been supine or seated for at least 5 minutes. Ideally, each subject's BP should be measured using the same arm. Systolic and diastolic BPs will be documented in mmHg. Temperature will be obtained in degrees Celsius or Fahrenheit. HR will be documented in beats per minute.

12.1.2. Weight

Body weight will be measured in pounds or kilograms. Body weight will be measured at Visits 1, 16, 29, 55, 81, and 107 or ET Visit.

12.1.3. Physical Examination

A complete physical examination will be performed at Visit 16. The complete physical examination will include assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and general neurologic examination. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff.

12.1.4. Electrocardiogram

A 12-lead ECG will be conducted at Visits 1, 16, 29, 55, 81, and 107 or ET Visit. 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 Sponsor to discuss the subject's continued eligibility to participate in this protocol.

12.1.5. Laboratory Assessments

Subjects will have biologic samples collected for analysis of various parameters according to the Schedule of Assessments (refer to [Section 7.2](#)). The central laboratory will supply established or generally acknowledged methods, normal reference ranges, and shipping instructions.

Chemistry panel, complete blood count and hemolytic markers, renal function measures, and serum pregnancy test (refer to [Appendix 5](#) for details) will be prepared and shipped according to the instructions in the laboratory manual to the central laboratory. Samples will be analyzed at the central laboratory. Routine hematology laboratory assessment, including complete blood count (CBC), will be performed at various time points as specified by the protocol and should be reviewed as soon as the laboratory result is available.

Blood samples for PK, PD, free C5, and blood samples for ADA analysis will be prepared and shipped according to the instructions in the laboratory manual to the central laboratory. Sample analysis will be conducted by the Sponsor or Sponsor's designee.

Samples for AChR Abs test will be prepared and shipped according to the instructions in the laboratory manual. Sample analysis will be conducted at the central laboratory.

Any clinically significant, abnormal laboratory result is to be reported as an AE.

12.1.6. Columbia-Suicidal Severity Rating Scale

The C-SSRS (Posner 2011) since Last Visit (refer to [Appendix 9](#)) will be performed by the Investigator or a trained designee according to the Schedule of Assessments (refer to [Section 7.2](#)). The "since last visit" period refers to the last visit the C-SSRS was administered. This is to ensure that subjects who are experiencing suicidal ideation or behavior are properly recognized and adequately managed or referred for further evaluation.

12.2. Adverse Events

12.2.1. Detection of Adverse Events

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

Adverse Events reported by the subject and/or parent or legal guardian and/or 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 12.2.3](#).

12.2.2. Definition of an Adverse Event

Adverse event means any untoward medical occurrence in a subject or clinical trial subject 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.

The definition of AE also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Situations where an untoward medical occurrence did not occur (social and/or convenience 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.

12.2.2.1. Procedure

Elective procedures that were pre-planned 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 non-invasive) such as surgery or angiography should not be reported as an AE or Serious Adverse Event (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).

12.2.2.2. 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 trial
- Test result requires significant additional treatment (ie, addition of new medication, significant increase in dose of current medication)

12.2.2.3. Lack of Efficacy

Since eculizumab treatment in subjects with refractory gMG is not an approved indication, lack of efficacy need not be reported as an AE.

12.2.2.4. Events of Interest (EOI)

Events of Interest (EOI) will be identified by the Sponsor during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from the trial, will be classified as EOIs. For each EOI, a narrative may be written and included in the Clinical Study Report.

12.2.3. Recording Adverse Events

All observed or volunteered AEs regardless of causal relationship must be recorded and reported as described in the [Section 12.2.7](#).

As this is an extension to the ECU-MG-301 trial, subjects may sign the ICF for the extension trial while still enrolled in the ECU-MG-301 trial. AEs with an onset date before Study Day 1 of ECU-MG-302 will be recorded in the eCRF of the ECU-MG-301 trial regardless of when the subject signed the ICF for the ECU-MG-302 trial. Any ongoing AEs at the time of Study Day 1 of the ECU-MG-302 trial will be recorded in the ECU-MG-302 eCRF (since this will be done automatically by the system, sites will not be required to record these data twice). AEs with an end date before Study Day 1 of ECU-MG-302 will be recorded only on the ECU-MG-301 CRF.

For all AEs the investigator must obtain adequate information for the following: 1) determine the outcome of the AE; 2) determine if the event meets criteria for a SAE; 3) assess the severity of the AE; and 4) determine the causality of the AE. For all AEs regardless of casual relationships the instigator must follow-up on the outcome of the event until the event or sequelae either resolve or stabilize.

AEs spontaneously reported by the subject, and/or parent or legal guardian and/or identified in response to an open-ended question from study personnel, or revealed by observation will be recorded during the study period by the Investigator. AE information will be collected from the signing of informed consent until 8 weeks after the last dose of IP (safety follow-up visit). No time limit exists on reporting SAEs that are thought to be causally related to the IP.

AEs must be documented in clear, unambiguous medical terms. Study personnel are advised not to use abbreviations or acronyms.

For each AE record only the diagnosis on the AE page of eCRF, do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available record each sign and symptom as an AE, when a diagnosis becomes available, study personnel are to update the AE page of the eCRF with relevant diagnosis only.

All AEs that later increase in the frequency and or severity (medical and scientific judgment should be exercised by the Investigator) will be considered new AEs and will be recorded on a new line on the AE page or the eCRF.

Initial AE should be closed-out with an end date consistent with the date that the AE increased in frequency and/or severity and the new AE recorded on a new line of the AE page with onset date consistent with the date of increase in frequency and or severity.

If an AE is a chronic or long-term medical condition diagnosed during the study (eg, hypertension, diabetes), once the patient is medically stable and/or a treatment plan is in place for the condition, the AE should be closed out with the end date consistent with the patient's stability and/or the implementation of the treatment plan.

12.2.4. Serious Adverse Event and SAE Criteria

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 subject 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. Hospitalization (Requires inpatient hospitalization or prolongation of existing hospitalization, [AEs 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 and 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
4. Results in persistent or significant disability/incapacity
 5. Is a congenital anomaly/birth defect
 6. Is an important medical event

NOTE: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered SAEs. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.2.4.1. Severity Assessment

Adverse Event severity 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 subject'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 subject'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.

12.2.4.2. Causality Assessment

An Investigator causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) must be provided for all AEs, both serious and non-serious. This assessment must be recorded in the CRF and any additional SAE forms as appropriate. The definitions for the causality assessments appear below.

- Not related (unrelated): This relationship suggests that there is no association between the IP and the reported event.
- Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than the IP but attribution cannot be made with absolute certainty and a relationship between the IP and AE cannot be excluded with complete confidence.
- Possibly related: This relationship suggests that treatment with the IP may have caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the IP, but could also have been produced by other factors.
- Probably related: This relationship suggests that a reasonable temporal sequence of the event with the IP administration exists and the likely association of the event with the IP. This will be based upon the known pharmacological action of the IP, known or previously reported adverse reactions to the IP or class of drugs, or judgment based on the Investigator's clinical experience.
- Definitely related: Temporal relationship to the IP, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event, corresponds with the known pharmaceutical profile, improvement on discontinuation or re-appearance on re-challenge.

12.2.5. Expectedness Assessment of Serious Adverse Event

The expectedness of a SAE is determined by the sponsor in the reference safety information (RSI). The RSI for interventional studies is the Investigator's Brochure.

12.2.6. Outcome

If a subject experiences a 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 subject 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.

12.2.6.1. Exposure during Pregnancy and Lactation

Pregnancy data will be collected during this trial for all subjects.

For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and followed. Exposure during pregnancy also called exposure *in-utero* (EIU) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

If a subject within this trial or a subject's partner becomes or is found pregnant while treated or exposed to IP, the investigator must submit a pregnancy form to Alexion via the same method as SAE reporting. Pharmacovigilance will supply the Investigator with a copy of a "Pregnancy Reporting and Outcome Form / Breast Feeding." Pharmacovigilance must be notified via the same method as SAE reporting.

Exposure of an infant to an Alexion product during breastfeeding would need to be reported in the "Pregnancy Reporting and Outcome Form / Breast Feeding," and any AEs an infant may experience following breastfeeding needs to be reported to the Sponsor.

The subject or female partner should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the subject discontinued IP or discontinues from the trial. When the outcome of the pregnancy becomes known the form should be completed and returned to the Sponsor. If additional follow-up is required, the Investigator will be requested to provide the information.

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

12.2.7. Reporting of Adverse Event(s) & Serious Adverse Event(s) to Sponsor

All non-serious AEs must be recorded in the eCRF upon awareness.

All SAEs must be reported to the Sponsor immediately or within 24 hours of the investigator or the site staff becoming aware of the event, regardless of the presumed relationship to the IP. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via Email or fax to contact information provided below:

Email: PPD [REDACTED]

Fax: PPD [REDACTED]

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information.

Additional follow-up information, if required or available, should be faxed to the Sponsor within 24 hours of the investigator site or their staff becoming aware of this additional information via same contact information as above. Follow-up information should be recorded on a follow-up

SAE eCRF and placed with the original SAE information and kept with the appropriate section of the eCRF and/or trial file.

These reporting timelines need to be followed for all initial SAE cases and follow-up versions of the initial cases.

All SAEs (related and unrelated) will be recorded from the signing of ICF until 8 weeks following the end of treatment exposure (follow-up time required depending on half-life of IP following the last dose of IP).

If the event meets fatal or life threatening SAE criteria, the investigator should notify the Sponsor immediately.

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)
- Outcome of the serious event(s)
- Medical records and laboratory / diagnostic information

12.2.8. Sponsor Reporting Requirements

The sponsor or legal representative is responsible for notifying the relevant regulatory authorities of SAE's meeting the reporting criteria as per regional and local regulations.

12.2.9. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for study investigators. It is the PI's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13. ASSESSMENT OF BIOMARKER

13.1. MG Disease Biomarker

Blood samples for assay of the AChR Ab will be collected at specified time points.

14. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

The population PK analysis of eculizumab in subjects with gMG will be performed to assess the concentration of eculizumab versus time. PK parameters such as maximum concentration as well as trough and peak eculizumab concentration during the induction and maintenance treatment phases will be reported. Clearance and terminal half-life will be estimated. PD analysis will be performed to assess pre- and post-treatment serum hemolytic activity and therefore C5 complement activity inhibition. Free C5 concentration may also be measured.

15. STATISTICS

15.1. General Considerations

Analyses will be produced using the data from this trial alone (Extension Trial) as well as combined analyses that will include data from the ECU-MG-301 trial (Combined Trial Analyses). The analyses will include safety, efficacy, and PK/PD analyses. The SAP will cover both the standalone trial analyses and the combined ECU-MG-301 and ECU-MG-302 trial analyses.

Treatment groups will be indicated by eculizumab/eculizumab for the subjects originally randomized to the eculizumab arm in the ECU-MG-301 trial and placebo/eculizumab for the subjects originally randomized to the placebo arm in the ECU-MG-301 trial. The Extension Trial analyses will be presented by treatment group. The Combined Trial Analyses, where the data is aligned based on the subject's first dose date of eculizumab, will only be presented as 1 combined eculizumab treatment group since all subjects will have received eculizumab.

Baseline for the Extension Trial analyses is defined as the last available assessment prior to starting treatment with eculizumab in ECU-MG-302. Baseline for the Combined Trial Analyses is defined as the last available assessment prior to starting treatment with eculizumab (that is, either in the ECU-MG-301 for subjects who received eculizumab in the ECU-MG-301 trial or in the ECU-MG-302 trial for subjects who received placebo in the ECU-MG-301 trial). For the Combined Trial Analyses, the analysis visits will be determined counting the subject's first dose date (Day 1) with eculizumab regardless of the trial in which that first dose of eculizumab occurred and defining the visits based on this Day 1 going forward according to the schedule of assessments in both studies.

15.2. Determination of Sample Size

This is an extension trial to the ECU-MG-301 trial. Approximately 92 subjects will be enrolled in the ECU-MG-301 trial and may participate in this trial.

15.3. Analyses Sets

15.3.1. Full Analysis Set (FAS)

15.3.1.1. Extension FAS Population

The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all subjects who have received at least 1 dose of eculizumab in this extension trial and have a post-trial drug infusion efficacy assessment.

15.3.1.2. Combined FAS Population

The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all subjects who have received at least 1 dose of eculizumab in either ECU-MG-301 or ECU-MG-302 and have a post-trial drug infusion efficacy assessment.

15.3.2. Per Protocol Set

15.3.2.1. Extension Per-Protocol (PP) Population

The PP population is a subset of the Extension Trial FAS population, excluding subjects with major extension trial protocol deviations. The Extension Trial PP population will include all subjects who:

- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
- Subjects who took at least 80% of the required eculizumab doses during participation in the extension trial.

15.3.2.2. Combined PP Population

The Combined PP population is a subset of the Combined FAS population, excluding subjects with major protocol deviations from either the ECU-MG-301 or ECU-MG-302 trial. The Combined PP population will include all subjects who:

- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
- Subjects who took at least 80% of the required eculizumab doses during participation in ECU-MG-301 and ECU-MG-302 trials.

The Extension PP population as well as the Combined PP population will be determined prior to database lock.

15.3.3. Safety Set

Safety analyses will be performed on the Extension Safety Population from the ECU-MG-302 trial and the Combined Safety Population from both the ECU-MG-301 and ECU-MG-302 trials. The Extension Safety Population includes all subjects who receive at least 1 dose of eculizumab in the ECU-MG-302 trial. The Combined Safety Population includes all subjects who receive at least 1 dose of eculizumab in either the ECU-MG-301 or ECU-MG-302 trial.

15.3.4. Other Set

PK/PD analyses will be performed on the PK/PD Analysis Set. The PK/PD Analyses Set will include subjects who have PK/PD data assessments during this trial.

15.4. Subject Disposition and Treatment Compliance

The number of subjects treated, completing the trial, and included in the safety and efficacy analysis sets will be tabulated by counts and percentage of subjects combined. Reasons for any subject withdrawals will be provided.

Treatment compliance with IP will be summarized using descriptive statistics. The extra usage of IP for subjects who are treated with PE during the trial will be summarized and listings will be produced.

15.5. Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHO drug), the most current version available at the time of the analyses.

15.5.1. Extension Trial Analyses

Concomitant medications taken during the extension trial will be summarized by treatment group and overall. Changes in IST usage (ie, increases, decreases, switching ISTs, etc.) will be summarized by treatment group and overall. Prior and concomitant medications will be listed in subject listings.

15.5.2. Combined Trial Analyses

Concomitant medications taken during eculizumab treatment will be summarized.

15.6. Efficacy Analyses

Efficacy analyses will be performed on the Extension Trial FAS (Extension FAS) population as well as the Extension Trial Per-Protocol (Extension PP) population. In addition, efficacy analyses will be performed on the Combined FAS population as well as the Combined Per Protocol (Combined PP) population from the combined ECU-MG-301 trial and this Extension trial.

15.6.1. Primary Efficacy Analyses

15.6.1.1. Extension Trial Analyses

The primary efficacy endpoint is the change from baseline in the MG-ADL total score. The primary analysis for the change from baseline in MG-ADL total score at a particular visit will be based on the repeated measures models with effects for baseline MG-ADL and visit. Since the subjects randomized to eculizumab in the ECU-MG-301 study would have already received 26 weeks of eculizumab treatment, a separate repeated measures model will be fit for the two treatment arms: placebo/eculizumab and eculizumab/eculizumab. Confidence intervals and p-values will be presented by treatment group and visit. Graphical displays over time by treatment group will be produced. Missing primary endpoint assessments will not be imputed.

15.6.1.2. Combined Trial Analyses

The primary efficacy endpoint is change from baseline in the MG-ADL total score. The primary analysis for the change from baseline in MG-ADL total score at a particular visit will be based on the repeated measures model with effects for baseline MG-ADL and visit. Confidence intervals and p-values will be presented by visit. Graphical displays over time will be produced. Missing primary endpoint assessments will not be imputed.

15.6.2. Secondary Efficacy Analyses

The secondary efficacy endpoints are:

1. Change from baseline in QMG total score.

2. Proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline and with no rescue therapy.
3. Proportion of subjects with at least a 5-point reduction in the QMG total score from baseline and with no rescue therapy.
4. Change from baseline in the Myasthenia Gravis Composite (MGC) score.
5. Change from baseline in MG-QOL15.

15.6.2.1. Extension Trial Analyses

The secondary endpoints that involve changes from baseline will be analyzed at a particular visit based on the repeated measures models with effects for the particular baseline covariate and visit. Since the subjects randomized to eculizumab in the ECU-MG-301 study would have already received 26 weeks of eculizumab treatment, a separate repeated measures model will be fit for the two treatment arms: placebo/eculizumab and eculizumab/eculizumab. Confidence intervals and p-values will be presented by treatment group and visit. Graphical displays over time will be produced by treatment group and visit. Missing secondary endpoint assessments will not be imputed.

The proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline with no rescue therapy will be summarized at each visit for the placebo/eculizumab treatment group. Confidence intervals and p-values will be presented. Summaries of the number and percentage of subjects that improve, remain the same, or worsen in regard to MG-ADL assessments over time will be produced by treatment group as specified in the SAP. Graphical displays over time maybe produced by treatment group.

The proportion of subjects with at least a 5-point reduction in the QMG total score from baseline with no rescue therapy will be summarized at each visit for the placebo/eculizumab treatment group. Confidence intervals and p-values will be presented. Summaries of the number and percentage of subjects that improve, remain the same, or worsen in regard to QMG assessments over time will be produced by treatment group as specified in the SAP. Graphical displays over time may be produced by treatment group.

15.6.2.2. Combined Trial Analyses

The secondary endpoints that involve changes from baseline will be analyzed at a particular visit based on the 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. Missing secondary endpoint assessments will not be imputed.

The proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline with no rescue therapy will be summarized at each visit. Confidence intervals and p-values will be presented. Summaries of the number and percentage of subjects that improve, remain the same, or worsen in regard to MG-ADL assessments over time will be produced as specified in the SAP. Graphical displays over time may be produced.

The proportion of subjects with at least a 5-point reduction in the QMG total score from baseline with no rescue therapy will be summarized at each visit. Confidence intervals and p-values will be presented. Summaries of the number and percentage of subjects that improve, remain the

same, or worsen in regard to QMG assessments over time will be produced as specified in the SAP. Graphical displays over time maybe produced.

15.6.3. Tertiary Efficacy Analyses

The tertiary efficacy endpoints are:

1. Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from baseline).
2. Change from baseline in Neuro-QOL Fatigue.
3. Change from baseline in EQ-5D.
4. Change from baseline in the MG-ADL individual items and change from baseline in the MG-ADL sub-categories for the bulbar (items 1, 2 and 3), respiratory (item 4), limb (items 5 and 6) and ocular (items 7 and 8) in subjects with abnormal baseline score for the particular item or sub-category.

15.6.3.1. Extension Trial Analyses

The time to response on the MG-ADL total score (3-point reduction in MG-ADL from baseline) will be summarized for the placebo/eculizumab treatment group. A Kaplan Meier curve will be produced.

The tertiary endpoints that involve changes from baseline will be analyzed at a particular visit based on the repeated measures models with effects for the particular baseline covariate and visit. Since the subjects randomized to ecolizumab in the ECU-MG-301 study would have already received 26 weeks of ecolizumab treatment, a separate repeated measures model will be fit for the two treatment arms: placebo/eculizumab and ecolizumab/eculizumab. Confidence intervals and p-values will be presented by treatment group and visit. Missing tertiary endpoint assessments will not be imputed.

A summary of subjects shifting from abnormal to normal or from normal to abnormal for NIF and FVC will be presented by treatment group and visit. A summary of subjects shifting from abnormal to normal or from normal to abnormal for particular MG-ADL individual items and sub-categories will be produced by treatment group and visit.

15.6.3.2. Combined Trial Analyses

The time to response on the MG-ADL total score (3-point reduction in MG-ADL from baseline) will be summarized. A Kaplan Meier curve will be produced.

The tertiary endpoints that involve changes from baseline will be analyzed at a particular visit based on the repeated measures model with effects for the particular baseline covariate and visit. Confidence intervals and p-values will be presented by visit. Missing tertiary endpoint assessments will not be imputed.

A summary of subjects shifting from abnormal to normal or from normal to abnormal for NIF and FVC will be presented. A summary of subjects shifting from abnormal to normal or from normal to abnormal for particular MG-ADL individual items and sub-categories will be produced.

15.7. Safety Analyses

Safety analyses will be performed on the Extension Safety Population and the Combined Safety Population from both studies. The Extension Safety Population includes all subjects who receive at least 1 dose of eculizumab in ECU-MG-302 trial. The Combined Safety Population includes all subjects who receive at least 1 dose of eculizumab in the ECU-MG-301 trial or ECU-MG-302 trial.

15.7.1. Physical Examinations and Vital Signs

Physical examinations will be summarized by visit. Vital signs (systolic and diastolic BP, temperature, and sitting or lying HR), weight and changes from baseline in vital signs (including weight) will be summarized by visit. Listings of physical examinations and vital signs will be produced.

15.7.2. Laboratory Assessments

15.7.2.1. Extension Trial Analyses

Changes from Baseline in laboratory assessments (chemistry and hematology) will be summarized by treatment group and overall. Shift tables (L [low], N [normal], H [high]) will be produced for clinical laboratory tests by treatment group and overall.

15.7.2.2. Combined Trial Analyses

Changes from Baseline in laboratory assessments (chemistry and hematology) will be summarized. Likewise, shift tables (L [low], N [normal], H [high]) will be produced for clinical laboratory tests.

15.7.3. AEs

15.7.3.1. Extension Trial Analyses

Onset of AEs on or after the first dose date for eculizumab will be summarized by incidence, preferred term, system organ class (SOC), seriousness, severity, and relationship to treatment by treatment group and overall.

15.7.3.2. Combined Trial Analyses

AEs that occurred on or after the first dose of eculizumab whether in the ECU-MG-301 or this extension trial (ECU-MG-302) will be summarized by incidence, preferred term, SOC, seriousness, severity, and relationship to treatment.

15.7.4. Columbia-Suicide Severity Rating Scale

Shift tables for the C-SSRS will be produced for the Extension Trial by treatment group and overall.

15.7.5. Other Safety Endpoints

Pregnancy tests will be summarized in subject listings. Electrocardiogram (ECG) data will be summarized for the Extension Trial by treatment group and overall.

15.8. PK/PD Analyses

Eculizumab concentrations, free C5 concentrations, and % hemolysis and immunogenicity as measured by ADA will be summarized in tabular form as well as a subject listing for both the Extension Trial and Combined Trial Analyses by treatment group and overall. A population PK and PK/PD analysis may be conducted based on the adequacy of the PK and PD data.

15.8.1. Biomarker Analysis

Changes from baseline in AChR Ab will be summarized and subject listings for the MG disease biomarker data will be created.

15.9. Other Statistical Issues

15.9.1. Significance Levels

All hypothesis testing will be two-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect on efficacy parameters will be accompanied by two-sided 95% confidence intervals for the effect size.

15.9.2. Missing or Invalid Data

For efficacy and safety analyses, missing post-baseline efficacy and safety data will not be imputed unless indicated in the described analyses in the SAP.

15.9.3. Interim Analyses

Interim statistical analyses for safety and the primary and secondary efficacy endpoints may be performed at the discretion of the Sponsor. All analyses will be prospectively defined in the statistical analysis plan. The final statistical analyses will be performed after the study ends and the database has been locked.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Trial Monitoring

Before an investigational site can enter a subject into the trial, a representative of Alexion Pharmaceuticals, Inc. or its designee will visit the investigational trial 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 its designee or its representatives. This will be documented in a Clinical Trial Agreement between the Sponsor or its designee and the Investigator.

During the trial, the Sponsor, its designee or representative will have regular contacts with the investigational site, for the following:

- 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 CRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the trial. This will require direct access to all original records for each subject (for example, 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 CRFs 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.

16.2. Audits and Inspections

Authorized representatives of the Sponsor or designee, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all trial-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 designee immediately if contacted by a regulatory agency about an inspection.

16.3. Institutional Review Board / Independent Ethics Committee

The PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this trial including the subject ICF and recruitment materials must be maintained by the Investigator and made available for inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Please refer to [Section 16.2](#) for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final trial 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 designee before he or she can enroll any subject into the trial.

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 written information to be provided to subjects for the trial. The protocol must be re-approved 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 or IEC with reports of any reportable serious adverse drug reactions from any other trial conducted with the IP. The Sponsor 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.

18.2. Ethical Conduct of the Study

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

18.3. Written Informed Consent

The PI(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any trial procedures.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

The Sponsor or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, subject charts and trial source documents, and other records relative to trial conduct.

19.2. Retention of Records

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

The PI must maintain all documentation relating to the trial 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 designee or the Regulatory Authority to review any documentation relating to the trial, the Investigator must permit access to such records.

20. LIST OF REFERENCES

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Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. *J Clin Invest*. 2006 Nov;116(11):2843-2854.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011 Dec;168(12):1266-1277.

Szende A, Williams A. Measuring Self-Reported Population Health: An International Perspective based on EQ-5D. 2004. Ref Type: Online Source

Vincent A, Drachman DB. Myasthenia gravis. *Adv Neurol*. 2002;88:159-188.

APPENDIX 1. QUANTITATIVE MYASTHENIA GRAVIS (QMG) SCORE FOR DISEASE SEVERITY

QUANTITATIVE MYASTHENIA GRAVIS TESTING FORM

Patient Name: _____ Patient #: _____ Date: _____
 MR#: _____ DOB: _____ Sex: ____ Ht.(in): _____ Wt.(kg): _____
 Evaluator: _____ Handedness: _____ Leggedness: _____ Time of Exam: _____
 Anticholinesterase Medication: _____
 Comments: _____

<u>TEST ITEMS WEAKNESS</u>	<u>NONE</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>SCORE</u>
GRADE	0	1	2	3	
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze) Sec.	60	11-59	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 following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Forced vital capacity	≥80%	65-79%	50-64%	<50%	
Rt hand grip: male (Kg) : female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4	
Left hand grip: male (Kg) : female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4	
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	
Right leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	
Left leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	

TOTAL MG SCORE: _____

APPENDIX 2. MG ACTIVITY 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 3. MYASTHENIA GRAVIS QUALITY-OF-LIFE (MG-QOL 15)

Patient and date

Please indicate how true each statement has been (over the past four weeks).

1. I am frustrated by my condition
2. I have trouble using my eyes
3. I have trouble eating
4. I have limited my social activity because of my condition
5. My condition limits my ability to enjoy hobbies and fun activities
6. I have trouble meeting the needs of my family
7. I have to make plans around my condition
8. My occupational skills and job status have been negatively affected
9. I have difficulty speaking
10. I have trouble driving
11. I am depressed about my condition
12. I have trouble walking
13. I have trouble getting around public places
14. I feel overwhelmed by my condition
15. I have trouble performing my personal grooming needs

Not at all	A little bit	Some-what	Quite a bit	Very much
0	1	2	3	4

Myasthenia Gravis Quality-of-Life
"MG-QOL15"
Burns TM, et al., Muscle and Nerve 2008

Total MG-QOL15 score

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APPENDIX 4. NEURO-QOL FATIGUE

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

	In the past 7 days ...	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG11	I felt that I had no energy.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG15	I felt fatigued.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG06	I was too tired to do my household chores.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG07	I was too tired to leave the house.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG14	I felt tired.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG02	I had to limit my social activity because I was tired.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG01	I needed help doing my usual activities because of my fatigue.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG03	I needed to sleep during the day.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG04	I had trouble starting things because I was too tired.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG05	I had trouble finishing things because I was too tired.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG08	I was too tired to take a short walk.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG09	I was too tired to eat.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG12	I was so tired that I needed to rest during the day.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG16	I felt weak all over.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG17	I needed help doing my usual activities because of weakness.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG18	I had to limit my social activity because I was physically weak.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
NQFTG20	I had to force myself to get up and do things because I was physically too weak.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

APPENDIX 5. SUMMARY OF LABORATORY PANELS AND TESTS

Chemistry Panel	Other
Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Alkaline phosphatase Alanine amino transferase (ALT) Aspartate amino transferase (AST) Total bilirubin Albumin Total protein Uric acid	Anti-drug antibody (ADA) Human Chorionic Gonadotropin (β -HCG) Anti-AChR Antibody Pharmacokinetics (PK) Pharmacodynamics (PD) Free C5
Complete Blood Count (CBC) & Differential	
White blood cell count (WBC) White blood cell differential Red blood cell count (RBC) RBC mean corpuscular volume RBC distribution width Hemoglobin Hematocrit Platelet count	

APPENDIX 6. MYASTHENIA GRAVIS FOUNDATION OF AMERICA (MGFA) MG 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)

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APPENDIX 7. MG COMPOSITE SCORE

Patient ID and Date

MG Composite Scale

<u>Ptosis, upward gaze</u> (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 2	Immediate = 3
<u>Double vision on lateral gaze, left or right</u> (physician examination)	> 45 seconds = 0	11 – 45 seconds = 1	1 – 10 seconds = 3	Immediate = 4
<u>Eye closure</u> (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
<u>Talking</u> (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
<u>Chewing</u> (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
<u>Swallowing</u> (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
<u>Breathing</u> (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
<u>Neck flexion or extension (weakest)</u> (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e. ~50% weak, +/- 15%) = 3	Severe weakness = 4
<u>Shoulder abduction</u> (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e. ~50% weak, +/- 15%) = 4	Severe weakness = 5
<u>Hip flexion</u> (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

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APPENDIX 8. MGFA POST-INTERVENTIONAL STATUS (MGFA-PIS)

TABLE 4. MGFA postintervention 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.
<i>Change in Status</i>	
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 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT QUESTIONNAIRE (VERSION 1/14/09)*

SUICIDAL IDEATION					
<p><i>Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes”, ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.</i></p>	Since Last Visit				
<p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one’s life/commit suicide (e.g., “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, “I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it.” <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to “I have the thoughts but I definitely will not do anything about them.” <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>	<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				

<i>INTENSITY OF IDEATION</i>		
<p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</i></p> <p>Most Severe Ideation: _____</p> <p style="text-align: center;"><i>Type # (1-5)</i> <i>Description of Ideation</i></p>		Most Severe
<p>Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p>		_____
<p>Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous</p>		_____
<p>Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts</p>		_____
<p>Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply</p>		_____
<p>Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others and to end/stop the pain (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply</p>		_____

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

<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicide:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><i>Answer for Actual Attempts Only</i></p>	<p>Most Lethal Attempt Date:</p>
<p>Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p><i>Enter Code</i> _____</p>
<p>Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	<p><i>Enter Code</i> _____</p>

Source: http://cssrs.columbia.edu/docs/C-SSRS_1-14-09-Since_Last_Visit.pdf

*"Since Last Visit" refers to the period since the last visit the C-SSRS scale was administered.

APPENDIX 10. EUROQOL (EQ-5D)

Health Questionnaire

(English version for the United States [US])

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility	
I have no problems in walking about	<input type="checkbox"/>
I have some problems in walking about	<input type="checkbox"/>
I am confined to bed	<input type="checkbox"/>
Self-Care	
I have no problems with self-care	<input type="checkbox"/>
I have some problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
Usual Activities (e.g. ,work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	<input type="checkbox"/>
I have some problems with performing my usual activities	<input type="checkbox"/>
I am unable to perform my usual activities	<input type="checkbox"/>
Pain/Discomfort	
I have no pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
Anxiety/Depression	
I am not anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100



Worst
imaginable
health state

APPENDIX 11. 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 follow-up information. An updated ICF (and/or an ICF Addendum) will be provided to all patients describing the reason for collecting follow-up information, the information that will be collected, and how the information will be used. The updated ICF (and/or ICF Addendum) will also be provided to discontinued patients, subject to IRB/IEC approval. The updated ICF (and/or ICF Addendum) will clearly state that the patient 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 updated ICF (and/or ICF Addendum) must be signed by the patient.

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 include the following:

- How has the patient's MG status changed since they left Study ECU-MG-302 (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-302
- Has the patient experienced any exacerbations (Clinical Deteriorations) of MG, or any myasthenic crises since leaving Study ECU-MG-302; if so how many times
- Has the patient experienced any MG-related hospitalizations since leaving Study ECU-MG-302; 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-302; if so how many times
- Has the patient had any assessments using the MG-ADL, QMG, MGC or the MG-QOL15 scale; if so, what are the results, and was it administered by the same person who did the assessment during the clinical trial
- Have there been any changes in non-drug therapy.