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)

Unique Protocol ID:	ECU-MG-302
NCT Number:	NCT02301624
EudraCT Number:	2013-002191-41
Date of SAP:	06 February 2019

Alexion Pharmaceuticals, Inc.

FINAL STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **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)

Author: PPD

Date: February 6, 2019

Version: 1.0

1. APPROVAL SIGNATURES

PPD

6-Feb-2019

Date dd Mmm yyyy

06 FEB 2019

Date dd Mmm yyyy

7-Feb-2019

Date dd Mmm yyyy

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
Ab(s)	Antibody(ies)
AChI	Acetylcholinesterase inhibitor
AChR	Acetylcholine Receptor
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse event of special interest
AZA	Azathioprine
BP	Blood Pressure
C5	Complement Protein 5
CI	Confidence interval
CBC	Complete Blood Count
CS	Compound Symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	European Quality of Life Health 5-item questionnaire
ET	Early Termination
FAS	Full Analysis Set
FVC	Forced Vital Capacity
gMG	Generalized Myasthenia Gravis
HR	Heart Rate
ICF	Informed Consent Form
IP	Investigational Product
IST	Immunosuppressant Therapy
IVIg	Intravenous Immunoglobulin
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living profile
MGC	Myasthenia Gravis Composite score
MGFA	Myasthenia Gravis Foundation of America
MG-QOL15	15-Item Myasthenia Gravis Quality of Life
MM	Minimal Manifestation
MMF	Mycophenolate Mofetil
MTX	Methotrexate
Neuro-QoL Fatigue	Quality of Life in Neurological Disorders Fatigue scale
NIF	Negative Inspiratory Force
NMJ	Neuromuscular Junction
oMG	Ocular Myasthenia Gravis
PD	Pharmacodynamics
PE	Plasmapheresis or Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	Pharmacological Remission

Abbreviation or Acronym	Explanation
PR duration	interval between the start of the P wave and the beginning of the QRS complex
PT	Preferred Term (MedDRA)
QRS	combination of reflections (Q wave, R wave, and S wave) in a typical electrocardiogram
QT	interval between the start of the Q wave and the end of the T wave
QTC	corrected QC interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
QMG	Quantitative Myasthenia Gravis score for disease severity
QOL	Quality of Life
REML	Restricted Maximum Likelihood
RR	Respiration Rate
SAS®	Statistical Analysis Software®
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class (MedDRA)
TEAEs	Treatment-Emergent Adverse Events
TESAEs	Treatment-Emergent Serious Adverse Events
TTO	Time Trade-Off
VAS	Visual Analog Scale
VC	Variance Component
WHO ATC	World Health Organization Anatomical Therapeutic Chemical
WHODrug	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

ECU-MG-302 is a Phase III, open-label, extension trial of ECU-MG-301 to evaluate the safety and efficacy of eculizumab for treatment of subjects with refractory generalized Myasthenia Gravis (gMG).

ECU-MG-302 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.

Subjects enter the ECU-MG-302 study within 2 weeks after they have completed Visit 17 (Week 26) in the ECU-MG-301 trial. There are 2 phases in the ECU-MG-302 study, the Blind Induction Phase and the Open-Label Maintenance Phase. 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. There is also a Safety Follow-up Period for subjects who withdraw from this trial or discontinue eculizumab treatment at any time and for any reason after receiving any amount of IP.

The primary objective of ECU-MG-302 trial is to evaluate the long-term safety of eculizumab in subjects with refractory gMG.

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) total score
  - Myasthenia Gravis Composite (MGC) total score
  - Improvement or maintenance in primary symptoms that are most clinically meaningful to the subject
- To characterize the effect of eculizumab on Quality of Life (QOL) measures
- To describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in subjects with refractory gMG

4.1. Changes from Analyses Specified in the Protocol

This is the final statistical analysis plan for Study ECU-MG-302. Not all analyses mentioned in the ECU-MG-302 protocol will be done for the final analysis. In 3 previous interim efficacy analyses, the Extension Full Analysis Set (FAS) population was used, but not the Extension Per-Protocol (PP) population. Likewise, for this final study analysis, only the Extension Full Analysis Set (FAS) population will be used for analysis of efficacy data. The protocol also mentions analyses with the Combined Full Analysis Set and Combined PP population for ECU-MG-301 and ECU-MG-302. However, those analyses were not done for the 3 previous interim analyses and will not be done for the final analysis. The reasons for not doing these

additional analyses is due to the high eculizumab treatment compliance and the fact that most patients (N = 117 out of 125) entered Study ECU-MG-302.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

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

5.1.1.1. MG-ADL

The Myasthenia Gravis Activities of Daily Living (MG-ADL) is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in MG subjects. The 8 items of the MG-ADL were derived from symptom-based components of the original 13-item Quantitative Myasthenia Gravis (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 eight items graded on the MG-ADL are:

- Talking
- Chewing
- Swallowing
- Breathing
- Impairment of ability to brush teeth or comb hair
- Impairment of ability to arise from a chair
- Double Vision
- Eyelid Droop

5.1.2. Secondary Endpoints

The secondary efficacy endpoints are:

1. Change from baseline in the 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 the 15-item Myasthenia Gravis Quality of Life (MG-QOL15) total score

5.1.2.1. QMG

The current Quantitative Myasthenia Gravis (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, (0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe). The range of the 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 items evaluated with the QMG test are:

- Double Vision (Lateral Gaze)
- Ptosis (Upward Gaze)
- Facial Muscles
- Swallowing (4 oz. Water (1/2 cup))
- Speech following counting aloud from 1-50 (onset of dysarthia)
- Right Arm Outstretched (90°; sitting)
- Left Arm Outstretched (90°; sitting)
- Forced Vital Capacity (FVC)
- Right Hand Grip
- Left Hand Grip
- Head, Lifted (45°, supine)
- Right Leg Outstretched (45-50%, supine)
- Left Leg Outstretched (45-50%, supine)

5.1.2.2. Myasthenia Gravis Composite (MGC)

The Myasthenia Gravis Composite is a validated assessment tool for measuring clinical status of subjects with myasthenia gravis. 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 of the protocol). The scales are weighted for clinical significance that incorporate subject-reported outcomes. The MGC total score ranges from 0 to 50 with lower scores indicating less functional impairment and higher scores indicating greater functional impairment. 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. The items evaluated with the MGC are:

- Ptosis (Upward Gaze) [Scores of 0, 1, 2 or 3]
- Double Vision (Lateral Gaze) [Scores of 0, 1, 3, or 4]
- Eye Closure [Scores of 0= Normal/Mild, 1 = Moderate, or 2 = Severe]
- Talking [Scores of 0, 2, 4, or 6]
- Chewing [Scores 0, 2, 4, or 6]

- Swallowing [Scores of 0, 2, 5, or 6]
- Breathing [Scores of 0, 2, 4, or 9]
- Neck flexion or extension [Scores of 0, 1, 3, or 4]
- Shoulder abduction [Scores of 0, 2, 4, or 5]
- Hip flexion [Scores of 0, 2, 4, or 5]

5.1.2.3. MG-QOL15

The 15-item Myasthenia Gravis Quality of Life scale (MG-QOL15) is a health-related quality of life evaluative instrument specific to subjects with MG. MG-QOL15 was designed to provide information about subjects' perception of impairment and disability and the degree to which disease manifestations are tolerated. The instrument was designed to be easy to administer and interpret. The MG-QOL15 will be completed by the subject. The scale values for the 15 items are: 0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, and 4 = Very much. The MG-QOL15 total score ranges from 0 to 60. Higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction.

5.1.3. Tertiary Endpoints

The tertiary efficacy endpoints for this study 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 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

5.1.3.1. Neuro-QOL Fatigue

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue, completed by the subject. Each item is scored according to: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always. The Neuro-QOL Fatigue total score ranges from 19 to 95. Higher scores indicate greater fatigue and greater impact of MG on activities.

5.1.3.2. EQ-5D

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. Each area has 3 levels: Level 1 (no problems), Level 2 (some problems), and Level 3 (extreme problems). 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.

5.1.4. Other Efficacy Assessments

5.1.4.1. 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.

5.1.4.2. 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) was not be used in the ECU-MG-302 study. For the purposes of assessing MGFA-PIS status in the ECU-MG-302, Baseline is defined as the pre-treatment baseline of ECU-MG-301.

5.2. Safety

The safety of eculizumab will be assessed based on treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and changes from baseline through trial completion in vital signs, ECG, and routine clinical laboratory tests (chemistry, hematology).

5.2.1. Adverse Events (AEs)

Adverse Events are defined in Protocol Section 12.2.

5.2.2. Vital Signs

Vital signs will be measured at every visit and will include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (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.

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.

5.2.3. Laboratory Assessments

Subjects will have biologic samples collected for analysis of various parameters. The central laboratory will supply established or generally acknowledged methods, normal reference ranges, and shipping instructions.

Chemistry panel, routine hematology laboratory assessment, including complete blood count (CBC) and serum pregnancy test (see Appendix 5 of the protocol for details) will be performed at various time points as specified by the protocol.

5.2.4. Other Safety

5.2.4.1. Physical Examination

A complete physical examination will be performed at Visit 16 (Week 26) and Visit 107 (Week 208) or early termination (ET) visit. The complete physical examination will include assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities, musculoskeletal, and general neurologic examination.

5.2.4.2. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be conducted at Visits 1, 16, 29, 55, 81, and 107 or early termination (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.

5.2.4.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a validated questionnaire and is extensively used across primary care, clinical practice, surveillance, research, and institutional settings to assess suicidal ideation and behavior. The C-SSRS Since last Visit will be performed by the Investigator or a trained designee according to the Schedule of Assessments in the protocol. 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.

5.2.4.4. Neisseria Meningitidis Vaccination

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.

5.3. Assessment of Biomarker

5.3.1. MG Disease Biomarker

Blood samples for AChR auto-antibody will be collected at specified time points. AChR Abs analysis will be conducted at the central laboratory.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

Efficacy analyses will be performed on the Extension Full Analysis Set (FAS) Population. 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.

6.1. Extension FAS Population

The Extension FAS Population is the population on which all efficacy analyses will be performed and consists of all subjects who have received at least 1 dose of eculizumab in this extension trial and have at least one post-trial drug infusion MG-ADL efficacy assessment.

6.2. Extension Safety Population and Combined Safety Population

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

Some safety analyses will be based on the Combined Safety Population. The Combined Safety Population includes all subjects who receive at least 1 dose of IP (placebo or eculizumab) in either the ECU-MG-301 or ECU-MG-302 trial.

Subjects will be analyzed for safety according to the treatment they actually received.

7. STATISTICAL ANALYSIS

ECU-MG-302 is a Phase III, open-label, extension trial of ECU-MG-301 to evaluate the safety and efficacy of eculizumab for treatment of subjects with refractory gMG.

Alexion will be responsible for data collection and editing, reviewing and validating all the information in the eCRFs, statistical analysis, and generation of the final clinical report.

The Alexion Quantitative Sciences Department will perform the statistical analysis of the data derived from this trial. The analysis will be performed using the SAS® statistical software system Version 9.4 or higher.

Treatment groups will be indicated by eculizumab/eculizumab for the subjects originally randomized and treated with eculizumab in the ECU-MG-301 trial and by placebo/eculizumab for the subjects originally randomized and treated with placebo arm in the ECU-MG-301 trial. Summaries will be presented by treatment group. For continuous variables, summary statistics will include the sample size, mean, standard deviation, median, minimum, and maximum. Frequencies and percentages will be calculated for categorical variables. Graphical displays will be produced, as appropriate. All data will be presented in by-subject data listings.

7.1. Study Subjects

7.1.1. Disposition of Subjects

The number of subjects enrolled in the study, treated, completing the trial, discontinuing from the trial, along with the reasons for discontinuation, will be tabulated. The number and percent of enrolled patients included in the Extension FAS Population and the Extension Safety Population, and excluded from these same populations, will be presented. A corresponding listing will be created.

7.1.2. Protocol Deviations

For each treatment group and overall, the number of major and minor protocol deviations and of each type of major or minor protocol deviation will be presented using the Extension Safety Population. Protocol deviations will also be summarized at the patient level using counts and percentages. A corresponding listing will be created.

7.1.3. Demographics and Medical/Surgical History

All demographic and baseline characteristics information including baseline MG disease characteristics will be summarized using the Extension Safety Population. Medical/surgical history will be summarized using the Extension Safety Population. Summary statistics will be presented by treatment group and overall. No formal hypothesis testing will be performed. A corresponding listing will be created.

Similarly, demographic and baseline characteristics information, including baseline MG disease characteristics, will be summarized for the subgroups of patients who were taking corticosteroids, AZA, and MMF at the start of Study ECU-MG-302. These summaries will be produced for:

- All patients taking these medications,
- All patients taking these medications who decreased and/or stopped these medications,
- All patients taking these medications who increased and/or started these medications,
- All patients taking these medications who did not have dose changes.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (years) at Day 1 (First Dose Date) in ECU-MG-302
- Sex
- Race and ethnicity
- Japanese descent

7.1.3.2. Disease Characteristics

The following MG disease characteristics including MG history will be summarized by treatment group and overall:

- Age at MG diagnosis (years)
- Duration of MG (Time from diagnosis to first dose date in ECU-MG-302 (in years))
- Type of First MG presentation (oMG or gMG)

7.1.3.3. Medical/Surgical History

Baseline medical/surgical history information, (i.e., number (%) of subjects who have a medical or surgical history), will be summarized by system organ class and preferred term by treatment group and overall. A corresponding listing will be created.

7.1.4. Concomitant Medications/Therapies

Concomitant medications are defined as medications taken or therapies received by subjects during the study on or after the first dose of eculizumab on Day 1 in the ECU_MG-302 study. Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) version in use by Alexion at the time of the analysis. Summaries will be presented based on the Extension Safety Population.

Concomitant medications will be summarized by treatment group and overall. The number (%) of subjects using concomitant medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 4 Class code and generic name.

MG Therapy Status will be summarized by treatment group and overall for the following time points: at Day 1, during the protocol specified visits in the open-label maintenance phase, and at the End of Study Visit.

Immunosuppressant therapies (ISTs) are allowed during the trial and include but are not limited to: corticosteroid, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX),

tacrolimus, cyclosporine, and cyclophosphamide. Concomitant supportive cholinesterase inhibitors and IST usage during the study period will be summarized by treatment group and overall. Changes in cholinesterase inhibitors, corticosteroids, and ISTs other than corticosteroids during the study period will be summarized by treatment group and overall.

In addition, a summary of changes in immunosuppressant therapy status indicating the number of IST changes and the number of patients and percentage of patients with IST changes will be presented by treatment group and overall. The type of changes (i.e. start of a new IST, stop of an existing IST, increase of the daily dose of one IST, decrease of the daily dose of one IST, increase of the daily dose of more than one IST, and decrease of the daily dose of more than one IST) and the primary reason for the change in IST status will also be summarized. Likewise, the timing of these changes in IST(s) in days from the first dose date in ECU-MG-302 will be summarized for the various types of changes by treatment group and overall.

Summaries of the daily dose as well as changes from the baseline daily dose of corticosteroids, AZA, and MMF over time in ECU-MG-302 will be produced by treatment group and overall. These summaries will be produced for all patients taking these medications, all patients who decreased and/or stopped these medications, and for all patients taking these medications who increased and/or started these medications. Patient listings of these medication usage will be produced.

A listing of patients taking a prohibited medication (rituximab) will be produced, which will show the patient's prohibited medication usage.

For patients experiencing clinical deterioration, concomitant medications, MG therapy status, Plasmapheresis/Plasma Exchange usage and rescue therapies will be summarized by treatment group and overall.

Non-drug therapies and procedures during the study period will be summarized by SOC and PT as well as by treatment group and overall for the entire Extension Safety Populations as well as for the patients experiencing clinical deterioration.

Corresponding listings will be created.

7.2. Efficacy Analyses

Efficacy analyses will be performed on the Extension FAS Population. Two baselines will be defined for efficacy analyses. The first baseline is the ECU-MG-302 study baseline and is defined as the Day 1 assessment in the ECU-MG-302 study for both the Placebo/Eculizumab and the Eculizumab/Eculizumab treatment group summaries that will be produced. The second baseline is the ECU-MG-301 baseline value used in the ECU-MG-301 efficacy analyses and this baseline will be used in some summaries for the Placebo/Eculizumab and Eculizumab/Eculizumab treatment groups.

7.2.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline in the MG-ADL total score. The primary analysis for the change from the ECU-MG-302 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.

For the Placebo/Eculizumab treatment group in the Extension FAS population, summaries of the MG-ADL total score at each visit in the ECU-MG-302 study as well as changes from the ECU-MG-302 baseline at each study visit will be summarized. In addition, for the Placebo/Eculizumab treatment group in the Extension FAS population, summaries of the MG-ADL total score at each visit as well as changes from the ECU-MG-301 baseline at each visit will be summarized.

For the Eculizumab/Eculizumab treatment group in the Extension FAS population, summaries of the MG-ADL total score at each visit in the ECU-MG-302 study as well as changes from the ECU-MG-302 baseline at each visit will be summarized. In addition, for the Eculizumab/Eculizumab treatment group in the Extension FAS population, summaries of the MG-ADL total score at each visit as well as changes from the ECU-MG-301 baseline at each visit will be summarized.

7.2.1.1. Handling of Dropouts or Missing Data

For the summary efficacy analyses, there is no planned imputation of missing or partially missing baseline or post-baseline assessments, regardless of the efficacy endpoint analyzed.

7.2.1.2. Multicenter Studies

Since a small number of patients are anticipated at each site, the ECU-MG-301 study was randomized across centers and not within centers. As such, center will not be used in the efficacy analyses of the ECU-MG-302 extension study.

7.2.1.3. Hypothesis Testing and Significance Level

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.

7.2.2. Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoints that involve changes from baseline (i.e., change from baseline in QMG total score, MGC total score, and MG-QOL15 total score) will be summarized and analyzed in a similar way as was described for the primary efficacy endpoint MG-ADL.

The proportion of subjects with at least a 3-point reduction in the MG-ADL total score from the ECU-MG-302 baseline with no rescue therapy prior to the given visit as well as without regard to rescue therapy will be summarized at each visit for the placebo/eculizumab treatment group. Exact (Clopper-Pearson) 95% confidence intervals for the true proportions will be presented.

The proportion of subjects with at least a 5-point reduction in the QMG total score from ECU-MG-302 baseline with no rescue therapy prior to the given visit as well as without regard to rescue therapy will be summarized at each visit for the placebo/eculizumab treatment group. Exact (Clopper-Pearson) 95% confidence intervals for the true proportions will be presented.

The proportion of subjects with at least a 3-point reduction in the MG-ADL total score from the ECU-MG-301 baseline with no rescue therapy prior to the given visit as well as without regard to rescue therapy will be summarized at each visit for the treatment groups. Exact (Clopper-Pearson) 95% confidence intervals for the true proportions will be presented.

The proportion of subjects with at least a 5-point reduction in the QMG total score from ECU-MG-301 baseline with no rescue therapy prior to the given visit as well as without regard to rescue therapy will be summarized at each visit for the treatment groups. Exact (Clopper-Pearson) 95% confidence intervals for the true proportions will be presented.

7.2.3. Tertiary Efficacy Endpoint Analyses

The time to response on the MG-ADL total score (3-point reduction in MG-ADL from baseline with and without regard to rescue therapy) will be summarized for the placebo/eculizumab treatment group. Kaplan Meier curves will be produced.

The tertiary efficacy endpoints that involve changes from baseline (i.e., change from baseline in Neuro-QOL Fatigue, EQ-5D Index, EQ-5D VAS, and 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) will be summarized and analyzed in a similar way as was described for the primary efficacy endpoint MG-ADL.

7.2.4. Other Efficacy Analyses

Summary tables of the number and percent of subjects experiencing clinical deterioration (i.e., MG Crisis, significant symptomatic worsening, or subject's health in jeopardy) will be produced by treatment group, as well as summaries of the number and percent of subjects requiring rescue therapy and the type of rescue therapy required and the number of clinical deterioration events requiring rescue therapy and the type of rescue therapy.

Supplemental IP dosing; MG therapy status at Day 1, during the protocol specified visits in the open label maintenance phase, and at the end of study visit; concomitant medications; plasmapheresis/plasma exchange; and non-drug therapies and procedures will each be summarized by treatment group for patients experiencing clinical deterioration using descriptive statistics or counts and percentages, as appropriate.

Summary tables of the number and percent of patients who improved, worsened, or remained unchanged based on changes from baseline in the MGFA PIS will be produced by treatment group over time. A summary table of the number and percentage of patients who achieved Minimal Manifestations (MM) or Pharmacological Remission (PR) of MG will be produced by treatment group over time.

Event rate analyses of MG exacerbations and MG Crisis for the Pre-study time period (1 year) and During Studies ECU-MG-301 and ECU-MG-302 will be produced based on a Generalized Estimating Equation (GEE) Poisson regression repeated measures model with the number of events as the dependent variable, the logarithm of patient-years as the offset variable, and the study or phase indicator (pre-study, Placebo, Eculizumab) as the factors assuming a compound symmetry correlation structure.

Summaries of the individual items for the MG-ADL, QMG, MGC, MG-QoL15, and Neuro-QOL Fatigue by treatment group over time showing the number and percentage of patients for each item will be produced.

Summaries of changes from both the ECU-MG-301 and ECU-MG-302 baselines for the MG-ADL and QMG total scores over time will be produced by treatment group for the subgroups of patients that were taking corticosteroids, AZA, and MMF at the start of the ECU-MG-302 study. These summaries will be produced for all patients taking these medications, all patients taking these medications who decreased and/or stopped these medications, for all patients taking these medications who increased and/or started these medications, and all patients without dosing changes for these medications.

There are 12 subgroups of patients based on Corticosteroids, AZA, and MMF:

1. Patients on Corticosteroids at ECU-MG-302 Study Baseline
2. Patients who Decreased and/or Stopped Corticosteroid Use
3. Patients who Increased and/or Started Corticosteroid Use
4. Patients on Corticosteroids without Dosing Changes
5. Patients on AZA at ECU-MG-302 Study Baseline
6. Patients who Decreased and/or Stopped AZA Use
7. Patients who Increased and/or Started AZA Use
8. Patients on AZA without Dosing Changes
9. Patients on MMF at ECU-MG-302 Study Baseline
10. Patients who Decreased and/or Stopped MMF Use
11. Patients who Increased and/or Started MMF Use
12. Patients on MMF without Dosing Changes

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.

7.2.5. Pharmacokinetic (PK) and Pharmacodynamic (PD) Analyses

PK/PD analyses will be described in a separate PK/PD analysis plan.

A summary table of Serum Eculizumab Concentrations (μg/mL) by Treatment Group over time will be produced. A summary table of Serum Free C5 (μg/mL) and Percentage of Baseline by Treatment Group over time will be produced. A summary table of Hemolysis (%) Measured by an Ex Vivo cRBC Assay by Treatment Group over time will be produced. Corresponding listings will also be created.

7.2.6. Biomarker Analyses

AChR auto-antibodies will be summarized by treatment and visits. Changes from baseline in AChR auto-antibody will be summarized and subject listings will be created.

7.3. Safety Analyses

All safety analyses will be conducted on the Extension Safety Population. All safety data will be provided in subject listings. No formal hypothesis testing is planned. Baseline is defined as the last available assessment prior to eculizumab treatment in the ECU-MG-302 trial for all subjects regardless of their treatment group. Generally, this baseline will be the Day 1 assessment in ECU-MG-302, if missing then the last available assessment in ECU-MG-301 study will be used for the particular parameter.

7.3.1. Study Duration, Treatment Duration, Treatment Compliance, and Exposure

Study duration, treatment duration, and exposure will be summarized by treatment group and overall using descriptive statistics for the Extension Safety populations. Treatment compliance will be summarized by treatment group and overall using counts and percentages.

Study duration will be calculated as the time in days from first eculizumab dose date in ECU-MG-302 study until the date of completion/discontinuation (or death) from the study (i.e., Study duration (days) = Date of completion/discontinuation (or death) – Date of First IP Dose Date + 1). Treatment duration will be calculated as the time in days from the first IP dose date of eculizumab in the ECU-MG-302 trial until the last IP dose date of eculizumab (i.e., Treatment duration (days) = Last IP Dose Date – First IP Dose Date + 1).

7.3.2. Adverse Events (AEs)

Adverse Events are defined in Protocol Section 12.2.

For the purposes of this SAP, two types of AEs will be noted:

- Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Serious Adverse Events (TESAEs)

TEAEs are AEs that onset on or after the first IP dose in the ECU-MG-302 study. Likewise, TESAEs are SAEs that onset on or after the first IP dose in the ECU-MG-302 study.

AEs will be coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) using the current dictionary version at the time of the final analysis.

For summary purposes, two different versions of related AEs will be used. In general for the general related AE tables, related AEs are defined as AEs that are possibly, probably or definitely related to study treatment. Unrelated AEs are defined as AEs that are unlikely or not related to study treatment. For the Japanese related AE tables, related AEs are defined as AEs that are unlikely, possibly, probably or definitely related to study treatment. Unrelated AEs are defined as AEs that are not related to study treatment.

7.3.2.1. Overall Summary of Adverse Events

The number of TEAEs and the number and percentage of patients with TEAEs will be presented for each treatment group and overall. Also, the number of TEAEs and the number and percentage of patients with TEAEs will be presented for the following event subcategories: related TEAEs, not related TEAEs, mild TEAEs, moderate TEAEs, severe TEAEs, and TEAEs

leading to withdrawal from the study. These statistics will be prepared for all TEAEs and, separately, for TESAEs. Additionally, the number of patients who died on study will be presented. See Section 9.3 for the definition of related TEAEs. A separate overall summary of adverse events will be produced using the Japanese definition of related TEAEs/TESAEs.

7.3.2.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs and the number and percentage of patients with TEAEs will be presented by SOC and PT for each treatment group and overall. At the patient level, patients are counted once in each SOC and PT. Percentages will be based on the total number of patients in the treatment group in the Extension Safety Population. SOCs will be listed in order of overall frequency of occurrence. A similar summary will be created for TESAEs and for all non-serious TEAEs.

Likewise, percentage of patients with TEAEs will be presented by PT for each treatment group and overall. At the patient level, patients are counted once in each PT. Percentages will be based on the total number of patients in the treatment group in the Extension Safety Population. PTs will be listed in order of overall frequency of occurrence.

Adverse events of special interest include infections (meningococcal infections, *Aspergillus* infections, sepsis, and any other serious infection), infusion-related reactions, serious cutaneous reactions, cardiac disorders, and angioedema. The number of TEAEs of Special Interest and the number and percentage of patients with TEAEs of Special Interest will be presented by SOC and PT for each treatment group and overall.

Adverse event rates for TEAEs, TESAEs, and TEAEs of Special Interest based on 100 patient-years (PY) of eculizumab exposure will be included in these tabular outputs.

7.3.2.3. AEs and SAEs by SOC, PT, and Relationship

TEAEs, TESAEs, and TEAEs of Special Interest will be summarized at the subject level by SOC, PT, and grouped relationship (related, unrelated) using frequencies and percentages. TEAEs will also be summarized at the subject level by SOC, PT, and relationship using frequencies and percentages. These summaries will be made by treatment group and overall.

7.3.2.4. AEs and SAEs by SOC, PT, and Severity

TEAEs and TESAEs will be summarized at the subject level by SOC, PT, and severity using frequencies and percentages by treatment group and overall.

7.3.2.5. Deaths, Other SAEs, and Other Significant Adverse Events

The number and percentage of patients with TEAEs leading to discontinuation from the study will be presented overall and by preferred term for each treatment group and overall. Similarly, the number and percentage of patients with TEAEs resulting in death will be presented overall and by preferred term for each treatment group and overall. Listings of patients with adverse events leading to discontinuation from the study and of patients with adverse events resulting in death will be produced, if applicable.

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

Two baselines will be defined for laboratory analyses. The first baseline is the ECU-MG-302 study baseline and is defined as the last available assessment prior to eculizumab treatment in the ECU-MG-302 trial for the Placebo/Eculizumab treatment group. Generally, this baseline will be the Day 1 lab assessment in ECU-MG-302, if missing then the last available assessment in ECU-MG-301 study will be used for the particular lab parameter.

The second baseline is the ECU-MG-301 baseline value used in the ECU-MG-301 laboratory analyses and this baseline will be used in some summaries for the Placebo/Eculizumab and Eculizumab/Eculizumab treatment groups in order to show changes and shifts from the start of ECU-MG-301 through all planned laboratory assessments in ECU-MG-302.

For the Placebo/Eculizumab treatment group, descriptive statistics will be presented by visit in ECU-MG-302 for the actual values and the changes from the ECU-MG-302 baseline for each quantitative laboratory test (hematology, serum chemistry). Shift tables for changes in status (low, normal, high) from the ECU-MG-302 baseline will also be presented by visit for each laboratory parameter for the Placebo/Eculizumab treatment group. All laboratory values will be classified as normal, below normal (low), or above normal (high) based on normal ranges supplied by the central laboratory.

For both treatment groups, descriptive statistics will be presented by visit for all protocol defined study visits in both the ECU-MG301 and ECU-MG-302 for the actual values and the changes from the ECU-MG-301 baseline for each quantitative laboratory test (hematology, serum chemistry). Shift tables for changes in status (low, normal, high) from the ECU-MG-301 baseline will also be presented by visit for all protocol defined study visits in both the ECU-MG301 and ECU-MG-302 for each treatment group for each laboratory parameter. All laboratory values will be classified as normal, below normal (low), or above normal (high) based on normal ranges supplied by the central laboratory.

A listing will be produced for pregnancy tests.

7.3.3.2. Vital Signs

Descriptive statistics will be presented by visit for each treatment group for the actual values and the changes from baseline for each vital sign (systolic and diastolic blood pressure (BP), temperature, respiration rate (RR), and seated or supine heart rate (HR)) and for body weight.

Vital sign and weight outlier tables by treatment group and overall will be produced reporting the number and percentage of subjects with at least one post-treatment outlier using the following criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C

• Respiratory rate: <12 breaths/min, > 20 breaths/min

7.3.3.3. Physical Examination

A listing of the physical exam data will be produced.

7.3.3.4. Other Safety Parameters of Special Interest

7.3.3.4.1. Electrocardiograms (ECG)

ECG results (normal; abnormal, not clinically significant; abnormal, clinically significant; not assessed/not applicable) will be summarized by visit for each treatment group using counts and percentages. For each treatment group, descriptive statistics will be presented by visit for each ECG parameter (ventricular rate, PR duration, QRS duration, QT duration, and RR duration). Counts and percentages will be presented by visit for each treatment group for QTC, QTcF, and QTcB for the following categories: < 450 msec, 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec. Counts and percentages will also be presented by visit for each treatment group for the change from baseline in QTC, QTcF, and QTcB for the following categories: ≤ 0 msec, > 0 to ≤ 30 msec, > 30 to ≤ 60 msec, and > 60 msec.

7.3.3.4.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be summarized by treatment group. Shift tables for the C-SSRS will be produced by treatment group.

The number and percentage of patients with treatment-emergent Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent based on the Columbia-Suicide Severity Rating Scale (C-SSRS) during the treatment period will be summarized by treatment group. Treatment-emergent Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent will be based on Visits 9, 16, 23, 29, 42, 55, 68, 81, 94, 107 or ET. In this summary, the number and percentage of patients who experience the particular event at least once during the treatment period will be summarized. The particular events are:

- Suicidal Ideation (1-5)

1. Wish to be Dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

- Suicidal Behavior (6-10)

6. Preparatory acts or behavior
7. Aborted attempt
8. Interrupted attempt
9. Non-fatal suicide attempt

10. Completed suicide
    - Self-injurious behavior without suicidal intent

For the composite endpoint of suicidal ideation (Categories 1-5), the number and percentage of patients who experience any one of the five suicidal ideation events at least once during the treatment period will be summarized by treatment group. For the composite endpoint of suicidal behavior (Categories 6-10), the number and percentage of patients who experience any one of the five suicidal behavior events at least once during the treatment period will be summarized by treatment group. For the composite endpoint of suicidal ideation or behavior (Categories 1-10), the number and percentage of patients who experience any one of the ten suicidal ideation or behavior events at least once during the treatment period will be summarized by treatment group.

A shift table to demonstrate changes in C-SSRS groupings from baseline will be produced by treatment group. The three groupings for the shift table are: (a) No suicidal ideation or behavior, (b) Suicidal Ideation, and (c) Suicidal Behavior. Suicidal Ideation includes any one of the five suicidal ideation events (Categories 1-5). Suicidal behavior includes any one of the five suicidal behavior categories (Categories 6-10). Each patient will be counted in one cell only for the table. Patients with both Suicidal Ideation and Suicidal Behavior are included in the Suicidal Behavior category.

7.3.3.4.3. Immunogenicity

Immunogenicity as measured by ADA will be summarized in tabular form by treatment group and presented in by-patient listing.

7.3.3.4.4. Non-Drug Therapies and Procedures

Non-drug therapies and procedures will be summarized by system organ class and preferred term for each treatment group using patient counts and percentages.

7.3.3.4.5. Neisseria Meningitidis Re-Vaccination

A by-patient listing of N. meningitidis re-vaccinations will be produced.

7.3.3.4.6. Hospitalizations

The number and percent of patients hospitalized during the study period and the total number of reported hospitalizations and the total number of pre-planned hospitalizations will be presented by treatment group. The duration of each hospitalization and the duration of each pre-planned hospitalization will be summarized at the hospitalization level using descriptive statistics for each treatment group.

Event rate analyses of MG related hospitalizations for the Pre-study time period (1 year) and During Studies ECU-MG-301 and ECU-MG-302 will be produced based on a Generalized Estimating Equation (GEE) Poisson regression repeated measures model with the number of events as the dependent variable, the logarithm of patient-years as the offset variable, and the study or phase indicator (pre-study, Placebo, Eculizumab) as the factors assuming a compound symmetry correlation structure.

8. REFERENCES

None.

9. APPENDICES

9.1. Protocol Schedule of Events

Refer to the protocol for a schedule of events. The visits in the ECU-MG-302 study are as follows:

Table 2: Visits in the ECU-MG-302 Study

Period/Phase	Trial Visit	Trial Weeks
Blind Induction	Visit 1	Day 1
	Visit 2	Week 1
	Visit 3	Week 2
	Visit 4	Week 3
Open-Label Maintenance	Visit 5	Week 4
	Visit 6	Week 6
	Visit 7	Week 8
	Visit 8	Week 10
	Visit 9	Week 12
	Visit 10	Week 14
	Visit 11	Week 16
	Visit 12	Week 18
	Visit 13	Week 20
	Visit 14	Week 22
	Visit 15	Week 24
	Visit 16	Week 26
	Visit 17	Week 28
	Visit 18	Week 30
	Visit 19	Week 32
	Visit 20	Week 34
	Visit 21	Week 36
	Visit 22	Week 38
	Visit 23	Week 40
	Visit 24	Week 42
	Visit 25	Week 44
	Visit 26	Week 46
	Visit 27	Week 48
	Visit 28	Week 50
	Visit 29	Week 52
	Visit 30	Week 54
	Visit 31	Week 56
	Visit 32	Week 58
	Visit 33	Week 60
	Visit 34	Week 62
	Visit 35	Week 64
	Visit 36	Week 66
	Visit 37	Week 68
	Visit 38	Week 70

	Visit 39	Week 72
	Visit 40	Week 74
	Visit 41	Week 76
	Visit 42	Week 78
	Visit 43	Week 80
	Visit 44	Week 82
	Visit 45	Week 84
	Visit 46	Week 86
	Visit 47	Week 88
	Visit 48	Week 90
	Visit 49	Week 92
	Visit 50	Week 94
	Visit 51	Week 96
	Visit 52	Week 98
	Visit 53	Week 100
	Visit 54	Week 102
	Visit 55	Week 104
	Visit 56	Week 106
	Visit 57	Week 108
	Visit 58	Week 110
	Visit 59	Week 112
	Visit 60	Week 114
	Visit 61	Week 116
	Visit 62	Week 118
	Visit 63	Week 120
	Visit 64	Week 122
	Visit 65	Week 124
	Visit 66	Week 126
	Visit 67	Week 128
	Visit 68	Week 130
	Visit 69	Week 132
	Visit 70	Week 134
	Visit 71	Week 136
	Visit 72	Week 138
	Visit 73	Week 140
	Visit 74	Week 142
	Visit 75	Week 144
	Visit 76	Week 146
	Visit 77	Week 148
	Visit 78	Week 150
	Visit 79	Week 152
	Visit 80	Week 154
	Visit 81	Week 156
	Visit 82	Week 158
	Visit 83	Week 160
	Visit 84	Week 162
	Visit 85	Week 164
	Visit 86	Week 166
	Visit 87	Week 168

	Visit 88	Week 170
	Visit 89	Week 172
	Visit 90	Week 174
	Visit 91	Week 176
	Visit 92	Week 178
	Visit 93	Week 180
	Visit 94	Week 182
	Visit 95	Week 184
	Visit 96	Week 186
	Visit 97	Week 188
	Visit 98	Week 190
	Visit 99	Week 192
	Visit 100	Week 194
	Visit 101	Week 196
	Visit 102	Week 198
	Visit 103	Week 200
	Visit 104	Week 202
	Visit 105	Week 204
	Visit 106	Week 206
	Visit 107/ET*	Week 208
Clinical Deterioration		
Unscheduled		
Post Treatment Safety Follow-up		+ week 8

* If a subject withdraws early from the trial, an Early Termination (ET) Visit will be performed using the same assessments as the Visit 55 (Week 104) assessments.

9.2. Sample Size, Power, and Randomization

The study design is an open-label extension trial of ECU-MG-301. As an open-label extension study, all patients who completed Study ECU-MG-301 were eligible to enroll into Study ECU-MG-302. No sample size or power calculations were performed for this study.

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

Age will be presented as the number of years between date of birth and the reference date (i.e., (Reference Date – Date of Birth)/365.25. The following ages will be computed, with reference dates indicated:

Table 3: Age and Reference Date

AGE	REFERENCE DATE
• Age at First IP Infusion	• Date of First IP Infusion

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing months will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

Definition of Baseline Values

Baseline is defined as the last available assessment prior to or on the day of first eculizumab treatment in ECU-MG-302 for all patients regardless of their treatment group.

Change from Baseline

Change from baseline will be calculated as

Change of Baseline = Assessment Value – Baseline Assessment Value.

QTcB and QTcF Calculations

The Bazett's formula, QTcB, is as follows:

QTcB = QT interval / sqrt(RR)

The Fridericia formula, QTcF, is as follows:

QTcF = QT interval / (RR)^ (1/3)

Adverse Events

The analysis of Adverse Events is described in detail in Section 7.3.2.

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first eculizumab dose in ECU-MG-302. If the start date of an AE is partially or completely missing and the end (stop) date of the AE does not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first eculizumab dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first eculizumab dose and
  - the start month is missing, then the AE is treatment emergent; else if
  - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else.
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered to be AEs prior to the start of the ECU-MG-302 study.

Patient percentages are based on the total number of patients in the Extension Safety Population in the particular treatment group or overall.

In general for the related AE tables, related AEs are defined as AEs that are possibly, probably or definitely related to study treatment. Unrelated AEs are defined as AEs that are unlikely or not related to study treatment.

For the Japanese related AE tables, related AEs are defined as AEs that are unlikely, possibly, probably or definitely related to study treatment. Unrelated AEs are defined as AEs that are not related to study treatment.

9.4. Additional Details on Statistical Methods

Not applicable