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Alexion Pharmaceuticals, Inc.

FINAL STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **ECU-MG-303**

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

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1. APPROVAL SIGNATURES

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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
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
CS	Compound Symmetry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	European Quality of Life Health 5-item questionnaire
FAS	Full Analysis Set
FVC	Forced Vital Capacity
gMG	Generalized Myasthenia Gravis
HR	Heart Rate
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
MMF	Mycophenolate Mofetil
MTX	Methotrexate
Neuro-QoL Fatigue	Quality of Life in Neurological Disorders Fatigue scale
oMG	Ocular Myasthenia Gravis
PD	Pharmacodynamics
PE	Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetics
PP	Plasmapheresis
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

Abbreviation or Acronym	Explanation
QOL	Quality of Life
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
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-303 is a Phase 3, open-label, multicenter study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous eculizumab in pediatric patients aged 6 to <18 years with acetylcholine receptor (AChR)-antibody (Ab) positive refractory gMG.

There will be 4 periods in this study: Screening Period (2 to 4 weeks), Primary Evaluation Treatment Period (26 weeks), Extension Period (up to an additional 208 weeks), and Follow-up Period (8 weeks). All patients who complete Week 26 of Study ECU-MG-303 will continue receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks. The 8-week Follow-up Period is required following the last dose of study drug for all patients upon withdrawal or discontinuation from the study or upon completion of the study when the patient is not continuing to receive eculizumab treatment.

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

The primary objective of ECU-MG-303 trial is to evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

The secondary objectives of this trial are to:

- Evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG

- Evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the following measures:
  - Myasthenia Gravis Activities of Daily Living profile (MG-ADL)
  - Myasthenia Gravis Composite score (MGC)

- Evaluate the effect of eculizumab on the following quality of life measures:
  - European Quality of Life 5-Dimension Youth (EQ-5D-Y) Questionnaire – EQ-5D-Y Proxy version for patients < 8 years of age or EQ-5D-Y version for patients ≥ 8 years of age
  - Neurological Quality of Life Pediatric Fatigue (Neuro-QoL Pediatric Fatigue) Questionnaire for patients ≥ 8 years of age
  - PROMIS Parent Proxy Short Form v2.0 – Fatigue 10a for patients < 8 years of age

- Evaluate MGFA Post-Interventional Status over time

- Describe the total number and percentage of patients with clinical deterioration, myasthenic crisis, and rescue therapy use over time

- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab treatment in pediatric refractory gMG patients to confirm the pediatric dosing regimen selected through modeling and simulation following 26 weeks of eculizumab treatment

The Extension Period objectives are to:

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

This statistical analysis plan (SAP) was developed and finalized prior to the primary analysis, which will be conducted upon completion of the 26-week Primary Evaluation Treatment Period (i.e. all patients have completed the 26-week Primary Evaluation Treatment Period or discontinued the study prior to the completion of this period).

Another SAP will be developed and finalized prior to the completion of the entire study (including the Extension Period).

4.1. Changes from Analyses Specified in the Protocol

This is the final statistical analysis plan for the primary analysis of Study ECU-MG-303. No change will be made from the planned analyses specified in the protocol.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary efficacy endpoint is the change from baseline in the QMG total score over time regardless of rescue treatment.

5.1.1.1. 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 item is graded from 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 an objective evaluation of therapy for MG recommended for use in prospective studies of therapies for MG by the MGFA task force, 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 degrees supine)
- Right Leg Outstretched (45 degrees supine)
- Left Leg Outstretched (45 degrees supine)

A modified QMG score has been developed for use in patients younger than 12 years of age that will be used for patients aged 6 to 11 years at the time of Screening and throughout the remainder of the study. The modified QMG omits the assessment of grip strength as well as leg strength, and uses a modified assessment of swallowing (slurp test) compared with the traditional QMG, with total scores ranging from 0 to 21.

In this study, patients will continue to be evaluated based on the type of QMG scale initially completed upon entry into the study.

5.1.2. Secondary Endpoints

The secondary efficacy endpoints are:

- Change from Baseline in the MG-ADL total score over time regardless of rescue treatment
- Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from Baseline over time with no rescue treatment
- Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from Baseline over time regardless of rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time with no rescue treatment
- Proportion of patients with ≥ 5-point reduction in the QMG total score from Baseline over time regardless of rescue treatment
- Change from Baseline in the MGC total score over time regardless of rescue treatment
- Change from Baseline in EQ-5D-Y over time regardless of rescue treatment
- Change from Baseline in Neuro-QoL Pediatric Fatigue over time regardless of rescue treatment
- MGFA Post-Interventional Status over time regardless of rescue treatment
- Total number and percentage of patients with clinical deterioration, myasthenic crisis, and rescue therapy use over time

5.1.2.1. 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 patients. 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 from 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24.

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

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

5.1.2.2. Myasthenia Gravis Composite (MGC)

The Myasthenia Gravis Composite is a validated assessment tool for measuring clinical status of patients with myasthenia gravis. The MGC assesses the 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 incorporate patient-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 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. EQ-5D-Y

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

will be administered at the protocol-specified time points at approximately the same time of day throughout the study.

5.1.2.4. Neuro-QOL Pediatric Fatigue

The Neuro-QoL Pediatric Fatigue questionnaire is a reliable and validated brief 11-item survey of fatigue, completed by the patient for patients ≥ 12 years of age (at time of assessment) and completed by the patient's caregiver or with caregiver assistance for patients <12 years of age. Higher scores indicate greater fatigue and greater impact of MG on activities. Patients will continue to be evaluated based on the survey initially completed upon entry into the study.

Patients who are younger than the lowest age range of the applicable scale (ie, patients < 8 years of age) will be evaluated using the PROMIS Parent Proxy Short Form v2.0 – Fatigue 10a questionnaire .The parent or legal guardian (the proxy) will complete the measure on the child's behalf following administration of these instructions: "The following questionnaires will ask about your child's symptoms and activity levels; his/her ability to think, concentrate and remember things; questions specific to his/her condition, and questions related to his/her quality of life. Please answer the following questions based on what you think your child would say."

The Neuro-QoL Pediatric Fatigue questionnaire (or the PROMIS Parent Proxy Short Form v2.0) will be administered at the protocol-specified time points at approximately the same time of day throughout the study.

5.1.2.5. 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 the presence of Minimal Manifestation status will be assessed by the PI or the same neurologist skilled in the evaluation of MG patients throughout the study.

5.1.3. Extension Period Efficacy Endpoints

The details of the analysis of the extension period efficacy endpoints will be provided in another SAP.

The extension period efficacy endpoints for this study are:

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

- Change from Baseline in MGFA Post-Interventional Status

5.2. Safety

All safety data during the 26 weeks primary evaluation treatment period and beyond week 26 that are included in the database lock for the primary analysis will be analyzed.

The safety endpoints of the study are:

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

5.2.1. Adverse Events (AEs)

All AEs (serious and nonserious) will be collected from the signing of the ICF.

An AE reported after informed consent but before study drug administration will be considered a pretreatment AE.

Treatment--emergent AEs (serious and nonserious) will be defined as all AEs starting on or after the first dose of study drug.

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

5.2.2. Vital Signs

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

5.2.3. Laboratory Assessments

Samples for urine pregnancy, hematology, and chemistry will be performed at the times specified for clinical laboratory tests in the Schedule of Assessments in the protocol. Specific laboratory assessments are provided in the protocol.

5.2.4. Physical Examination

Each examination will include the following assessments: general appearance of skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and general neurologic system. Physical growth (height [cm], weight [kg]) will be assessed. The accurate weighing of patients is vital as part of their management, as eculizumab dosing will depend on the patient's

recorded body weight at the most recent dosing visit. It is recommended that patients should be weighed in the same amount of clothing in each instance where weight is assessed.

5.2.4.1. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be collected according to the Schedule of Assessments in the protocol. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results.

5.2.4.2. Immunogenicity

Blood samples will be collected to test for the presence and titer of ADAs to eculizumab in serum.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

In general, the Full Analysis Set (FAS) Population will be used for efficacy analyses and the modified FAS (mFAS) will be used for the analyses of the primary and secondary efficacy endpoints during the 26-week Primary Evaluation Treatment Period.

All safety analyses will be performed on the Safety Set Population.

6.1. FAS and mFAS Population

The FAS Population is the population on which all efficacy analyses will be performed and consists of all patients who have received at least 1 dose of eculizumab.

A subset of the FAS that includes older patients (12 to < 18 years of age) only will be used for analyses of the primary and secondary endpoints during the 26-week Primary Evaluation Treatment Period and will be defined as the modified FAS (mFAS).

6.2. Safety Set Population

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

6.3. Other Analysis Set

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

A separate analysis plan will be written for the PK/PD analyses.

7. STATISTICAL ANALYSIS

ECU-MG-303 is a Phase 3, open-label, multicenter study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of eculizumab in pediatric patients aged 6 to <18 years with refractory gMG.

The primary analysis will be conducted when all patients have completed the 26-week Primary Evaluation Treatment Period or discontinued prior to the completion of the Primary Evaluation Treatment Period. This analysis will include the first 26 weeks of efficacy and PK/PD data, and all available safety data included in the database lock at the time of the primary analysis for regulatory submission purposes.

A separate analysis plan will be written for the PK/PD analyses.

Another SAP will be developed and finalized prior to the completion of the entire study (including the Extension Period).

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.

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-patient data listings.

In general, statistical summaries will be presented by age group (older patients: ≥12 - < 18 years, vs younger patients: <12 years), and all age groups combined where appropriate, with age as determined at screening visit. For the younger patients (<12 years), summary statistics will be provided if 2 or more patients are enrolled; otherwise only data listings will be provided.

For the analysis of the primary and secondary efficacy endpoints on the mFAS population, statistical summaries will also be presented by the status of maintenance IVIg at study entry [yes, no], and overall.

7.1. Study Patients

7.1.1. Disposition of Patients

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

7.1.2. Protocol Deviations

The number and type of important and non-important protocol deviations will be presented using the Safety Set 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 and background therapy will be summarized using the Safety Set Population. Medical history will be summarized using the Safety Set Population. Summary statistics will be presented by age group and overall. No formal hypothesis testing will be performed. A corresponding listing will be created.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (years) at screening
- Sex
- Race and ethnicity
- Japanese descent

7.1.3.2. Disease Characteristics

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

- Age at MG diagnosis (years)
- Duration of MG (Time from diagnosis to first dose date (in years))
- Type of First MG presentation (oMG or gMG)
- Maximum Classification since the Diagnosis prior to Screening
- Requirement of ventilatory support prior to study entry (Yes/No)
- MG exacerbation including MG crisis (Yes/No) [if Yes, MG exacerbation and MG crisis will be summarized separately]
- MGFA Clinical Classification at Screening

7.1.3.3. Medical/Surgical History

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

7.1.4. Prior and Concomitant Medications/Therapies

Prior medications are defined as medications taken or therapies received by patients before the first dose of eculizumab from this study.

Concomitant medications are defined as medications taken or therapies received by patients during the study on or after the first dose of eculizumab. 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 Safety Set Population.

Prior and concomitant medications will be summarized by Age group and overall. The number (%) of patients using 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 during the primary evaluation treatment period and the prior MG therapy status will be summarized by Age group.

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.

The number and percentage of patients with baseline IST therapies as well as changes in IST usage during the primary evaluation treatment period will be summarized by Age group.

In addition, summary statistics of the daily dose at baseline of corticosteroids, AZA, and MMF will be produced by age group and overall. In addition, the number and percent of patients with the following categories of baseline daily dose will also be presented:

- Corticosteroids:
  - >15 mg/day
  - >10 to 15 mg/day
  - >5 to 10 mg/day
  - >0 to ≤5 mg/day
  - 0 mg/day
- AZA:
  - >200 mg/day
  - 100 to 200 mg/day
  - 50 to <100 mg/day
  - >0 to <50 mg/day
  - 0 mg/day
- MMF:
  - ≥2000 mg/day
  - 1500 to <2000 mg/day

- 1000 to <1500 mg/day
- >0 to <1000 mg/day
- 0 mg/day

A data listing will be provided to show the immunosuppressant medications taken by all the patients, who decreased and/or stopped these medications, and who increased and/or started these medications.

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

The number and percent of patients with usage of immunosuppressant therapies, IVIg and plasma exchange during the primary evaluation treatment period as well as prior to study treatment will be summarized by Age group. A data listing will also be provided.

Non-drug therapies and procedures during the study period will be summarized by SOC and PT as well as by age group and overall.

A data listing will be provided for supplemental investigational product exposure for rescue therapy.

7.2. Efficacy Analyses

All efficacy data up to and including assessment at Week 26 will be included in the primary efficacy analyses.

The mFAS Population will be used for the analysis of the primary and secondary endpoints during the 26-week Primary Evaluation Treatment Period, whereas the FAS Population will be used for all other efficacy results summaries by including younger patients (<12 years) if any are enrolled.

For the analysis of the primary and secondary efficacy endpoints, summary statistics will be provided of actual results and changes from baseline results at each visit by the status of maintenance IVIg at study entry [yes, no], and overall patients in the mFAS.

Baseline is the last assessment prior to first dose on Day 1.

7.2.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from Baseline in the QMG total score over time regardless of rescue treatment, using the mFAS Population.

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

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

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

The primary efficacy analysis for the change from Baseline in the QMG total score will be conducted at Week 12 in order to assess the effect of eculizumab treatment during the 12 weeks in which MG medications (ie, ISTs, IVIg) are continued at a stable dose. For the purpose of

satisfying specific requirements of the Paediatric Committee (PDCO) of the European Medicines Agency, a primary efficacy analysis will also be conducted at Week 26.

A Repeated-Measures model will be used to analyze observed change in QMG with baseline QMG score and visits as covariates. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested: (compound symmetry (CS) or variance component (VC)). The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will be used in the analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The least-squares mean at Week 12 will be used to test the primary hypothesis at a significance level of 5%. The least-squares mean at Week 26 will be used to test the PDCO-specific primary hypothesis at a significance level of 5%. The p-value, standard error of the least-squares mean and 95% confidence interval of the least-squares mean will be produced. Missing primary endpoints at post-baseline visits will not be imputed.

Summaries of the QMG at each visit as well as changes from baseline at each study visit will also be provided.

In addition, if two (2) or more younger patients (<12 years) are enrolled, summaries of the modified QMG assessed at each visit as well as changes from baseline at each study visit will be provided; otherwise a data listing will be provided instead.

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, center will not be used in the efficacy analyses of the 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.

7.2.1.4. Sample Size Re-Estimation

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

A table of summary statistics (N, Mean, SD, Median, Min, Max) will be produced for the change from baseline of QMG at Week 26 for the 6 patients.

7.2.2. Secondary Efficacy Endpoint Analyses

The following secondary efficacy endpoints that involve changes from baseline regardless of rescue treatment during the primary 26 weeks treatment period will be summarized and analyzed

in a similar way as was described for the primary efficacy endpoint QMG using the mFAS Population:

- MG-ADL total score
- MGC total score
- EQ-5D-Y
- Neuro-QoL Pediatric Fatigue

In addition, summaries of the MG-ADL total score, the MGC total score, EQ-5D-Y (or proxy) VAS score, and Neuro-QoL Pediatric Fatigue total score regardless of rescue treatment at each visit as well as changes from baseline during the primary treatment period will be provided for the younger patients (<12 years old) if 2 or more such patients are enrolled. Otherwise data listings will be provided instead.

Summaries of the PROMIS Parent Proxy Short Form V2.0-Fatigue 10A total score for patients <8 years of age and the Neuro-QoL Pediatric Fatigue total score for patients ≥ 8 years of age and < 12 years of age at each visit as well as changes from baseline at each visit will be provided if 2 or more such patients are enrolled. Otherwise data listings will be provided instead.

The proportion of patients with at least a 5-point reduction in the QMG total score from 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 mFAS Population. Exact (Clopper-Pearson) 95% confidence intervals for the true proportion and the p-value to test the null hypothesis of no reduction from baseline will be presented. For the purpose of statistical implementation using SAS, the p-value will be calculated using SAS PROC FREQ procedure using the hypothesized proportion of 1% under the null hypothesis.

The proportion of patients with at least a 3-point reduction in the MG-ADL total score from 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 mFAS Population in the same manner as the OMG totals score.

The proportions of patients with various point reductions from baseline at each visit will be presented for QMG and MG-ADL total scores respectively, with and without rescue therapy.

In addition, the 95% confidence intervals and p-values will be presented for the proportions of patients with at least a 3,4,6 to 10-point reduction in QMG total score, and at least a 2, 4 to 8-point reduction in MG-ADL total score from baseline to Week 26 respectively, with and without regard to rescue therapy.

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

7.2.3. Other Efficacy Analyses

The MGFA Post-interventional status over time regardless of rescue treatment will be summarized by age group and overall using the FAS population if 2 or more patients < 12 years old are enrolled. Otherwise data will be summarized using the mFAS population and data listings for patients < 12 years will be provided instead.

A summary table of the number and percent of patients who achieved Minimal Manifestations (MM) of MG will be produced by age group and overall.

Summary tables of the number and percent of patients experiencing clinical deterioration, and MG Crisis will be produced by age group and overall, as well as summaries of the number and percent of patients 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.

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

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

Summary tables of Serum Eculizumab Concentrations (μg/mL), Serum Free C5 (μg/mL), and Hemolysis (%) Measured by an Ex Vivo cRBC Assay will be provided by Age Group over time. Corresponding data listings will also be created.

7.2.5. Biomarker Analyses

Anti-AChR antibody values at screening will be summarized by Age group. Patient data listings will be created.

7.3. Safety Analyses

All safety data (including data collected beyond week 26) in the primary analysis database cut will be included in the Safety Analyses.

All safety analyses will be conducted on the Safety Population. All safety data will be provided in patient listings. No formal hypothesis testing is planned. Baseline is defined as the last available assessment prior to eculizumab treatment.

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

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

Study duration will be calculated as the time in days from first eculizumab dose date 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 until the last IP dose date of eculizumab (i.e., Treatment duration (days) = Last IP Dose Date – First IP Dose Date + 1).

Compliance will be calculated as 100*(total amount of study drug infused (ml)/total amount of study drug expected (ml).

7.3.2. Adverse Events (AEs)

Adverse Events are defined in Protocol Section 9.6.

Pretreatment AEs will be provided in a data listing.

For the purposes of this SAP, TEAEs will be noted as:

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

TEAEs are AEs that onset during or after the first IP dose. Likewise, TESAEs are SAEs that onset during or after the first IP dose.

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.

7.3.2.1. Overall Summary of Adverse Events

The number of TEAEs and the number and percent of patients with TEAEs will be presented for each Age group and overall. Also, the number of TEAEs and the number and percent 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.

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

The number of TEAEs, the number and percent of patients with TEAEs, and the TEAE rate per 100 patient-years will be presented by SOC and PT for each Age 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 Age group in the Safety Population. 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 Age 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 Age group in the Safety Population.

Adverse events of special interest (AESI) 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 (AESI), the number and percentage of patients with AESIs, and the AESI rate per 100 patient-years will be presented by SOC and PT for each age group and overall. Related AESIs will also be summarized in a similar way.

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

TEAEs, and TESAEs will be summarized at the patient level by SOC, PT, and grouped relationship (related, unrelated) using frequencies and percentages. These summaries will be presented by Age group and overall.

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

TEAEs will be summarized at the patient level by SOC, PT, and severity using frequencies and percentages by Age 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 Age 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 Age 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

Descriptive statistics will be presented by visit for each Age Group for the actual values and the changes from the baseline for each quantitative laboratory test (hematology, serum chemistry). Shift tables for changes in status (low, normal, high) from baseline will also be presented by visit for each laboratory parameter for each Age 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.

A listing will be produced for urinalysis and pregnancy tests.

7.3.3.2. Vital Signs

Descriptive statistics will be presented by visit for each Age 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 Age group and overall will be produced reporting the number and percentage of patients 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

Summary statistics will be provided for abnormal physical examination. In addition, a data 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 Age group and overall using counts and percentages. For each Age group and overall, descriptive statistics will be presented by visit for each ECG parameter (ventricular rate, PR duration, QRS duration, QT duration, and RR duration). Shift changes over time from baseline will be summarized by age group.

Counts and percentages will be presented by visit for each Age 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 Age 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. Immunogenicity

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

7.3.3.4.3. 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.

7.3.3.4.4. Protocol Required Vaccination

A by-patient listing of protocol required vaccinations will be produced.

7.3.3.4.5. Hospitalizations

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

A corresponding data listing will be provided.

8. REFERENCES

None.

9. APPENDICES

9.1. Protocol Schedule of Events

The visits in the ECU-MG-303 study that are included for the primary analysis are as follows:

Table 2: Visits for the Primary Evaluation Treatment Period in the ECU-MG-303 Study

Period/Phase	Trial Visit	Trial Weeks
Weight Cohorts ≥ 40 kg, 30 to <40 kg, and 20 to <30 kg	Visit 2	Day 1
	Visit 3	Week 1
	Visit 4	Week 2
	Visit 5	Week 3
	Visit 6	Week 4
	Visit 7	Week 6
	Visit 8	Week 8
	Visit 9	Week 10
	Visit 10	Week 12
	Visit 11	Week 14
	Visit 12	Week 16
	Visit 13	Week 18
	Visit 14	Week 20
	Visit 15	Week 22
	Visit 16	Week 24
	Visit 17	Week 26
Weight Cohort 10 to <20 kg	Visit 2	Day 1
	Visit 3	Week 1
	Visit 4	Week 3
	Visit 5	Week 5
	Visit 6	Week 7
	Visit 7	Week 9
	Visit 8	Week 11
	Visit 9	Week 13
	Visit 10	Week 15
	Visit 11	Week 17
	Visit 12	Week 19
	Visit 13	Week 21
	Visit 14	Week 23
	Visit 15	Week 25
	Visit 16	Week 27
Clinical Deterioration		
Unscheduled		
Post Treatment Safety Follow-up		+ week 8

9.2. Sample Size, Power, and Randomization

Calculations of sample size and power are described in Section 10.3 of the protocol. The study is open-label with all patients being treated with Eculizumab, therefore there is no need for randomization of patients.

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 for all patients.

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. 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.

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

9.4. Additional Details on Statistical Methods

Not applicable