Alexion Pharmaceuticals, Inc.

Final Clinical Study Report
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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2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
AChR	acetylcholine receptor
ADA	antidrug antibody
AE	adverse event
AESI	Adverse event of special interest
AZA	azathioprine
BP	blood pressure
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
EQ-5D-Y	European Quality-of-Life 5-Dimension Youth version
FAS	Full Analysis Set
gMG	generalized myasthenia gravis
HLT	High-level term
HR	Heart Rate
IP	investigational product
IST	immunosuppressant therapy
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living profile
MGC	Myasthenia Gravis Composite Scale
MGFA	Myasthenia Gravis Foundation of America
MMF	mycophenolate mofetil
Neuro-QoL Fatigue	Neurological Quality of Life-Fatigue questionnaire
PD	pharmacodynamic(s)
PDCO	Paediatric Committee of the European Medicines Agency
PK	pharmacokinetic(s)
PT	Preferred Term
QMG	Quantitative Myasthenia Gravis score for disease severity
QTC	corrected QC interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RR	respiration rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQ (N)	standard MedDRA query (narrow)
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VAS	visual analogue scale

4. DESCRIPTION OF THE PROTOCOL

ECU-MG-303 is a Phase 3, open-label, multicenter study to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous eculizumab in pediatric patients aged 6 to < 18 years with acetylcholine receptor (AChR)-antibody positive refractory generalized myasthenia gravis (gMG).

There are 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 completed Week 26 of Study ECU-MG-303 continued receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks. The 8-week Follow-up Period was required following the last dose of the study drug for all patients upon withdrawal or discontinuation from the study or upon completion of the study when the patient was not continuing to receive eculizumab treatment.

Patients may continue the use of acetylcholinesterase inhibitors, 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 as follows:

- To evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG
- To 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)
- To 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 (not applicable as no patients < 8 years of age at Screening were treated) 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 (not applicable as no patients < 8 years of age at Screening were treated)
- To evaluate Myasthenia Gravis Foundation of America (MGFA) Post-Interventional Status over time
- To describe the total number and percentage of patients with clinical deterioration, myasthenic crisis, and rescue therapy use over time

- To describe the PK and PD of eculizumab treatment in pediatric patients with refractory gMG to confirm the pediatric dosage regimen selected through modeling and simulation following 26 weeks of eculizumab treatment

The Extension Period objectives are as follows:

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

This SAP describes the statistical methods used in the final analysis and statistical analyses performed for the final clinical study report (CSR) using data from both Primary Evaluation Treatment Period and Extension Period.

The interim analysis of this study was conducted based on a data cutoff date of 06 Jan 2022, according to the SAP v1.0 (finalized on 30 Oct 2019) and SAP addendum (finalized on 18 Jan 2022) to fulfill specific requirements of the Paediatric Committee of the European Medicines Agency (PDCO) based on the 26-Week Primary Evaluation Treatment Period data.

Analyses included in this final comprehensive CSR consist of select interim analyses focusing on the Primary Evaluation Treatment Period data only and aggregated analyses using both Primary Evaluation Treatment Period and Extension Period data.

4.1. Changes From Analyses Specified in the Protocol

This is the final SAP for the final 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 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 myasthenia gravis (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 as follows:

- Double vision (lateral gaze)
- Ptosis (upward gaze)
- Facial muscles
- Swallowing (4 oz. water (1/2 cup))
- Speech following counting aloud from 1 to 50 (onset of dysarthria)
- Right arm outstretched (90°; sitting)
- Left arm outstretched (90°; sitting)
- Forced vital capacity
- Right hand grip
- Left hand grip
- Head, lifted (45° supine)
- Right leg outstretched (45° supine)
- Left leg outstretched (45° 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 continued 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 as follows:

- 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 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 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 the 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 8 items graded on the MG-ADL are as follows:

- 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. MGC

The MGC is a validated assessment tool for measuring the clinical status of patients with MG. 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 as follows:

- 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 the 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 were to continue to be evaluated based on the survey initially completed upon entry into the study. Change in age during the study was not to 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 assessments were 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 the 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 continued to be evaluated based on the survey initially completed upon entry into the study.

Patients who were younger than the lowest age range of the applicable scale (ie, patients < 8 years of age) would be evaluated using the PROMIS Parent Proxy Short Form v2.0 – Fatigue 10a questionnaire. The parent or legal guardian (the proxy) would 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 questionnaire was 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 was assessed using the MGFA Post-Intervention Status. Change in status categories of Improved, Unchanged, Worse, as well as the presence of Minimal Manifestation status were 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 Extension Period efficacy endpoints for this study are as follows:

- 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

Analyses and summary of Extension Period efficacy endpoints will be reported together with the Primary Evaluation Treatment Period data (primary and secondary endpoints) as described in Section 7.

5.2. Safety

All aggregated safety data in the database lock for the final analysis will be analyzed.

The safety endpoints of the study are as follows:

- Frequency of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (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 (ECG) parameters
- Change from Baseline in laboratory assessments

5.2.1. Adverse Events

All adverse events (AEs; serious and nonserious) were collected from the signing of the informed consent form.

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

TEAEs (serious and nonserious) are defined as all AEs starting on or after the first dose of the study drug.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that was current at the time of the analysis.

5.2.2. Vital Signs

Vital sign measurements were taken after the patient had been resting for at least 5 minutes and will include systolic and diastolic blood pressure (BP; mmHg), heart rate (HR; beats/minute), respiratory rate (RR; breaths/minute), and temperature (°C or °F). Vital signs were taken prior to each administration of the study drug.

5.2.3. Laboratory Assessments

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

5.2.4. Physical Examination

Each examination was to 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] and weight [kg]) was assessed. The accurate weighing of patients is vital as part of their management, as eculizumab dosing was to depend on the patient's recorded body weight at the most recent dosing visit. It was recommended that patients should be weighed in the same amount of clothing in each instance where weight is assessed.

5.2.4.1. ECG

A 12-lead ECG was 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 was responsible for reviewing the ECG to assess whether the ECG was within normal limits and to determine the clinical significance of the results.

5.2.4.2. Immunogenicity

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

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set and Modified Full Analysis Set Population

The Full Analysis Set (FAS) Population consists of all patients who have received at least 1 dose of eculizumab.

A subset of the FAS that includes adolescent 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).

Given that there are no patients dosed in the age group of 6 to < 12 years old, FAS and mFAS are identical. Only mFAS will be used for all efficacy analyses.

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

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

7. STATISTICAL ANALYSIS

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

Alexion will be responsible for data collection and editing, reviewing, and validating all the information in the electronic case report forms, statistical analysis, and generation of the final CSR.

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

For continuous variables, summary statistics will include the sample size, mean, SD, 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.

For the analysis of the efficacy endpoints on the mFAS Population, descriptive statistical summaries will also be presented by the status of maintenance IVIg at study entry (yes or no), and overall.

7.1. Study Patients

7.1.1. Disposition of Patients

The number of patients enrolled in the study, treated, who completed the trial, and discontinued from the trial (Primary Evaluation Treatment Period and Extension Period separately), along with the reasons for discontinuation, will be tabulated. The number and percentage 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.

7.1.2. Protocol Deviations

The number and type of important and non-important protocol deviations during the Primary Evaluation Treatment Period, during the Extension Period, as well as throughout the entire study will be presented separately using the Safety Set Population. Protocol deviations will also be summarized at the patient level using counts and percentages.

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.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (years) at Screening
- Sex
- Race and ethnicity
- Japanese descent
- Height
- Weight
- Body mass index

7.1.3.2. Disease Characteristics

The following MG disease characteristics including MG history will be summarized:

- Age at MG diagnosis (years)
- Duration of MG (time from diagnosis to first dose date (in years))
- Type of the first MG presentation (ocular MG 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, (ie, number [%] of patients who have a medical or surgical history), will be summarized by System Organ Class (SOC) and Preferred Term (PT).

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 version in use by Alexion at the time of the analysis. Summaries will be presented based on the Safety Set Population.

Prior medications (MG or non-MG medication) will be summarized. Concomitant medications (MG or non-MG medication) taken during the Primary Evaluation Treatment Period, during the Extension Period, and overall will be summarized separately. The number (%) of patients using medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical Level 4 class code and generic name.

MG therapy status during the study by study visit and the prior MG therapy status will be summarized.

ISTs are allowed during the trial and include but are not limited to corticosteroid, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate, tacrolimus, cyclosporine, and cyclophosphamide.

The number and percentage of patients with baseline IST therapies as well as changes in IST usage (corticosteroid and other IST) and cholinesterase inhibitor during the Primary Evaluation Treatment Period and Extension Period, and overall will be summarized separately.

In addition, summary statistics of the daily dose of corticosteroids, AZA, and MMF at Baseline and at the last reported visit on study treatment will be produced. In addition, the number and percentage 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 percentage of patients with usage of ISTs, IVIg, and plasma exchange during the study, as well as prior to study treatment will be summarized separately.

Prior and concomitant non-drug therapies and procedures during the Primary Evaluation Treatment Period and Extension Period, and overall will be summarized separately by SOC and PT.

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

7.2. Efficacy Analyses

All efficacy data collected from the study (Primary Evaluation Treatment Period and Extension Period through study completion/discontinuation) will be included in the final analyses.

The mFAS Population will be used for all efficacy analyses.

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 or no), and overall patients in the mFAS Population.

The Baseline is the last assessment prior to the 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 the primary endpoint for this study are described as follows:

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

where μ represents the mean change 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 was conducted at Week 12 in order to assess the effect of eculizumab treatment during the 12 weeks in which MG medications (ie, ISTs and IVIg) are continued at a stable dose. For the purpose of satisfying specific requirements of the PDCO of the European Medicines Agency, a primary efficacy analysis was also conducted at Week 26. Both analyses were based on the same Repeated-Measure model analysis as described below using only the 26-Week Primary Evaluation Treatment Period data. The same analysis as performed at the interim analysis will be repeated in the final CSR.

A Repeated-Measure model will be used to analyze the observed change in QMG with baseline QMG score and visits as covariates. A compound symmetry (co)variance structure will be used to model the within-patient errors. 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 (CI) of the least-squares mean will be produced. Missing primary endpoints at post-Baseline visits will not be imputed. In

addition, a separate Repeated-Measure model analysis using change from Baseline data through Week 52 will be conducted to assess longer-term treatment effects, following the same approach as described above.

Summaries of the QMG at each visit during the study (both 26-Week Primary Evaluation Treatment Period and Extension Period) as well as changes from Baseline at each study visit (including the "last assessment" visit, which is defined as the last assessment of each subject) will also be provided.

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 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 2-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect (change from Baseline with eculizumab treatment) on efficacy parameters will be accompanied by 2-sided 95% CIs for the effect size.

7.2.2. Secondary Efficacy Endpoint Analyses

The following secondary efficacy endpoints that involve changes from Baseline over time regardless of rescue treatment 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

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 (including the last assessment visit) for the mFAS Population. Exact (Clopper-Pearson) 95% CIs 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 the 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 (including the last assessment visit) for the mFAS Population in the same manner as the QMG totals score.

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

In addition, the 95% CIs 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 over time showing the number and percentage of patients for each item will be produced.

7.2.3. Other Efficacy Analyses

The MGFA post-interventional status over time (including the last assessment visit) regardless of rescue treatment will be summarized using the mFAS Population.

A summary table of the number and percentage of patients who achieved minimal manifestations of MG will be produced.

Summary tables of the number and percent of patients experiencing clinical deterioration, and MG crisis during the Primary Evaluation Treatment Period and Extension Period, and overall will be produced separately, as well as summaries of the number and percentage 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 during the Primary Evaluation Treatment Period, Extension Period, and overall.

7.2.4. PK and PD Analyses

Summary tables of serum eculizumab concentrations (μg/mL), serum free complement protein 5 (μg/mL), and hemolysis (%) measured by an ex vivo cRBC assay during the study will be provided over time. Corresponding data listings will also be created.

7.2.5. Biomarker Analyses

Anti-AChR antibody values at Screening will be summarized. Patient data listings will be created.

7.3. Safety Analyses

All safety data in the final database lock 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. The 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 (during Primary Evaluation Treatment Period and overall), treatment duration (during Primary Evaluation Treatment Period and overall), and exposure will be summarized using descriptive statistics for the Safety Populations. Treatment compliance (during Primary Evaluation Treatment Period and overall) will be summarized using counts and percentages.

Study duration will be calculated as the time in days from the first eculizumab dose date until the date of completion/discontinuation (or death) from the study (ie, 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 (ie, 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 as per dosing schedule [mL] as of the last dosing study visit). (Note: Supplemental doses for any purposes are excluded from this calculation.) Compliance (during Primary Evaluation Treatment Period and overall) will be calculated and summarized.

7.3.2. AEs

AEs 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 follows:

- TEAEs
- TESAEs

TEAEs are AEs that onset during or after the first IP dose. Likewise, TESAEs are serious adverse events (SAEs) that onset during or after the first IP dose.

AEs will be coded by primary SOC and PT using the MedDRA using the current dictionary version at the time of the final analysis.

7.3.2.1. Overall Summary of AEs

The number of TEAEs and the number and percentage of patients with TEAEs during the study will be presented. 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 the study will be presented.

Overview of TEAEs will also be summarized based on the start day of TEAE by time period.

7.3.2.2. AEs and SAEs by SOC and PT.

The number of TEAEs, the number and percentage of patients with TEAEs, and the TEAE rate per 100 patient-years will be presented by SOC and PT. 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 Safety Population. A similar summary will be created for TESAEs and for all non-serious TEAEs.

Summary table of TEAE, TESAE by SOC and PT will also be performed based on the start day of AE by time period.

Likewise, the percentage of patients with TEAEs will be presented by PT. At the patient level, patients are counted once in each PT. Percentages will be based on the total number of patients in the Safety Population. The same analysis will also be performed based on the start day of AE by time period.

Adverse events of special interest (AESIs) for eculizumab include the following:

- Infections:
  - **Meningococcal infections**: Defined as any TEAEs for the following MedDRA PTs**:** "Meningococcal bacteraemia," "Meningitis meningococcal," "Meningococcal infection," "Meningococcal sepsis," "Meningococcal carditis," "Encephalitis meningococcal," "Endocarditis meningococcal," "Myocarditis meningococcal," "Optic neuritis meningococcal," and "Pericarditis meningococcal"
  - **Aspergillus Infections**: Defined as any TEAEs for the PTs in the MedDRA high-level term (HLT): "Aspergillus infections" and the preferred term of **"**Aspergillus test positive"
  - **Other Serious Infections**: Defined as any SAE for the PTs in the MedDRA SOC "Infections and infestations," excluding the PTs listed for the AESIs of Meningococcal Infections, Aspergillus Infections, and Sepsis
  - **Sepsis**: Defined as any TEAEs for the PTs within the Sepsis, Bacteraemia, Viraemia, and Fungaemia NEC HLT.
- **Infusion Reactions**: Defined as any treatment-related TEAEs for the PTs in the standard MedDRA query (narrow) (SMQ [N]): "Anaphylactic reaction" and the SMQ (N): "Hypersensitivity"

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. 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 or unrelated) using frequencies and percentages. These summaries will be presented.

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.

7.3.2.5. Deaths, Other SAEs, and Other Significant AEs

The number and percentage of patients with TEAEs leading to discontinuation from the study will be presented overall and by PT. Similarly, the number and percentage of patients with TEAEs resulting in death will be presented overall and by PT. Listings of patients with AEs leading to discontinuation from the study and of patients with AEs 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 the actual values and the changes from the Baseline for each quantitative laboratory test (hematology or serum chemistry). Shift tables for changes in status (low, normal, or high) from Baseline will also be presented by visit 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.

7.3.3.2. Vital Signs

Descriptive statistics will be presented by visit for the actual values and the changes from Baseline for each vital sign (systolic and diastolic BP, temperature, RR, and seated or supine HR) and for body weight.

Vital sign and weight outlier tables will be produced reporting the number and percentage of patients with at least 1 post-treatment outlier using the following criteria:

- Systolic BP: < 90 mmHg, > 140 mmHg, or > 160 mmHg
- Diastolic BP: < 50 mmHg, > 90 mmHg, or > 100 mmHg
- Pulse Rate: < 60 bpm or > 100 bpm
- Body Weight: Decrease of ≥ 7% from Baseline and increase of ≥ 7% from Baseline
- Temperature: > 38.0°C or < 36.0°C
- RR: < 12 breaths/min or > 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 examination data will be produced.

7.3.3.4. Other Safety Parameters of Special Interest

7.3.3.4.1. ECG

ECG results (normal; abnormal, not clinically significant; abnormal, clinically significant; and not assessed/not applicable) will be summarized by visit using counts and percentages. 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.

Counts and percentages will be presented by visit for corrected QC interval (QTC), Fridericia's corrected QT interval (QTcF), and Bazett's corrected QT interval (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 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 and presented in by-patient listing.

7.3.3.4.3. Non-Drug Therapies and Procedures

Non-drug therapies and procedures used during the Primary Evaluation Treatment Period and Extension Period, and overall will be summarized separately by SOC and PT 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 percentage of patients hospitalized during the study and the total number of reported hospitalizations will be presented. The duration of each hospitalization will be summarized at the hospitalization level using descriptive statistics.

8. REFERENCES

None.

9. APPENDICES

9.1. Sample Size, Power, and Randomization

Calculations of sample size and power are described in Section 10.3 of the Protocol. This is an open-label study with all patients being treated with eculizumab; therefore, there was no need for patient randomization.

9.2. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

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 15 Jun.

Definition of Baseline Values

The 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 follows:

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)

AEs

The analysis of AEs is described in detail in Section 7.3.2.

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.

9.3. Additional Details on Statistical Methods

Not applicable.