TITLE PAGE

STATISTICAL ANALYSIS PLAN

Final Analysis

Version Number: Final 2.0

Protocol Title: A Phase 3, Prospective, Multicenter, Double-blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eculizumab in Patients With Guillain-Barré Syndrome (GBS)

Protocol Number: ECU-GBS-301

Protocol Amendment Number: Not applicable

Compound: Eculizumab (SOLIRIS®)

Short Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Eculizumab in Guillain-Barré Syndrome

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

VERSION HISTORY

This statistical analysis plan (SAP) for Study ECU-GBS-301 is based on protocol amendment 1.0, dated 28 Oct 2021.

SAP Version	Version Date	Change	Rationale
1	02 Dec 2021	Not applicable	Original version
2	30 Jun 2022	See Section 6.2 (Appendix 2) for detailed changes.	The definition of treatment-emergent adverse event was made consistent with the protocol in SAP Version 2.0. The Pharmacokinetic Analysis Set was revised to include patients who received placebo. The Pharmacodynamic Analysis Set was added. Efficacy analyses to assess the impact of Coronavirus Disease 2019 were revised using the while-on-treatment strategy. Subgroup analyses on treatment-emergent adverse event were added. Multiple imputations using linear regression model were used to predict missing Functional Grade scores after discontinuation. As a sensitivity analysis, baseline observation carried forward was used to impute the missing values for patients who discontinued the study. This reflects the worst-case scenario.

APPROVAL SIGNATURES

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for the final analysis for Study ECU-GBS-301. Standard data presentation instructions and table, figure, and listing specifications are contained in the data presentation plan in a separate document.

All data collected in this protocol except for the exploratory biomarker data will be included for the final database lock and statistical analysis. The statistical analysis of biomarker data will be provided in a separate document.

This SAP is finalized before database lock and study unblinding.

The planned interim analysis for sample size re-estimation is provided in a separate interim analysis plan (IAP).

1.1. Objectives and Endpoints

The objectives and endpoints for this study are provided in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the efficacy of eculizumab in patients with GBS	• Time to first reaching a Hughes FG score ≤ 1
Key Secondary	
To further characterize the efficacy of eculizumab over time in patients with GBS	• Proportion of patients with a Hughes FG score ≤ 1 at Week 24 • Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24 • Proportion of patients with a Hughes FG score ≤ 1 at Week 8
Other Secondary	

To further characterize the impact of eculizumab on medical resource utilization in patients with GBS	• Hospital LOS
	• ICU stay
	   o LOS in the ICU
	   o Proportion of patients admitted to the ICU
	• Disposition post hospital discharge

To evaluate the effect of eculizumab compared with placebo on respiratory function in patients with GBS	• Ventilator support
	   o Duration of ventilator support
	   o Proportion of patients requiring ventilator support

To characterize the PK/PD attributes of eculizumab in patients with GBS	• Concentration of eculizumab in serum • Free C5 in serum • Hemolytic complement activity in serum
To assess the formation of ADAs in response to eculizumab treatment	• Incidence of ADAs
Safety	
To characterize the overall safety and tolerability of eculizumab in patients with GBS	• Incidence of TEAEs, SAEs, and AEs leading to study drug discontinuation

Table 1:   Objectives and Endpoints

Objectives	Endpoints
Tertiary/Exploratory	
To characterize the functional status of patients with GBS postacute phase	• Change from Baseline in the functional scales of GBS (R-ODS and ONLS) • Change from Baseline in strength measurements (MRC-SS and MMT) • Change from Baseline in the Hughes FG score over time
To evaluate the effect of eculizumab compared with placebo on pain in patients with GBS	• Change from Baseline in the SF-MPQ-2 score
To evaluate the effect of eculizumab compared with placebo on mood in patients with GBS	• Change from Baseline in the DASS-21 score
To evaluate the effect of eculizumab compared with placebo on fatigue in patients with GBS	• Change from Baseline in the Chalder score
To evaluate the effect of eculizumab compared with placebo on QoL in patients with GBS	• Change from Baseline in the EQ-5D-5L score • Change from Baseline in the WPAI score
To evaluate complement, inflammation, and neurodegeneration biomarkers in patients with GBS	• Change from Baseline in biomarker levels in blood

Abbreviations: ADA = antidrug antibody; AE = adverse event; C5 = complement component 5; Chalder = Chalder Fatigue Scale; DASS -21 = Depression, Anxiety, and Stress Scale, Short Form, 21 Questions; EQ-5D-5L = European Quality of Life – 5 Dimensions – 5 Levels; FG = Functional Grade; GBS = Guillain-Barré syndrome; ICU = intensive care unit; LOS = length of stay; MMT = Manual Muscle Testing; ONLS = Overall Neuropathy Limitations Scale; PD = pharmacodynamic; PK = pharmacokinetic; QoL = quality of life; R-ODS = Rasch-Built Overall Disability Scale; SAE = serious adverse event; SF-MPQ-2 = Short Form McGill Pain Questionnaire 2; TEAE = treatment-emergent adverse event; WPAI = Work Productivity and Activity Impairment

1.2.   Study Design

Study ECU-GBS-301 is a Phase 3, prospective, multicenter, placebo-controlled, double-blind, randomized study to investigate the efficacy and safety of eculizumab in patients with severe Guillain-Barré syndrome (GBS), defined using the Hughes Functional Grade (FG) score (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997) as progressively deteriorating FG3 or FG4/FG5 within 2 weeks from onset of weakness due to GBS. Eligible GBS patients will be randomized in a 2:1 ratio to either eculizumab intravenous (IV) infusion or placebo IV infusion within each stratum as defined in Table 2. All patients will be on concomitant IV immunoglobulin (IVIg) therapy per standard of care (400 mg/kg body weight daily for 5 days).

Table 2:   Randomization Strata

Strata	FG Score	Diarrhea
	Progressively Deteriorating FG3 vs Stable or Progressively Deteriorating FG4/5	**Present vs Absent < 4 Weeks Prior to Onset of Neurological Symptoms**
1	Progressively deteriorating FG3	Present
2	Progressively deteriorating FG3	Absent

Table 2:   Randomization Strata

Strata	FG Score	Diarrhea
	Progressively Deteriorating FG3 vs Stable or Progressively Deteriorating FG4/5	**Present vs Absent < 4 Weeks Prior to Onset of Neurological Symptoms**
3	Stable or progressively deteriorating FG4/5	Present
4	Stable or progressively deteriorating FG4/5	Absent

Abbreviations: FG = Functional Grade; vs = versus

There will be 3 periods in the study as follows:

- Screening Period: up to 1 week
- Treatment Period: 4 weeks
- Follow-up Period: 20 weeks

Approximately 57 patients (eculizumab = 38 and placebo = 19) will be randomized. The total duration of study participation for each patient will be up to 25 weeks. Efficacy and safety will be monitored through 24 weeks after the first dose of the study drug. An interim analysis is planned for the unblinded sample size re-estimation when approximately 60% (ie, at least 12 events) of the planned events (FG score ≤ 1) are observed.

Eculizumab will be administered via IV infusion at a dose of 900 mg once per week for 4 weeks. A supplemental dose of 600 mg will be given with the first dose on Day 1.

Placebo will be administered via IV infusion once per week for 4 weeks. Placebo is a matching sterile, clear, colorless solution with the same buffer components but without active ingredient, in an identical 30-mL vial. A supplemental dose of placebo will be administered with the first dose on Day 1 to maintain the blind.

Treatment allocation will be blinded to patients, study site, the Sponsor, and the Sponsor's delegates throughout the study.

There is no data monitoring committee for this study, but an independent analysis center (IAC) will be established for the interim analysis.

The final statistical analysis will occur when the last patient has completed the 20-week Follow-up Period and the last scheduled visit or prematurely discontinued from the study and when the database is locked.

Figure 1:   Study Design Schematic
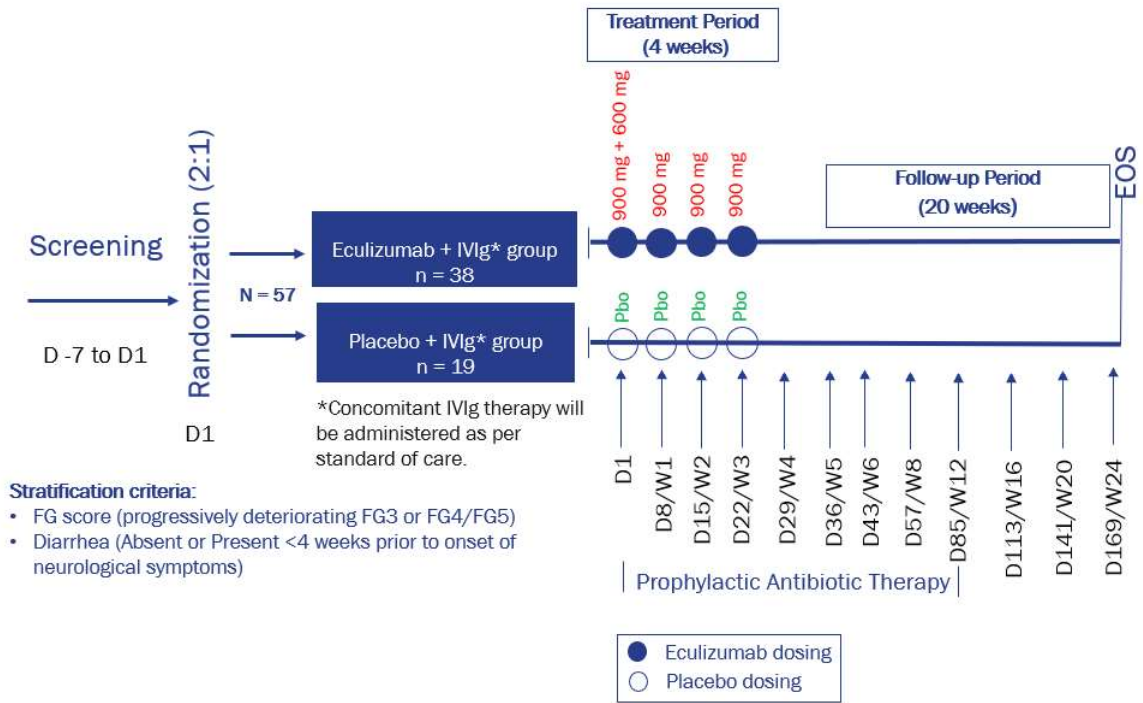
Abbreviations: D = day; EOS = end of study; FG = Functional Grade; IVIg = intravenous immunoglobulin;
     N = number of patients randomized; n = number of patients in each treatment group; Pbo = placebo; W = week

2.   STATISTICAL HYPOTHESES

2.1.   Primary Hypothesis

The primary null hypothesis is that the effect of eculizumab is no different from placebo in time to first reaching a Hughes FG score ≤ 1. The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab based on time to first reaching a Hughes FG score ≤ 1.

2.2.   Key Secondary Hypotheses

The null hypothesis associated with the key secondary objectives is that eculizumab is no different from placebo for the respective endpoints. The alternative hypotheses are described as follows:

- Proportion of patients with a Hughes FG score ≤ 1 at Week 24: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score ≤ 1 at Week 24.

- Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score improvement of ≥ 3 at Week 24.

- Proportion of patients with a Hughes FG score ≤ 1 at Week 8: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score ≤ 1 at Week 8.

2.3.   Multiplicity Adjustment

The primary hypothesis will be tested with a 2-sided type 1 error of 0.05.

Hypothesis testing associated with the key secondary endpoints will proceed only if the null hypothesis associated with the primary endpoint is rejected and will proceed from the highest rank ([1] proportion of patients with a Hughes FG score ≤ 1 at Week 24) to the lowest rank ([3] proportion of patients with a Hughes FG score ≤ 1 at Week 8). If statistical significance is not achieved at an endpoint (2-sided $p \leq 0.05$), then the endpoint of lower rank will not be considered to be statistically significant. Confidence intervals (CIs) and p-values will be presented for all key secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure.

An unblinded interim analysis on at least 12 events (FG score ≤ 1; approximately 60% of the planned events) will be conducted for only the sample size re-estimation based on the conditional power. Details are provided in a separate IAP. The method by Gao et al (Gao, 2008) will be used for controlling the type 1 error rate due to the interim analysis.

Further details are provided in Sections 5.8 and 6.2.1.

3.   SAMPLE SIZE DETERMINATION

The sample size for this study is based on results from the Investigator-initiated study in Japan (Misawa, 2018). Assuming a 2:1 randomization of patients with GBS to eculizumab and placebo, a dropout rate of approximately 10%, a cumulative probability of response at 24 weeks of 70% for eculizumab and 20% for placebo (corresponding to a true hazard ratio of 5.4), 1-sided type 1 error of 0.025, and a fixed Follow-up Period of 24 weeks for each patient with approximately an average enrollment rate of 1 patient per week, a total sample size of 57 patients with approximately a total of 19 events (responders) would provide at least 90% power using a log-rank test for the primary endpoint, time to first reaching a Hughes FG score ≤ 1.

The total sample size of 57 patients (assuming a dropout rate of approximately 10%) will provide at least 90% power to detect a treatment difference of 50% in favor of eculizumab for the first key secondary endpoint FG score ≤ 1 at Week 24, assuming a placebo response rate of 20%; at least 85% power to detect a treatment difference of 43% in favor of eculizumab for the second key secondary endpoint FG improvement of ≥ 3 at Week 24, assuming a placebo response rate of 27%; and approximately 85% power to detect a treatment difference of 40% in favor of eculizumab for the third key secondary endpoint FG score ≤ 1 at Week 8, assuming a placebo response rate of 20%.

An interim analysis is planned for the unblinded sample size re-estimation when approximately 60% (ie, at least 12 events) of the planned events (FG score ≤ 1) are observed. The sample size will be increased to a maximum of 72 patients to generate a maximum of approximately 32 events using a conditional power approach. Further details will be provided in the IAP.

The sample size calculation was performed in EAST 6.5 using the log-rank test for the primary endpoint and 2-sample test for the difference in proportions with unpooled variance estimate for the key secondary endpoints.

4.   ANALYSIS SETS

The analysis sets are defined in Table 3.

Table 3:   Analysis Sets

Analysis Set	Description
FAS	All randomized patients who received at least 1 dose of study drug and have a baseline FG score and at least 1 postbaseline FG score. Patients will be analyzed according to the treatment group assigned by randomization.
SS	All patients who received at least 1 dose of study drug. Patients will be analyzed according to the study drug they actually received. For a participant to be analyzed according to the treatment they actually received, they would have to receive that treatment for the entire duration of the study treatment period.
PPS	All FAS patients without any major protocol deviations.
PKAS	All patients who received at least 1 dose of study drug and who have at least 1 postdose PK sample.
PDAS	All patients who received at least 1 dose of study drug and who have at least 1 postdose PD sample.

Abbreviations: FAS = Full Analysis Set; FG = Functional Grade; PD = pharmacodynamic;
    PDAS = Pharmacodynamic Analysis Set; PK = pharmacokinetic; PKAS = Pharmacokinetic Analysis Set;
    PPS = Per Protocol Set; SS = Safety Set

In general, all efficacy analyses will be based on the Full Analysis Set (FAS). Supplemental per-protocol analyses for the primary efficacy endpoint will be performed based on the Per Protocol Set (PPS) in the same manner as done for the FAS. Safety analyses will be performed on the Safety Set (SS).

Further details on addressing Coronavirus Disease 2019 (COVID-19) impacts are provided in Section 6.5.

5. STATISTICAL ANALYSES

5.1. General Considerations

Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings, and figures. Inference from efficacy analyses will be based on a 2-sided type 1 error (α) = 0.05 unless stated otherwise.

The summary statistics for continuous variables will include, but will not be limited to, the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

The baseline value for analysis and reporting will be based on the last nonmissing measurement on or prior to the first dose of the study drug unless stated otherwise.

Analyses will be performed using the Statistical Analysis System (SAS®) software version 9.4 or higher.

Alexion will be responsible for collecting data, reviewing and validating all the information in the electronic case report forms (CRFs), performing statistical analysis, and generating the final clinical report.

The Alexion Quantitative Sciences Department will perform the statistical analysis of the data derived from this study.

Medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2021 or higher). Therapies will be coded using Medical Dictionary for Regulatory Activities (MedDRA; version 24.0 or higher).

Adverse events (AEs) will be coded by primary system organ class (SOC) and preferred term (PT) using MedDRA (version 24.0 or higher).

The impacts of COVID-19 on the planned analyses are described in Section 6.5.

5.2. Study Patients

5.2.1. Disposition of Patients

The number of patients screened, the number of screen failures and the reasons for screen failures, the number of patients randomized and treated in the study, the number of patients who completed the study, and the number of patients who discontinued from the study and the reasons for discontinuation will be tabulated. The number and percentage of patients included in the FAS, the SS, and the PPS and excluded from these same populations will be presented.

Summary statistics of study duration will also be provided for all randomized patients. The study duration (weeks) will be calculated as $\frac{(last\ date\ on\ study - date\ of\ first\ dose + 1)}{365.25} * 52$, rounded to 1 decimal. The last date on study is the visit date of Week 24 for patients who have completed the study, or the date of discontinuation for patients who discontinued the study early.

The number of patients who discontinued from the study will also be provided for the following time periods:

- The 4-week Treatment Period

- The 20-week Follow-up Period

The number and percentage of patients within each stratum will be summarized by treatment group.

5.2.2.   Protocol Deviations

The number and percentage of patients with important protocol deviations for the categories provided in Table 4 will be summarized by treatment group and overall using the FAS population.

Table 4:   Protocol Deviation Categories

1. Eligibility and entry criteria	6. Visit schedule
2. Investigational product	7. Study procedure/tests
3. Concomitant medication	8. Randomization
4. Informed consent	9. Safety reporting
5. Laboratory assessment	10. Source document
	11. Other

All protocol deviations will also be provided at the patient level using data listings.

For the purpose of defining the PPS, patients have met any of the following important protocol deviation criteria will be considered for exclusion from the PPS:

- Patients with unscheduled readministration of IVIg within 4 weeks of first dose of study drug

- Patients with plasma exchange

- Patients who took < 3 doses of study drug

- Patients who took < 4 doses of IVIg

- Patients who were incorrectly stratified for randomization

- Patients with deviation from the following inclusion criteria:

  o #2 Patients who meet the 2019 consensus GBS criteria

  o #3 Patients who are able to run prior to onset of GBS symptoms

  o #4 Patients with onset of weakness due to GBS < 2 weeks before Screening

  o #5 Patients unable to walk unaided for ≥ 5 meters (progressively deteriorating FG3 or FG4 to FG5)

  o #6 Patients who are already on IVIg or deemed eligible for and who will start IVIg

  o #7 Patients who can start their first dose of the study drug before the end of the IVIg treatment period

- Patients with deviation from the following exclusion criteria:
  - #8 Patients who have previously received or are currently receiving treatment with complement modulators
  - #9 Patients who have received rituximab within 12 weeks prior to Screening
  - Patients who have received plasmapheresis
  - #11 Patients who have received immunosuppressive treatment (eg, azathioprine, cyclosporine, tacrolimus, or > 20mg prednisolone daily) during the 4 weeks prior to providing consent
- Patients who took any of the protocol-prohibited medications/procedures during the study:
  - Rituximab
  - Plasmapheresis
  - Steroid pulse therapy (> 500 mg/day of methylprednisolone)
  - Immunosuppressive drugs
  - Other investigational drugs
  - Other complement inhibitory agent

The list of patients identified to be excluded from the PPS will be documented in the final data review meeting minutes before database lock.

The COVID-19-related important protocol deviations will also be identified and provided in data summaries and listings (see Section 6.5).

5.2.3.   Demographics and Medical History

All demographic and baseline characteristics information including baseline GBS disease characteristics and background therapy will be summarized using the FAS population. Medical history will be summarized using the FAS population. Summary statistics will be presented by treatment group and overall.

The same summaries will also be provided for the SS if it differs from the FAS.

5.2.3.1.   Demographics

The following demographic variables will be summarized:

- Age (years)
- Sex
- Race and ethnicity
- Baseline weight (kilograms)
- Baseline height (centimeters)

5.2.3.2. Disease Characteristics

The following GBS disease characteristics will be summarized by treatment group and overall:

- Baseline FG stratification (progressively deteriorating FG3, stable, or progressively deteriorating FG4/FG5)

- Diarrhea < 4 weeks prior to onset of neurological symptoms (present or absent)

- Days since GBS onset calculated as follows: (Date of first dose − Date of GBS onset + 1)
  - < Median days since GBS onset
  - ≥ Median days since GBS onset

- Baseline Medical Research Council sum score (MRC-SS; see Section 5.5.1.3)
  - < Median baseline MRC-SS
  - ≥ Median baseline MRC-SS

- Baseline modified Erasmus GBS outcome score (mEGOS; see Section 6.3.5)
  - < Median mEGOS
  - ≥ Median mEGOS

- Days since IVIg calculated as follows: (Date of first dose − Date of first IVIg dose + 1)
  - One to 3 days since IVIg
  - Four to 5 days since IVIg

- GBS subtype (acute inflammatory demyelinating neuropathy [AIDP], acute motor axonal neuropathy [AMAN], and indeterminate)

5.2.3.3. Medical History

Baseline medical history information (ie, number [percentage] of patients who have a medical history) will be summarized by SOC and PT for the FAS population. By-patient listings will be created for medical history.

5.2.4. Prior and Concomitant Medications/Nonpharmacologic Therapies

Prior medications or therapies are defined as medications taken or therapies received by patients prior to the first dose in the study. Concomitant medications or therapies are defined as medications taken or therapies received by patients during the study on or after the first dose.

Summaries will be performed on the FAS population. The number (percentage) of patients using prior and concomitant medications will be summarized based on the WHO Anatomical Therapeutic Chemical Level 3 class code and generic name.

By-patient listings of all reported medications will be produced.

If prohibited medications as defined by clinical review are used by patients in this study, then a listing of those patients and the respective prohibited medication(s) will be produced.

Any antibiotic details, meningococcal vaccination status, and IVIg details will also be provided in patient data listings.

Nonpharmacologic therapies and procedures will be summarized by SOC and PT for each treatment group.

5.3. Primary Endpoint Analysis

The FAS will be used for the analysis of the primary endpoint. The PPS will also be used as a supplemental analysis of the primary endpoint.

The details of the statistical analyses of the primary endpoint are provided in the following sections and in Table 7. Further details of addressing COVID-19 impacts are provided in Section 6.5.

5.3.1. Primary Endpoint

The primary endpoint is the time to first reaching a Hughes FG score ≤ 1.

An event will be considered as achieving an FG score ≤ 1. Time (days) to first event (FG score ≤ 1) will be calculated as follows:

$$Time\ (days)\ to\ first\ event = Date\ of\ first\ event - Date\ of\ first\ dose + 1$$

For patients who have experienced an event, the date when the first event was reported will be used in the calculation. Patients who have not experienced any event by Week 24 of the Follow-up Period will be censored at the last visit, and patients who discontinued prematurely without ever achieving an event will be censored at the date of early discontinuation.

Additional sensitivity analyses of handling missing data will be provided in Section 5.3.3.

5.3.2. Main Analytical Approach

Treatment comparison in the primary endpoint will be performed via the log-rank test stratified by the 4 randomization strata as defined in Section 5.2.1.

The study will be concluded as positive if the 2-sided p-value from the log-rank test is less than the final alpha level adjusted for the interim analysis in favor of eculizumab (section to interim analysis.). If the final sample size is not increased due to unblinded interim analysis, the final alpha will be 0.05 (2-sided). Further details are in Section 6.4.1.1.

In addition, to estimate the hazard ratio, a stratified Cox proportional hazard model will be used with time to event as the dependent variable, treatment group as the fixed effect in the model, stratified by randomization strata. In this analysis, the baseline hazard function will be allowed to vary across strata. Tied event times will be handled using Efron's method (Efron, 1977). Firth adjustment (Firth, 1993) is applied if no event observed in a treatment group and stratum.

The estimated hazard ratio (eculizumab versus placebo) and the 95% CI of the hazard ratio from the stratified Cox proportional hazard model will be presented. An estimated hazard ratio greater than 1 will be indicative of benefit favoring eculizumab versus placebo, if statistically significant.

In addition, a Kaplan-Meier curve will be presented for the cumulative proportion of patients reaching the response (FG score ≤ 1); the 95% CIs of the proportion based on complementary

log-log transformation will be presented over the 24-week period, along with the 25th percentile, 50th percentile (median), 75th percentile of time to event (days), and the 95% CIs of the 25th, 50th, and 75th percentiles of time to event will also be summarized for each treatment group.

5.3.3.   Sensitivity Analysis

5.3.3.1.   Sensitivity Analysis to Handle Missing Primary Endpoint

To assess the robustness of the primary analysis of this endpoint in terms of handling missing data, the following sensitivity analyses will also be performed:

1. **Sensitivity Analysis 1:** In this sensitivity analysis, if the last FG score prior to discontinuation is ≤ 1, then no imputation will be done and the observed time to first event will be used for analysis. If the last FG score prior to discontinuation is > 1, then the baseline FG score will be carried forward (baseline observation carried forward [BOCF]) for all visits after discontinuation. Based on this imputation, the censoring time will be derived as Week 24 for these patients.

2. **Sensitivity Analysis 2:** In this sensitivity analysis, if the last FG score prior to discontinuation is ≤ 1, then the last FG score will be carried forward (last observation carried forward [LOCF]) for all visits after discontinuation in order to have a complete response profile for the responders. The time-to-event for such patients will still be based on the first observed FG response. The intermittent missing FG scores will be imputed based on the LOCF approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are missing at random (MAR). The missing FG scores for patients will be imputed at each post-discontinuation visit. Imputation will be implemented using a linear regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5. Based on this imputation the time-to-event and censoring time will be rederived for these patients.

3. **Sensitivity Analysis 3:** In this sensitivity analysis, if the last FG score prior to discontinuation is ≤ 1, then the last FG score will be carried forward (LOCF) for all visits after discontinuation in order to have a complete response profile for the responders. The time-to-event for such patients will still be based on the first observed FG response. The intermittent missing FG scores will be imputed based on the LOCF approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are missing not at random (MNAR). The missing FG scores for patients will be imputed at each post-discontinuation visit based on the placebo patients who continue to that visit. Imputation will be implemented using a linear regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5. Based on this imputation, the time-to-event and censoring time will be rederived for these patients. The same analyses as described in Section 5.3.2 will be performed on the imputed data. Further details, including the SAS program code, are described in Section 6.4.1.3.

5.3.3.2.   **Sensitivity Analysis: Unstratified Analyses for Primary Endpoint**

Sensitivity Analysis 4: As a sensitivity analysis to assess the impact of stratification, the
2 treatment groups will be compared using an unstratified log-rank test. The hazard ratio together
with the associated 95% CI obtained using the unstratified Cox regression model will also be
presented.

5.3.4.   **Supplementary Analyses**

Supplemental analyses will be performed on the primary endpoint based on the PPS.

5.4.   Secondary Endpoints Analysis

The analysis of the secondary endpoints will be performed on the FAS. Detailed analyses are
described in the following sections and in Table 7.

If the primary endpoint is statistically significant, the hypothesis testing of the key secondary
endpoints will be performed in a hierarchical order as described in Section 2.3.

5.4.1.   **Key Secondary Endpoints**

The key secondary endpoints are described in Table 1 and are as follows:

- Proportion of patients with a Hughes FG score ≤ 1 at Week 24

- Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24

- Proportion of patients with a Hughes FG score ≤ 1 at Week 8

5.4.2.   **Definition of Endpoints**

The definitions of each key secondary endpoints are provided in Table 5.

Table 5:   Definition of Key Secondary Endpoints

Endpoint	Definition
A Hughes FG score ≤ 1 at Week 24	If a patient has an FG score ≤ 1 prior to or at Week 24, then the patient is considered a responder; otherwise, patients discontinued prior to Week 24 or with an FG score > 1 at Week 24 are nonresponders.
A Hughes FG score improvement of ≥ 3 at Week 24	If a patient has a change from Baseline in FG score (value at Week 24 − baseline value) ≤ −3, then the patient is considered a responder. Discontinued patients will be considered nonresponders.
A Hughes FG score ≤ 1 at Week 8	If a patient has an FG score ≤ 1 prior to or at Week 8, then the patient is considered a responder; otherwise, patients discontinued prior to Week 8 or with an FG score > 1 at Week 8 are nonresponders.

Note: An FG score ≤ 1 is considered not reversible once it is achieved during the study.
Abbreviation: FG = Functional Grade

5.4.3.   Main Analytical Approach

5.4.3.1.   Proportion of Patients With a Hughes FG Score ≤ 1 at Week 24

The analysis will be performed on the FAS population using the definition from Table 5.

The treatment comparison for this endpoint will be performed with a logistic regression model, with response (Yes and No) as the dependent variable and treatment group and randomization strata as the fixed effects. Firth adjustment (Firth, 1993) is applied if convergence of the logistic regression model cannot be achieved due to complete separation. The p-value, the estimated odds ratio (OR) of response between eculizumab and placebo, and the 2-sided 95% CI of the OR from the logistic regression model will be presented. The p-value from this analysis will be used for multiplicity adjustment.

As an additional analysis, a Mantel-Haenszel (MH) test will be performed to compare the 2 proportions between eculizumab and placebo, stratified by randomization strata. The p-value, the estimated difference in the 2 proportions, and the 2-sided 95% CI of the difference using the MH stratum weights (Mantel, 1959) and the Sato variance estimator will be presented.

In addition, the difference in the proportion of patients with a response, p-value, and the 95% CI of the difference between the treatment groups, as well as the number and proportion of patients with a response for each treatment, will be presented.

5.4.3.2.   Proportion of Patients With a Hughes FG Score Improvement of ≥ 3 at Week 24

The analysis will be performed on the FAS population using the definition from Table 5.

The treatment comparison in this endpoint will be performed with the same analysis methods as described in Section 5.4.3.1.

In addition, the number and proportion of patients with FG score improvements of ≥ 1, 2, 3, 4, and 5 over time will also be presented for each treatment group.

5.4.3.3. Proportion of Patients With a Hughes FG Score ≤ 1 at Week 8

The analysis will be performed on the FAS population using the definition from Table 5.

The treatment comparison in this endpoint will be performed with the same analysis methods as described in Section 5.4.3.1.

5.4.4. Sensitivity Analyses to Handle Missing Data

To assess the robustness of the main analyses of those key secondary endpoints in terms of handling of missing data, the following sensitivity analyses will also be performed:

Sensitivity Analysis 1: This sensitivity analysis is applicable only to the first and the third key secondary endpoints.

In this analysis, if a patient died during the study, he/she is considered a nonresponder.

Table 6: Definition of Key Secondary Endpoints for Sensitivity Analysis 1

Endpoint	Definition
A Hughes FG score ≤ 1 at Week 24	If a patient has an FG score ≤ 1 at or prior to Week 24, then the patient is considered a responder for this endpoint if the patient does not discontinue the study due to death; otherwise, discontinued patients will be considered nonresponders.
A Hughes FG score ≤ 1 at Week 8	If a patient has an FG score ≤ 1 at or prior to Week 8, then the patient is considered a responder for this endpoint if the patient does not discontinue due to death before Week 8; otherwise, patients discontinued prior to Week 8 will be considered nonresponders.

Abbreviation: FG = Functional Grade

Sensitivity Analysis 2: If the last FG score prior to discontinuation is ≤ 1, then the last FG score will be carried forward (LOCF) for all visits after discontinuation in order to have a complete response profile for the responders. The intermittent missing FG scores will be imputed based on the last observation carried forward (LOCF) approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are MAR. The missing FG scores for patients will be imputed at each post-discontinuation visit. Imputation will be implemented using a linear regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5.

Sensitivity Analysis 3: In this sensitivity analysis, if the last FG score prior to early discontinuation is ≤ 1, then the last FG score will be carried forward (LOCF) for all visits after discontinuation in order to have a complete response profile for the responders. The intermittent missing FG scores will be imputed based on the last observation carried forward (LOCF) approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are missing not at random (MNAR). The missing FG scores for patients will be imputed at each post-discontinuation visit based on the placebo patients who continue to that visit. The missing FG scores for patients will be imputed at each post-discontinuation visit. Imputation will be implemented using a linear

regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5.

The same analyses as described in Section 5.4.3.1 will be performed on the imputed data.

In addition, the number and proportion of patients with an FG score ≤ 1, as well as each category of FG scores over time, will also be presented for each group.

5.4.5. Supplementary Analyses

Supplemental analyses will be performed on the key secondary endpoints based on the PPS.

Analysis described in Section 5.4.3.1 to Section 5.4.3.3 will be conducted using the PPS.

Table 7: Summary of Analyses of Primary and Key Secondary Endpoints

Endpoint	Analysis	Population	Method	Missing Data Handling
Primary				
Time to first reaching a Hughes FG score ≤ 1	Primary	FAS	Stratified log-rank test and stratified Cox proportional hazard model	Patients who discontinued early without achieving FG ≤ 1 will be censored at the time of discontinuation.
	Sensitivity 1	FAS	Stratified log-rank test and stratified Cox proportional hazard model	Time to event after discontinuation will be based on BOCF for patients whose last FG score > 1. The censoring time will be derived as Week 24 for these patients.
	Sensitivity 2	FAS	Stratified log-rank test and stratified Cox proportional hazard model	Time to event after discontinuation will be based on MAR multiple imputation as described in Section 5.3.3 for patients whose last FG score > 1.
	Sensitivity 3	FAS	Stratified log-rank test and stratified Cox proportional hazard model	Time to event after discontinuation will be based on MNAR multiple imputation as described in Section 5.3.3 for patients whose last FG score > 1.
	Sensitivity 4	FAS	Unstratified log-rank test and unstratified Cox proportional hazard model	Patients who discontinued early without achieving FG ≤ 1 will be censored at the time of discontinuation.
	Supplemental	PPS	Stratified log-rank test and stratified Cox proportional hazard model	Patients who discontinued early without achieving FG ≤ 1 will be censored at the time of discontinuation.
Secondary				
First: Proportion of patients with a Hughes FG score ≤ 1 at Week 24	Primary	FAS	Logistic regression	See Table 5 for details.
	Supportive	FAS	Stratified CMH	
	Sensitivity 1	FAS	Logistic regression and stratified CMH	Patients who died during the study are nonresponders.
Third: Proportion of patients with a Hughes FG score ≤ 1 at Week 8	Sensitivity 2	FAS	Logistic regression and stratified CMH	MAR-based multiple imputation for patients whose last FG score > 1 prior to discontinuation as described in Section 5.4.4; otherwise, the patients are considered as responders.

Table 7:   Summary of Analyses of Primary and Key Secondary Endpoints

Endpoint	Analysis	Population	Method	Missing Data Handling
	Sensitivity 3	FAS	Logistic regression and stratified CMH	MNAR-based multiple imputation for patients whose last FG score > 1 prior to discontinuation as described in Section 5.4.4; otherwise, the patients are considered as responders.
	Supplemental	PPS	Logistic regression and stratified CMH	See Table 5 for details.
Second: Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24	Primary	FAS	Logistic regression	See Table 5 for details.
	Supportive	FAS	Stratified CMH	
	Sensitivity 1	FAS	Logistic regression and stratified CMH	MAR-based multiple imputation for patients whose last FG score > 1 prior to discontinuation as described in Section 5.4.4; otherwise, LOCF imputation.
	Sensitivity 2	FAS	Logistic regression and stratified CMH	MNAR-based multiple imputation for patients whose last FG score > 1 prior to discontinuation as described in Section 5.4.4; otherwise, LOCF imputation.
	Supplemental	PPS	Logistic regression and stratified CMH	See Table 5 for details.

Abbreviations: BOCF = baseline observation carried forward; CMH = Cochran-Mantel-Haenszel; FAS = Full Analysis Set; FG = Functional Grade; LOCF = last observation carried forward; MAR = missing at random; MNAR = missing not at random; PPS = Per Protocol Set

5.4.6.   Other Secondary Endpoints

There is no formal statistical hypothesis testing for any of the endpoints in this section, and only summary statistics are provided. In some cases, nominal p-values and 95% CIs are also presented for hypothesis-generating purposes.

5.4.6.1.   Medical Resource Utilization

Analysis of medical resource utilization will be based on the FAS population for index hospitalizations.

The number and proportion of patients (n [%]) will be presented in each treatment group for the following:

- Any index hospitalizations during the study
- When hospitalized:
  - Type of hospitalization
    - Hospitalization without intensive care unit (ICU) stay
    - ICU stay
  - Disposition post hospital discharge
    - Discharged to rehabilitation hospital/facility
    - Discharged to nursing home

> ▪ Discharged to home

Summary statistics will also be provided for each treatment group among those hospitalized for each type of hospitalization and overall:

- Number of hospitalizations without ICU

- Number of ICU admissions

- Number of hospitalizations including ICU

- Total length of stay (LOS; days) of each type of hospitalizations calculated as follows:

  o Date of discharge − Date of admission + 1

  o If the hospitalization is still ongoing, then the date of the last visit will be used in place of the date of discharge.

- Total LOS (days) in the hospitalizations without ICU

- Total LOS (days) in ICU

- Total LOS (days) in the hospitalizations including ICU

The treatment effect on total LOS of hospitalizations including ICU will be evaluated based on an ANCOVA model with LOS of hospitalizations as the dependent variable and the following list of independent variables as fixed effects: treatment group and randomization strata. The model-estimated mean difference in LOS between eculizumab and placebo and the 95% CI of the difference will be presented.

5.4.6.2. Respiratory Support

The respiratory support data are collected on the CRF page, and the statistical analysis will be based on the FAS population.

Only respiratory support received during the index hospitalization period will be analyzed.

The number and proportion of patients (n [%]) will be presented in each treatment group for the following:

- Any respiratory support (Yes and No) during the index hospitalization period

- Method of support among those who received respiratory support

  o Supplemental oxygen without intubation

  o Noninvasive mechanical ventilation

  o Intubation with mechanical ventilation

Summary statistics will be provided for each treatment group among those who received respiratory support:

- Duration of respiratory support calculated as follows:

  o End date − Start date + 1

- o If respiratory support is ongoing, then the date of the last visit will be used in place of the end date

- o The duration of respiratory support will be summarized by method of respiratory support (for example, Noninvasive mechanical ventilation).

5.5. Exploratory Endpoints Analysis

For each exploratory endpoint in this section, the FAS population will be used in the statistical analysis. All data collected will be provided in patient data listings.

Unless otherwise stated, missing item data for each questionnaire will not be imputed.

Analyses of exploratory endpoints are supportive in nature, with 95% CIs and p-values presented for hypothesis-generating purposes only.

5.5.1. Functional Status Postacute Phase

5.5.1.1. Rasch-Built Overall Disability Scale

The Rasch-Built Overall Disability Scale (R-ODS) score is a 24-item linearly weighted self-administered scale that specifically captures activity and social participation limitations in patients with neurological conditions such as GBS (van Nes, 2011). If a patient has difficulty completing the questionnaire due to muscular weakness, a family member/caregiver may record the patient's self-evaluation in the questionnaire.

Each item/activity on the scale is scored according to the patient's self-evaluation of their usual ability to perform a task as follows: 0 = "not possible to perform," 1 = "possible but with some difficulty," or 2 = "possible without any difficulty."

The patient total score equals the sum of individual item scores and ranges from 0 to 48. A patient total score indicates higher limitations in activities of daily living for patients. If a patient did not complete all 24 items, then the total score will be set to missing.

Changes in R-ODS score from Baseline at each visit will be analyzed using a restricted maximum likelihood-based repeated measures approach (ie, MMRM [Mallinckrodt, 2008]) and all available longitudinal data. The model will include fixed effects for baseline R-ODS score, randomization strata, treatment group, visit, and visit-by-treatment group interaction. The treatment effect will be evaluated via contrast for the treatment-by-visit term at each visit. An unstructured covariance structure will be used to model the correlations among repeated measures within each patient. If the model fails to converge, the following structures will be tested, and the final covariance structure will be determined by Akaike's information criterion: first-order autoregressive, compound symmetry, and Toeplitz. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The model-estimated mean difference in change from Baseline in R-ODS score between eculizumab and placebo and the 95% CI of the difference will be presented.

In addition, summary statistics of R-ODS scores and changes from Baseline in R-ODS scores at each visit will also be presented for each treatment group.

5.5.1.2.   Overall Neuropathy Limitations Scale

The Overall Neuropathy Limitations Scale (ONLS) consists of a checklist for interviewing patients regarding current subjective symptoms in their hands or arms (numbness, tingling, or weakness) and legs (difficulty with running or climbing stairs, difficulty with walking, etc.). The ONLS is completed by clinicians who ask and observe/examine enrolled patients to determine their ability to perform specific arm- or leg-related activities.

Based on a clinician's assessment, a score should have been assigned to each patient's arm (ranging from 0 to 5), and another score should have been assigned to each patient's leg (ranging from 0 to 7).

Score	Interpretation for the Arm	Interpretation for the Leg
0	Normal	Walking/climbing stairs/running is not affected
1	Minor symptoms in 1 or both arms but not affecting any of the functions listed	Walking/climbing stairs/running is affected, but gait does not look abnormal
2	Disability in 1 or both arms affecting but not preventing any of the functions listed	Walks independently but gait looks abnormal
3	Disability in 1 or both arms preventing at least 1 but not all functions listed	Requires unilateral support to walk 10 meters (stick, single crutch, and 1 arm)
4	Disability in both arms preventing all functions listed but purposeful movement still possible	Requires bilateral support to walk 10 meters (sticks, crutches, crutch and arm, and frame)
5	Disability in both arms preventing all purposeful movements	Requires wheelchair to travel 10 meters but able to stand and walk 1 meter with the help of 1 person
6	Not applicable (NA)	Restricted to wheelchair, unable to stand and walk 1 meter with the help of 1 person, but able to make some purposeful leg movements
7	NA	Restricted to wheelchair or bed most of the day and unable to make any purposeful movements of the legs

A patient's total ONLS score will be calculated by summing the patient's individual arm and leg scores, which range from 0 to 12, with 0 meaning no movement disability in a patient's legs and arms and 12 meaning maximum disability. A higher patient total ONLS score indicates higher neuropathy limitations in that patient's limbs (Graham, 2006).

If a clinician did not complete all items, then the total ONLS score will be set to missing.

The statistical analysis of the changes from Baseline in total ONLS score will be performed using the same method as described in Section 5.5.1.1.

5.5.1.3.   Medical Research Council Sum Score

The MRC-SS is a summation of the strength score of 6 peripheral muscle groups on each patient's side (12 muscle groups in total per patient) as evaluated and scored by a clinician according to the MRC-SS scale described in the table below (Medical Research Council Memorandum No. 45, 1976; Kleyweg, 1991). The peripheral muscles that will be tested in this study on both sides of the body are those responsible for the following movements:

- Abduction of the arm

- Flexion of the forearm

- Extension of the wrist

- Flexion of the leg

- Extension of the knee

- Dorsal flexion of the foot

A patient's MRC-SS ranges from 0 to 60 (ie, 12 muscle groups, each scored from 0 to 5). A lower patient MRC-SS indicates lower peripheral muscle strength. If a clinician did not complete all 12 items, then the total MRC-SS will be set to missing.

Score	Description
0	No visible contraction
1	Visible contraction without movement of the limb (not existent for hip flexion)
2	Movement of the limb but not against gravity
3	Movement against gravity over (almost) the full range
4	Movement against gravity and resistance
5	Normal

The statistical analysis of the changes from Baseline in MRC-SS will be performed using the same method as described in Section 5.5.1.1.

5.5.1.4.   Manual Muscle Testing

The Manual Muscle Testing (MMT) evaluates the muscle strength of the following major muscles in the body: deltoid, biceps brachii, wrist extension, iliopsoas, quadriceps muscle, and tibialis anterior muscle (each on both sides of the body), as well as neck anteflexion. The strength of each muscle group will be graded according to the table below, and the grade of each muscle will be totaled into a patient's final total score (Medical Research Council Memorandum No. 45, 1976), which will range from 0 to 65. A lower patient total MMT score indicates lower muscle strength while the maximum score of 65 indicates normal muscle strength in the 13 muscle groups assessed. If a clinician did not complete all items, then the total MMT score will be set to missing.

Grade	Description
0	No contraction
1	Flicker or trace of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

The statistical analysis of the changes from Baseline in total MMT score will be performed using the same method as described in Section 5.5.1.1.

5.5.1.5.   Hughes FG Scores Over Time

The number and percentage of patients with various levels of FG score improvement from Baseline at each visit will be tabulated for each treatment group.

The statistical analysis of change from Baseline in Hughes FG score at each visit will be performed with the same model described in Section 5.5.1.1.

5.5.2. Pain, Mood, and Fatigue

5.5.2.1. Short Form McGill Pain Questionnaire 2

The Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) is a multidimensional measure of perceived neuropathic and non-neuropathic pain in adults with chronic pain. The SF-MPQ-2 is a self-administered questionnaire and includes 22 pain descriptor items that are each rated on a rating scale of 0 to 10, as experienced by the patient over the week prior to completing the questionnaire (Dworkin, 2009).

The patient's total SF-MPQ-2 score will be calculated as the mean of all item ratings for the patient. Similarly, subscale scores for the 4 dimensions will be calculated as the mean of the corresponding item ratings for each dimension for the patient, as indicated in the table below.

If a patient did not complete all items, then the total SF-MPQ-2 score will be set to missing. Similarly, if a patient did not complete all items for a subscale score, then that subscale score will be set to missing. A lower score indicates lower pain intensity, with 0 indicating no pain and 10 indicating worst possible pain. The scale is subdivided into 4 dimensions as follows:

Dimension	Number of Items	Items Belonging to the Dimension	Value	Range
Continuous pain	6	Throbbing, cramping, gnawing, aching, heavy, and tender pain	Total score for the 6 items ÷ 6	0–10
Intermittent pain	6	Shooting, stabbing, sharp, splitting, electric-shock, and piercing pain	Total score for the 6 items ÷ 6	0–10
Neuropathic pain	6	Hot-burning, cold-freezing, caused-by-light-touch, itching, tingling, and numbness pain	Total score for the 6 items ÷ 6	0–10
Affective descriptors	4	Tiring-exhausting, sickening, fearful, and punishing-cruel pain	Total score for the 4 items ÷ 4	0–10

The statistical analyses of changes from Baseline in total SF-MPQ-2 score, as well as the subscale scores, will be performed using the same method as described in Section 5.5.1.1.

5.5.2.2. Depression, Anxiety, and Stress Scale - Short Form 21 Questions

The Depression, Anxiety, and Stress Scale Short Form, 21 Questions (DASS-21) is an instrument set of 3 self-report scales designed to measure the emotional states of depression, anxiety, and stress (Depression Anxiety Stress Scales [DASS]). Each of the 3 DASS-21 scales contains 7 items and is divided into subscales of items with similar content as follows:

- The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia: items 3, 5, 10, 13, 16, 17, and 21

- The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect: items 2, 4, 7, 9, 15, 19, and 20

- The stress scale is sensitive to levels of chronic nonspecific arousal. It assesses difficulty relaxing; nervous arousal; and being easily upset/agitated, irritable/overreactive, and impatient: items 1, 6, 8, 11, 12, 14, and 18

Patients are asked to use a 4-point severity/frequency scale to rate the extent to which they have experienced each of the 21 states over the week prior to completing the questionnaire. The severity/frequency points are scored as follows:

Severity/Frequency Point	Score
Did not apply to me at all	0
Applied to me to some degree or some of the time	1
Applied to me to a considerable degree or a good part of time	2
Applied to me very much or most of the time	3

Patient scores for each subscale (depression, anxiety, and stress) will be calculated by summing the scores for the corresponding items indicated above. If a patient did not complete all items for a DASS-21 scale, then the score will be set to missing for that scale. The summed scores for each subscale will be multiplied by 2 for statistical analyses.

The statistical analyses of changes from Baseline in DASS-21 scale scores will be performed using the same method as described in Section 5.5.1.1.

In addition, the number and proportion of patients in each of the following categories for each DASS-21 scale score will be tabulated over time for each treatment group:

	Depression	Anxiety	Stress
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33
Extremely severe	≥ 28	≥ 20	≥ 34

5.5.2.3. The Chalder Fatigue Scale

The Chalder Fatigue Scale (Chalder) is a self-report instrument that measures subjective symptoms of fatigue and covers 7 physical fatigue dimensions and 4 mental fatigue dimensions (eg, concentration and memory). It contains 11 items to produce a global score and 2 domains of physical and mental fatigue (Cella, 2010). Patients use a 4-point Likert scale to indicate on each of the 11 fatigue dimensions measured how they felt during the month prior to responding to the questionnaire or, if feeling tired for longer than a month, in comparison to the last time they felt well. These points are (scores in parentheses) as follows: less/better than usual (0), no more/worse than usual (1), more/worse than usual (2), and much more/worse than usual (3). An individual patient score is then calculated by summing the scores of all items and ranges from 0 to 33, where 0 indicates much less fatigue and 33 indicates much more fatigue than usual. If a patient did not complete all 11 items, then the total score will be set to missing.

The statistical analyses of changes from Baseline in total Chalder score will be performed using the same method as described in Section 5.5.1.1.

5.5.3. Quality of Life

5.5.3.1. European Quality of Life – 5 Dimensions – 5 Levels

The European Quality of Life (EuroQoL) – 5 Dimensions – 5 Levels (EQ-5D-5L) is a widely used self-report 2-part health status instrument. It was developed by the EuroQoL Group to

provide a concise, generic instrument that could be used to measure, compare, and value health status across disease areas (Devlin, 2017). The instrument is used to measure health status at the time of completing the questionnaire.

The descriptive system section of the EQ-5D questionnaire produces a 5-digit health state profile that represents the level of reported problems (of the following 5 levels [scores in brackets]: no [1], slight [2], moderate [3], severe [4], or unable to/extreme problems [5]) on each of the 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For example, the EQ-5D-5L health state 21143 represents a patient who indicates slight problems on the mobility dimension, no problems on the self-care and usual activities dimensions, severe pain or discomfort dimension, and moderate problems on the anxiety/depression dimension. These health states should be converted into a single utility value or score as described in Section 6.3.8.

The second section of the questionnaire, a visual analog scale (VAS), records the respondent's own assessment of their health status on a scale from 0 to 100, where 100 indicates the best health you can imagine and 0 indicates the worst health you can imagine.

The statistical analyses of the changes from Baseline in EQ-5D-5L utility score and the VAS score will be performed using the same method as described in Section 5.5.1.1.

Additionally, the number and proportion of patients will be tabulated at each level for each dimension in each treatment over time.

5.5.3.2.   Work Productivity and Activity Impairment

The Work Productivity and Activity Impairment (WPAI) is a frequently used questionnaire related to work productivity and activity impairment (Reilly, 1993). For people who are able to answer themselves, this patient-reported activity/outcome questionnaire has 6 questions and is self-administered.

The WPAI analyzes the impact of a disease or condition, such as GBS, on working status, absenteeism and presenteeism, and regular activities of daily life.

The number and proportion of patients with each level of employment status (employed and not employed), as well as shift changes from Baseline at each visit, will be tabulated for each treatment group.

Summary statistics will be provided for the following items for each treatment group at each post Baseline timepoint (see Section 6.3.9 for further details about calculations):

- If employed:
  - Number of hours worked
  - Number of hours missed from work due to GBS
  - Number of hours missed from work due to other reasons
  - Total number of hours missed from work
  - Percentage of work time missed due to health
  - Percentage of impairment while working due to health

     o Percentage of overall work impairment due to health

        ▪ Percentage of activity impairment due to health

- If not employed:

     o Ability affected by GBS to do daily activities

     o Percentage of activity impairment due to health

All data will be provided in patient data listings.

Further details of score calculations and statistical analyses will be provided in Section 6.3.9.

5.5.4.　　　　Biomarkers

Statistical analysis of biomarker data for this study will be provided in a separate document.

5.6.　　Safety Analyses

All safety analyses will be conducted on the SS population. No formal hypothesis testing is planned.

Further details of addressing COVID-19 impacts are provided in Section 6.5.

5.6.1.　　　　Extent of Exposure

Treatment duration will be summarized by treatment group for the SS population.

Summary statistics will be provided for treatment duration (days) and total dose (milligrams) for each treatment group.

The number and percentage of patients with the following treatment compliance (%) will be presented for each treatment group: 100%, 75%, 50%, 25%, and 0%.

Treatment duration will be calculated only for patients randomized and treated as the time in days from the first dose date of the study drug until the last dose date of study drug (ie, treatment duration (days) = Last dose date − First dose date + 1).

Treatment compliance will be calculated as follows: (actual number of doses taken/planned number of doses) × 100.

In addition, IVIg treatment, as well as study drug exposure data, will be provided in patient data listings.

5.6.2.　　　　Adverse Events

For the purpose of this SAP, the following types of AEs will be noted:

- Pretreatment adverse events (PTAEs) and pretreatment serious adverse events (PTSAEs):

     o PTAEs and PTSAEs are defined as the AEs and serious adverse events (SAEs), respectively, that occur between the signing of informed consent and the first dose of the study drug.

- Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs):

    o TEAEs and TESAEs are defined as the AEs and SAEs, respectively, with onset on or after the first dose of the study drug.

All statistical summaries of AEs/SAEs with onset on or after the first dose of the study drug will be provided for each treatment group for the following time periods:

- First dose to Day 85 (Week 12)

- After Day 85

- Overall (first dose to end of study)

The PTAEs/PTSAEs will be summarized by treatment group only.

5.6.2.1.   Overall Summary of AEs

An overview of AEs with onset on or after the first dose of the study drug will be presented, showing the number of AEs and the number and percentage (n [%]) of patients who:

- Experienced any AE

- Discontinued study drug due to an AE

- Experienced an AE considered related to study drug

- Experienced an AE considered not related to study drug

- Experienced an AE considered related to antibiotics

- Experienced an AE considered not related to antibiotics

- Experienced an AE by each toxicity grade: Grades 1 to 5

- Experienced an AE leading to death

These statistics will also be prepared for all SAEs, except toxicity grade.

5.6.2.2.   AEs and SAEs by SOC and PT

The number of AEs/SAEs with onset on or after the first dose of the study drug and the number and percentage of patients with events will be presented by both SOC and PT and by PT alone. Patients will be counted once in each SOC and PT.

Percentages will be based on the total number of patients in the SS in each treatment group. The SOCs will be listed alphabetically, and PTs within each SOC will be listed in order of decreasing frequency of occurrence (percentage) overall. A summary table will also be produced for events occurring in $\geq 5\%$ of patients in either treatment group. Another table will be produced for events occurring in ≥ 2 patients in either treatment group.

The number of nonserious AEs and the number and percentage of patients with nonserious events will be presented by SOC and PT.

The incidence of AEs/SAEs leading to study drug discontinuation and death will be summarized.

Summary of event rate (per 100 patient-years [PY]) of AEs/SAEs by SOC and PT will also be provided for each treatment group. Total PY is defined as the sum of study duration (days)/365.25 for all patients. For event rate tables, the rate per 100 PY will be calculated as follows:

$$\text{Event Rate} = 100 \times \text{Total number of events/Total PY}$$

Detailed listings of patients who experienced AEs/SAEs will be presented. These listings will include period (pretreatment, first dose to Day 85 [Week 12], and after Day 85 to end of the study), seriousness, toxicity grade, and relationship to treatment, as well as action taken regarding study treatment, other action taken, and patient outcome. A separate listing of patients who discontinued from the study due to an AE/SAEs will also be provided, as well as AEs/SAEs resulting in death.

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

Summaries of AEs and SAEs with onset on or after the first dose of the study drug by relationship (related versus not related) to study drug will be provided by treatment group.

Similar summaries of AEs and SAEs with onset on or after the first dose of the study drug by relationship (related versus not related) to antibiotics will be provided by treatment group.

5.6.2.4. AEs by SOC, PT, and Toxicity Grade

Summaries of AEs with onset on or after the first dose of the study drug by worst toxicity grade (Grades 1 to 5) will be provided by treatment group.

5.6.2.5. Other Significant Adverse Events

A by-patient listing of AEs of special interest (meningococcal infections) will be provided.

The listing will include periods (first dose to Day 85 [Week 12] and after Day 85 to end of study) in which the AE occurs.

5.6.3. Additional Safety Assessments

Other safety parameters will be summarized by treatment group for all patients in the SS population with data available.

For the purpose of statistical analysis, the data collected on scheduled visits will be used for summary statistics, and the data collected on scheduled and unscheduled visits will be used for shift tables.

5.6.3.1. Analyses for Laboratory Tests

Each laboratory parameter will be summarized by treatment group and visit, as applicable. Changes from Baseline will be presented. An overall shift table will also be summarized by visit. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges.

Summary statistics will be based on central laboratory data. Data from the local laboratory will be provided in data listings only.

5.6.3.2.   Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, and heart rate [HR]) and changes from Baseline in vital signs will be summarized by treatment group and visit.

Body weight (kilograms) and height (centimeters) at Baseline will be provided in data listings only.

5.6.3.3.   Physical Examinations

Number (%) of patients with abnormal physical examinations will be summarized by treatment group at each visit. Listings will also be produced.

5.6.3.4.   Electrocardiogram

Electrocardiogram (ECG) results will be summarized by treatment group and visit. Descriptive statistics will be presented for each ECG parameter (including HR, PR interval, QRS interval, QT interval, and RR interval values) and for change from Baseline. Listings of ECG results will be produced.

5.6.3.5.   Other Safety Parameters of Special Interest

Urine and serum pregnancy tests will be summarized in by-patient listings.

5.7.   Other Analyses

5.7.1.   Other Variables and/or Parameters

Other parameters will be summarized by treatment group. All data will be presented in by-patient listings.

5.7.1.1.   Nerve Conduction Test

The nerve conduction test is performed at Screening and Week 4 to determine the GBS subtype (AMAN versus AIDP versus "indeterminate") for FAS.

By-patient listings of nerve conduction test will be produced for all patients in the FAS.

5.7.1.2.   Immunogenicity

For assessment of immunogenicity, the presence of confirmed positive antidrug antibodies (ADAs) will be summarized for all patients in SS by treatment group and visit. A by-patient listing showing ADA results by visit will include positive/negative ADA, and for confirmed positive ADA samples, the ADA titer and the presence of neutralizing antibodies will also be assessed.

5.7.1.3.   Pharmacokinetic and Pharmacodynamic Analyses

Blood samples will be collected to evaluate eculizumab concentrations over time. Descriptive statistics of eculizumab concentration data will be presented for patients in the Pharmacokinetic Analysis Set (PKAS) at each scheduled time point.

PD analysis will be performed for all participants in Pharmacodynamic Analysis Set (PDAS). Blood samples will also be collected to evaluate free complement component 5 (C5) concentrations, as well as hemolytic complement activity in serum. Descriptive statistics will be presented by treatment group and for each scheduled sampling time point. Free C5 concentrations and hemolytic complement activity in serum will be evaluated by assessing the absolute values and the changes and the percent changes from Baseline as appropriate. Boxplots by visit will also be provided, as appropriate.

By-patient listings of eculizumab concentrations, free C5 concentrations, and hemolytic complement activity in serum will be produced.

5.7.2. Subgroup Analyses

All subgroup analyses will assess the consistency of the treatment effect across different levels for the following subgroups:

- Randomization stratification factors:
  - FG scores: progressively deteriorating FG3 and FG4/FG5
  - Diarrhea: present or absent (< 4 weeks prior to onset of neurological symptoms)
- Age group (< 60 years and ≥ 60 years)
- Sex (male and female)
- Days since GBS onset (< median and ≥ median)
- Baseline MRC-SS (< median and ≥ median)
- Baseline mEGOS (< median and ≥ median; see Section 6.3.5)
- Days since IVIg (One to 3 days since IVIg and Four to 5 days since IVIg)
- GBS subtype (acute inflammatory demyelinating neuropathy [AIDP], acute motor axonal neuropathy [AMAN], and indeterminate)

TEAE analysis will be summarized by SOC and PT for the following subgroups (no p-values will be produced for these subgroup analyses).

- Sex (male and female)
- Age group (< 60 years and ≥ 60 years)
- Baseline weight category (< median, ≥ median)

For subgroup analyses of categorical endpoints, a logistic regression model or proportional hazard model using the Firth correction (Firth, 1993) will be used to obtain a p-value for the treatment-by-subgroup interaction.

The detailed statistical analyses for each subgroup are summarized in Table 8.

Table 8: Subgroup Analysis for Efficacy

Endpoint	Analysis for Each Subgroup
Time to first FG ≤ 1	Number of events in each treatment group

Table 8:   **Subgroup Analysis for Efficacy**

Endpoint	Analysis for Each Subgroup
	Median time (days) to first event (95% CI[1]) in each treatment group
	Hazard ratio (95% CI[2]) (eculizumab vs placebo)
An FG score ≤ 1 at Week 24	Number (percentage) of patients with response in each treatment group
	Odds ratio (95% CI[3]) in response (eculizumab vs placebo)
	Difference (95% CI[4]) in percentages of response between the 2 treatment groups
An FG score improvement of ≥ 3 at Week 24	Number (percentage) of patients with response in each treatment group
	Odds ratio (95% CI[3]) in response (eculizumab vs placebo)
	Difference (95% CI[4]) in percentages of response between the 2 treatment groups
An FG score ≤ 1 at Week 8	Number (percentage) of patients with response in each treatment group
	Odds ratio (95% CI[3]) in response (eculizumab vs placebo)
	Difference (95% CI[4]) in percentages of response between the 2 treatment groups

[1] 95% CI will be calculated using the Kaplan-Meier method.
[2] 95% CI will be calculated using the stratified Cox proportional hazard model with treatment-by-subgroup interaction term.
[3] 95% CI will be calculated using the logistic model containing the treatment-by-subgroup interaction term.
[4] 95% CI will be calculated using Miettinen and Nurminen method (Miettinen, 1985).
Abbreviations: CI = confidence interval; FG = Functional Grade; vs = versus

5.8.   Interim Analyses

A preplanned interim analysis for a sample size increase will be performed by an IAC when, approximately, the first 12 events (FG score ≤ 1) are observed. The sample size will be increased to 72 patients if the conditional power at the interim analysis falls within the prespecified promising zone. Details are provided in a separate IAP.

As described in Section 6.2.1, to control the study-level type 1 error due to the unblinded interim sample size increase, Gao et al's method (Gao, 2008) will be used for the adjusted final critical value as follows:

$$c' = \frac{1}{\sqrt{\tau}}\left[\frac{\sqrt{\tau - t_1}}{\sqrt{t - t_1}}\left(z_{1-\alpha}\sqrt{t} - \sqrt{t_1}z_1\right) + \sqrt{t_1}z_1\right]$$

where $t_1 = \widehat{E_1} * \widehat{r_1} * (1 - \widehat{r_1})$

$$t = E * r * (1 - r)$$

$$\tau = E_f * r * (1 - r)$$

with $E, E_f, and\ \widehat{E_1}$ being the target number of events from the original sample size, the number of events after the sample size increase, and the number of events observed at the interim analysis, respectively.

Note:

1. If the sample size is not increased, $t = \tau, as\ E = E_f$.

2. $\widehat{E_1} = 12$ if interim analysis occurs.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

Abbreviations	Definition
ADA	antidrug antibody
AE	adverse event
AIDP	acute inflammatory demyelinating neuropathy
AMAN	acute motor axonal neuropathy
BOCF	Baseline observation carried forward
C5	complement component 5
Chalder	Chalder Fatigue Scale
CHW	Cui, Hung, and Wang
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRF	case report form
DASS-21	Depression, Anxiety, and Stress Scale, Short Form, 21 Questions
ECG	electrocardiogram
EQ-5D-5L	European Quality of Life – 5 Dimensions – 5 Levels
EuroQoL	European Quality of Life
FAS	Full Analysis Set
FG	Functional Grade
GBS	Guillain-Barré syndrome
HR	heart rate
IAC	independent analysis center
IAP	interim analysis plan
ICU	intensive care unit
IV	intravenous
IVIg	intravenous immunoglobulin
LOCF	last observation carried forward
LOS	length of stay
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mEGOS	modified Erasmus GBS outcome score
MH	Mantel-Haenszel
MMT	Manual Muscle Testing
MNAR	missing not at random
MRC-SS	Medical Research Council Sum Score
NA	not applicable
ONLS	Overall Neuropathy Limitations Scale
OR	odds ratio
PDAS	Pharmacodynamic Analysis Set
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PT	preferred term
PTAE	pretreatment adverse event
PTSAE	pretreatment serious adverse event
PY	patient-years
QT	interval between the start of the Q wave and the end of the T wave in an ECG
R-ODS	Rasch-Built Overall Disability Scale
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviations	Definition
SAS®	Statistical Analysis System (software)
SF-MPQ-2	Short Form McGill Pain Questionnaire 2
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VAS	visual analog scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

6.2.   Appendix 2: Changes to Protocol-Planned Analyses

6.2.1.   Changes From Protocol to SAP V1.0

The protocol states that the Cui, Hung, and Wang (CHW) method (Cui, 1999) will be used for controlling the type 1 error due to the interim analysis. This has been changed to the Gao et al's method (Gao, 2008). As demonstrated by Gao et al (Gao, 2008), in a 2-stage design with only 1 interim analysis, Gao et al's method controls the type 1 error and is equivalent to the method proposed by CHW. The type 1 error control is also further demonstrated in the simulations as provided in the IAP.

6.2.2.   Changes From SAP V1.0 to SAP V2.0

The following table summarizes the changes in the planned analyses compared to the SAP version 1.0.

Section Number and Name	Description of Changes	Brief Rationale
4 ANALYSIS SETS Analysis Sets	The following text has been changed: *PKAS: All patients who received at least 1 dose of study drug and who have at least 1 postdose PK sample.* The following text has been added: *PDAS: All patients who received at least 1 dose of study drug and who have at least 1 postdose PD sample.*	PKAS is defined to include placebo-treated patients. PDAS is used to perform PD analysis.
5.2.2 Protocol Deviations	The following text has been changed: *For the purpose of defining the PPS, patients have met any of the following important protocol deviation criteria will be considered for exclusion from the PPS:* The following text has been added: *#2 Patients who meet the 2019 consensus GBS criteria*	Update criteria being used for exclusion from PPS

Section Number and Name	Description of Changes	Brief Rationale
5.3.1 Primary Endpoint	The following text has been deleted: *A sensitivity analysis will be performed by censoring at the last FG assessment date in case the last observed date is later than the last FG assessment for patients without ever achieving an event at their last visit on study.*	Not meaningful given the FG scores are available at the last observed date.
5.3.2 Main Analytical Approach	The following text has been deleted: *If the proportional hazard assumption used for the primary analysis method cannot be supported by graphical methods, an analysis using the restricted mean survival time method will be performed (Guo, 2019).*	To clarify the single analysis approach for the primary endpoint.
5.3.3.1 Sensitivity Analysis 1	The following text has been added: *If the last FG score prior to discontinuation is > 1, then the baseline FG score will be carried forward (baseline observation carried forward [BOCF]) for all visits after discontinuation.*	BOCF is used as the worst-case scenario.
5.3.3.1 Sensitivity Analysis 2	The following text has been added: *The time-to-event for such patients will still be based on the first observed FG response. The intermittent missing FG scores will be imputed based on the LOCF approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are missing at random (MAR). The missing FG scores for patients will be imputed at each post-discontinuation visit. Imputation will be implemented using a linear regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5. Based on this imputation, the time-to-event and censoring time will be rederived for these patients.*	Actual value of FG scores is imputed.

Section Number and Name	Description of Changes	Brief Rationale
5.3.3.1 Sensitivity Analysis 3	The following text has been added: *The intermittent missing FG scores will be imputed based on the LOCF approach. If the last FG score prior to discontinuation is > 1, then missing FG scores will be imputed using a multiple imputation approach, assuming that data are missing not at random (MNAR). The missing FG scores for patients will be imputed at each post-discontinuation visit based on the placebo patients who continue to that visit. Imputation will be implemented using a linear regression model and the monotone method with the treatment group and randomization strata as the fixed effects and the baseline FG score as covariate. A score of 0 will be assigned if the imputed score is <0; A score of 5 will be assigned if the imputed score is >5. Based on this imputation, the time-to-event and censoring time will be rederived for these patients.*	Actual value of FG scores is imputed.
5.3.4 Supplementary Analyses	The following text has been added: *Supplemental analyses will be performed on the primary endpoint based on the PPS.*	PPS on the primary endpoint is planned as supplementary analysis.
5.4.3.1 Proportion of Patients With a Hughes FG Score ≤ 1 at Week 24	The following text has been revised from: *The treatment comparison in this endpoint will be performed with a logistic regression model, with response (Yes and No) as the dependent variable, treatment group as the fixed effect, and stratification factors at randomization (progressively deteriorating FG3 or FG4/FG5 and diarrhea present or absent < 4 weeks prior to onset of neurological symptoms) as stratification factors.* to: *The treatment comparison in this endpoint will be performed with a logistic regression model, with response (Yes and No) as the dependent variable and treatment group and randomization strata as the fixed effects. Firth adjustment (Firth, 1993) is applied if convergence of the logistic regression model cannot be achieved due to complete separation.*	Clarify the randomization strata is used in the model. Add Firth adjustment if convergence cannot be achieved.
5.4.4 Sensitivity Analyses to Handle Missing Data	The following texts have been added: *To assess the robustness of the main analyses of those key secondary endpoints in terms of handling of missing data, the following sensitivity analyses will also be performed:* ***Sensitivity Analysis 1:*** *This sensitivity analysis is applicable only to the first and the third key secondary endpoints.* *In this analysis, if a patient died during the study, he/she is considered a nonresponder.*	Add sensitivity analysis to handle deaths during the study.

Section Number and Name	Description of Changes	Brief Rationale
5.4.6.1 Medical Resource Utilization	The following text has been added: *The treatment effect on total LOS of hospital and/or ICU will be evaluated based on an ANCOVA model with LOS of hospitalizations as the dependent variable and the following list of independent variables as fixed effects: treatment group and randomization strata. The model-estimated mean difference in length of stay between eculizumab and placebo and the 95% CI of the difference will be presented.*	Add statistical analysis for total LOS of hospitalization.
5.4.6.2 Ventilator Support	Ventilator support is changed to respiratory support.	
5.5.1.5 Hughes FG Scores Over Time	The following text has been added to replace the shift analysis: *The number and proportion of patients with various levels of FG score improvement from Baseline at each visit will be tabulated for each treatment group.* The following text has been deleted: *The statistical analysis of change from Baseline of an FG score at Week 24 will be performed with a nonparametric ANOVA approach.*	The new analysis is more clinically meaningful. The treatment effect will be evaluated by a more powerful method (MMRM).

5.5.3.2 Work Productivity and Activity Impairment	The following text has been added:
	
	The number and proportion of patients with each level of employment status (employed and not employed), as well as shift changes from Baseline at each visit, will be tabulated for each treatment group.
	
	The following text has been deleted:
	
	The number and percent of patients with the following categories will be tabulated for each treatment group at each timepoint:
	
	• *Employment status (employed and not employed)*
	
	   o *If status = "employed," then*
	
	     ▪ *Hours worked*
	
	     ▪ *Hours missed from work due to GBS*
	
	     ▪ *Hours missed from work due to other reasons*
		Work Productivity and Activity Impairment questionnaire at baseline does not contain hours missed due to GBS and due to other reasons.

Section Number and Name	Description of Changes	Brief Rationale
5.6 Safety Analyses	The definition of TEAE has been revised as follows: *TEAEs and TESAEs are defined as the AEs and SAEs, respectively, with onset on or after the first dose of the study drug.* The following text replaces the analyses by period of first 12 weeks, 12-24 weeks, and overall: *All statistical summaries of AEs/SAEs with onset on or after the first dose of the study drug will be provided for each treatment group for the following time periods:* • *First dose to Day 85 (Week 12)* • *After Day 85* • *Overall (first dose to end of study)*	Clarification of analysis method.
5.6.3.3 Physical Examinations	The shift analysis has been deleted, and the following text has been added: *Abnormal physical examinations will be summarized by treatment group at each visit. Listings will also be produced.*	Shift analysis is not deemed necessary.
5.7.1.1 Nerve Conduction Test	The following text has been added: *The nerve conduction test is performed at Screening and Week 4 to determine the GBS subtype (AMAN versus AIDP versus "indeterminate") for FAS.* *By-patient listings of nerve conduction test will be produced for all patients in the FAS.*	Add the listing of nerve conduction test.
5.7.1.2 Immunogenicity	The original analysis that summarized patient randomized and treated with eculizumab has been deleted.	Summarize by treatment group.
5.7.2 Subgroup Analysis	The following subgroup analyses for TEAE has been added: *TEAE analysis will be summarized by SOC and PT for the following subgroups (no p-values will be produced for these subgroup analyses):* • *Sex (male and female)* • *Age group (< 60 years and ≥ 60 years)* • *Baseline weight category (< median, ≥ median)* The following text has been added: *For subgroup analyses of categorical endpoints, a logistic regression model or proportional hazard model using the Firth correction (Firth, 1993) will be used to obtain a p-value for the treatment-by-subgroup interaction.*	New analysis. Subgroup analysis using the model along with treatment-by-subgroup interaction term.

Section Number and Name	Description of Changes	Brief Rationale
6.3.3 Visit Window	The following is the definition of Analysis Day 1: **SAP V1** **SAP V2** Visit Day Window (Days) Visit Day Window (Days) • First row: 4 1 • Second row: [4, 12) [2, 12) • Last row: [155, 183) ≥155	Days after Day 1 are mapped to next visit.
6.5.2 Efficacy Assessments	The following text has been deleted: *The planned analyses in Sections 5.3 and 5.4 will be repeated with the efficacy data from patients impacted by the following COVID-19-related assessments handled using the hypothetical strategy as follows:* *Efficacy assessments for patients who had COVID-19-related SAE will be excluded from the planned analysis from the date of the event up to 2 weeks from resolution of the SAE.* *Efficacy assessments for patients who had a change in the GBS concomitant treatment due to COVID-19 will be excluded from the planned analysis until the dose returns to baseline levels.* *Efficacy assessments for patients who missed 1 dose of study drug due to COVID-19-related disruptions will not be excluded from the planned analysis.* *Efficacy assessment for patients who missed 2 or more sequential doses of study drug due to COVID-19 will be excluded from the planned analysis up to 2 weeks from initiating study drug administration.* *Missing efficacy assessment due to COVID-19 will be handled as MAR.* The following text has been added: *The planned analyses in Sections 5.3 and 5.4 will be repeated with the efficacy data to assess the impact of COVID-19 using the while-on-treatment strategy as follows:* *a. Efficacy assessments for patients who had COVID-19 impact will be censored at the date when patients had first COVID-19-related events or disruptions.* *This strategy is used to evaluate the treatment effect prior to the occurrence of the intercurrent COVID-19 events.*	Analyses have been streamlined.
Throughout the document	Editorial changes	Editorial changes

6.3. Appendix 3: Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis. For all dates (except AE and medication 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 month will be imputed as June.

6.3.1.   Definition of Baseline Values

Baseline is defined as the last available assessment on or before the first dose for all patients.

6.3.2.   Change From Baseline

Change from Baseline will be calculated as follows:

Change from Baseline = assessment value − baseline assessment value

6.3.3.   Visit Window

For the purpose of statistical analysis, data collected on the scheduled visits from the protocol and CRFs will be used.

In case of an early discontinuation visit, an unscheduled, or "out of window" visit, an analysis visit will be assigned, where necessary, according to the table below using the number of days from the first dose as calculated below:

Visit day = Date of visit − Date of first dose + 1

Visit Day Window (Days)	Analysis Day	Analysis Visit
1	1	Day 1
(2, 12)	8	Week 1
(12, 19)	15	Week 2
(19, 26)	22	Week 3
(26, 33)	29	Week 4
(33, 40)	36	Week 5
(40, 50)	43	Week 6
(50, 71)	57	Week 8
(71, 99)	85	Week 12
(99, 127)	113	Week 16
(127, 155)	141	Week 20
≥ 155	169	Week 24

6.3.4.   Definitions of Durations

6.3.4.1.   Duration of Ventilation Support

Number of days on ventilation = End date − Start date + 1

6.3.4.2.   Duration of Hospitalization

Number of days in the hospital = Date of discharge − Date of admission + 1

If "ongoing," then the date of the last visit will be used for the date of discharge.

Note that the admission date could happen before first dose date.

6.3.4.3.   Duration of ICU

Number of days in ICU = Date of discharge from ICU − Date of admission into ICU + 1

If "ongoing," then the date of the last visit will be used for the date of discharge.

6.3.5. Definition of mEGOS

The baseline value of mEGOS will be calculated as the total sum of scores assigned to the prognostic factors according to the following table, with the mEGOS ranging from 0 to 9. The MRC-SS collected at the earliest date of Screening or Day 1 will be used. If the date of MRC-SS is 4 or more days after hospital admission, then the baseline value of mEGOS is set to missing.

Table 9: Modified Erasmus GBS Outcome Scores

Prognostic Factors	Score
Age at onset	
≤ 40	0
41–60	1
> 60	2
Preceding diarrhea	
Absent	0
Present	1
MRC-SS (within 3 days after admission to hospital, on the earliest date of Screening or Day 1)	
51–60	0
41–50	2
31–40	4
0–30	6

Walgaard, 2011

Abbreviations: GBS = Guillain-Barré Syndrome; MRC-SS = Medical Research Council sum score

6.3.6. Derivation of Treatment-Emergent Adverse Events for Missing or Incomplete Date of Onset

The analysis of AEs is described in Section 5.6.2.

If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do 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 dose, then the AE is treatment emergent.

- If the start year is the same as the year of the first dose and:

  o If the start month is missing, then the AE is treatment emergent.

  o If the start month is present and is the same as or after the month of the first dose, then the AE is treatment emergent.

- If the start date is completely missing, then the AE is treatment emergent.

If both start and end dates of AEs are completely missing, no imputation will be performed, and those AEs will be considered treatment emergent.

If the start date is partial:

1. If only the day is missing:

1.1. If the month/year of the start date is the same as those of the first study drug administration date, then the missing day will be imputed as the smaller nonmissing value of (day of first study drug administration, day of the AE end date).

1.2. Otherwise, impute the missing day as "01."

2. If both day and month are missing:

2.1. If the year of the AE start date coincides with the year of the first study drug administration date, the partial start date will be set as the first study drug date. If this leads to a date after the AE end date, then the missing day and month of the AE start date will be imputed as the day and month of the AE end date.

2.2. If the year of the AE start date is different from the year of the first study drug administration date, the missing day and month of the AE start date will be imputed as the "01" and "01."

If the stop date is partial:

1. If only the day is missing:

1.1. The missing day will be imputed as the last of the month, adjusting for the leap year.

2. If both day and month are missing:

2.1. If the year of the AE end date coincides with the maximum of (the year of first study drug administration date or the year of the last study drug administration), then the missing month will be imputed as the month of the corresponding study drug administration date (first or last) and the missing day will be imputed as the last of the month adjusting for the leap year.

2.2. Otherwise, the missing day and month of the AE stop date will be imputed as "31" and "12."

AEs with missing relationship will be assumed to be related to study treatment. AEs with missing toxicity grade will be summarized as a separate category.

6.3.7. Derivation of Prior and Concomitant Medication for Missing or Incomplete Dates

If both start and end dates of medications are completely missing, no imputation will be performed, and those medications will be considered both prior and concomitant medications.

If the end date is partial:

1. If only the day is missing:

1.1. If the year and month coincide with those of the last study drug administration date, then the end of medication will be set to the last study drug administration date.

1.2. If the year and month do not coincide with those of the last study drug administration date, then the missing day will be imputed as the last day of the month considering leap year and month in consideration.

2. If both day and month are missing:

    2.1. If the year coincides with that of the last study drug administration date, then missing month and day will be imputed as the month and day of the last study drug administration.

    2.2. If the year does not coincide with that of the last study drug administration date, then the missing month and day will be imputed as "12" and "31," respectively.

If the start date is partial:

1. If only the day is missing:

    1.1. If the year coincides with that of the first study drug administration date, then do the following:

    1.2. If the month does not coincide with that of the first study drug administration date, then impute the missing day as "01."

    1.3. If the month coincides with that of the first study drug administration date:

        1.3.1. If the end date is greater than the first study drug administration date, then impute the missing day as the day of the first study drug administration date.

        1.3.2. If the end date is less than or equal to the first study drug administration date, then impute the missing day as the day of the end date of medication.

    1.4. If the year and the month do not coincide with those of the first dose date, then impute the missing day as "01."

2. If both day and month are missing:

    2.1. If the year does not coincide with that of the first study drug administration date, then impute missing month as "01" and missing day as "01."

    2.2. If the year coincides with that of the first study drug administration date:

        2.2.1. If the end date is greater than the first study drug administration date, then impute the missing day and month as those of the first study drug administration.

        2.2.2. If the end date is less than or equal to the first study drug administration date, then impute the missing day and month as those of the end date of the medication.

    2.3. If the start date is completely missing, the missing start date will be set as the earlier of the first study drug administration date and end of the medication date.

For meningococcal vaccination, the missing end date will not be imputed.

6.3.8. EQ-5D-5L Calculations

The EQ-5D-5L is a widely used self-report 2-part health status instrument. It was developed by the EuroQoL Group to provide a concise, generic instrument that could be used to measure, compare, and value health status across disease areas (Devlin, 2017). The instrument is used to measure health status at the time of completing the questionnaire.

The descriptive system section of the EQ-5D questionnaire produces a 5-digit health state profile that represents the level of reported problems (of the following 5 levels [scores in brackets]: no [1], slight [2], moderate [3], severe [4], or unable to/extreme problems [5]) on each of the 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For example, the EQ-5D-5L health state 21143 represents a patient who indicates slight problems on the mobility dimension, no problems on the self-care and usual

activities dimensions, severe pain or discomfort dimension, and moderate problems on the anxiety/depression dimension. These health states should be converted into a single utility value or score using 1 of the standard EQ-5D-5L value sets.

An EQ-5D-5L utility score is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The score is calculated by deducting the appropriate absolute weights from 1, the value for full health (ie, state 11111), and rounding the result to 3 decimals. For this purpose, as patients are currently recruited from Japan, the value set for Japan below will be used.

Important note for programming: The utility score should be calculated for each patient and at each time point using the weights of the value set from Table 10. Each level of answer from the questionnaire corresponds to a weight from Table 10, except for the level 1 answers for which the weight is 0. Below are examples of how to calculate utility scores from the answers to the EQ-5D-5L questionnaire.

For an EQ-5D-5L health state reported as 21143, the equation for calculating the utility score is as follows:

$$
\begin{aligned}
1 &- 0.060924\ (intercept\ weight) - 0.063865(level\ 2\ answer\ for\ mobility) \\
&+ 0\ (as\ level\ 1\ answer\ for\ self-care) \\
&+ 0\ (as\ level\ 1\ answer\ for\ usual\ activities) \\
&- 0.131436(level\ 4\ answer\ for\ pain/discomfort) \\
&- 0.110496(level\ 3\ answer\ for\ anxiety/depression) = 0.633279
\end{aligned}
$$

Of note, the utility score of the health state (11111) = $1 - 0.06924$ (*intercept*) = 0.939076 is presenting the value of perfect health in the general population in Japan and therefore cannot be equal to 1. Similarly, the worst possible utility score (health state 55555) is negative: -0.025449.

Table 10:   EQ-5D-5L Scoring

Domain	Value	Weight
Intercept weight	-	-0.060924
Mobility	2	-0.063865
	3	-0.112618
	4	-0.179043
	5	-0.242916
Self-care	2	-0.043632
	3	-0.076660
	4	-0.124265
	5	-0.159659
Usual activities	2	-0.050407
	3	-0.091131
	4	-0.147929
	5	-0.174786
Pain/discomfort	2	-0.044545
	3	-0.068178
	4	-0.131436
	5	-0.191203
Anxiety/depression	2	-0.071779
	3	-0.110496

Table 10:   EQ-5D-5L Scoring

Domain	Value	Weight
	4	-0.168171
	5	-0.195961

Abbreviation: EQ-5D-5L = European Quality of Life – 5 Dimensions – 5 Levels

6.3.9.   WPAI Calculations

The WPAI is the most used questionnaire related to work productivity and activity impairment asked in the general population or in patients with different diseases. This is a self-administered questionnaire (a patient-reported activity/outcome questionnaire).

6.3.9.1.   WPAI Scoring and Calculations

The WPAI includes 6 questions. Unemployed patients only answer Question 6.

- Employment status (STATUS):

  o STATUS = "employed" if Q1 = YES or Q1 = NO or missing and hours missed or worked > 0.

  o STATUS = "not employed" if Q1 = missing and hours missed and worked = 0.

- Hours missed

  o If hours worked = 0, then productivity while at work is NA.

  o If the line or box is slashed through or there is a response of NA, code as 0. If the respondent enters a range of hours, enter the midpoint. If the respondent records "+" after the number of hours, ignore the "+." Hours are usually rounded to 1 decimal.

- Missing or unreadable response

  Responses from other assessments should not be used to eliminate missing data. For example, if a patient indicates that he works 40 hours at 1 assessment but leaves that question blank on a subsequent assessment, the blank response is coded missing.

- Productivity and regular activity questions

  If the words at the end of the scale are circled, enter the corresponding number (ie, a "0" or "10"). If 2 responses are circled, enter the midpoint, and round off to the nearest integer.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes) as follows:

- Questions:

  o Q1 = currently employed

  o Q2 = hours missed due to health problems

  o Q3 = hours missed due to other reasons

- o Q4 = hours actually worked

- o Q5 = degree health affected productivity while working

- o Q6 = degree health affected regular activities

- Scores:

  - o Multiply scores by 100 to express in percentages

  - o Percentage of work time missed due to health: Q2/(Q2 + Q4)

  - o Percentage of impairment while working due to health: Q5/10

  - o Percentage of overall work impairment due to health:
    Q2/(Q2 + Q4) + [(1 - (Q2/(Q2 + Q4)))× (Q5/10)]

  - o Percentage of activity impairment due to health: Q6/10

6.4. Appendix 4: Additional Details on Statistical Methods

6.4.1. SAS Code for Key Efficacy Endpoints Analyses

The SAS codes in this section are provided as a general guidance and may be slightly different from the actual codes used in the final analysis.

6.4.1.1. SAS Code for the Primary Efficacy Endpoint

The primary endpoint will be performed using a stratified log-rank test. The basic SAS code for this is as follows:

    PROC LIFETEST data=<dataset name>;

        TIME <time >*<status (0)>;   (0 =censored data; 1=event data)

        STRATA <strata >/GROUP=<treatment group >;

    RUN;

The supportive analysis will be performed using a stratified Cox proportional hazard model. The basic SAS code for this is as follows:

    PROC PHREG data=<dataset name>;

        CLASS <treatment group>*<status (0)>=<treatment group>/ties=efron;

        STRATA <strata > ;

    RUN;

6.4.1.2. SAS Code for the Key Secondary Efficacy Endpoints

The statistical analyses of the key secondary efficacy endpoints as described in Section 5.4.1 will be performed using a logistic regression. The basic SAS code for this is as follows:

    PROC LOGISTIC DATA=<dataset name>;

        CLASS <treatment group> <strata > ;

```
          MODEL <response>=<treatment group> <strata >/ dist=bin link=logit;
     RUN;
```

The supportive analysis will be performed using the randomization-based Cochran-MH approach. The basic SAS code is the following:

```
     PROC FREQ DATA=<dataset name>;
          TABLES <strata > **<treatment group>*<resp>/cmh commonriskdiff(test=mh);
     RUN;
```

6.4.1.3.   SAS Code for the Multiple Imputations

For the sensitivity analyses described in Section 5.3.3, missing data will be imputed using a multiple imputation approach.

The sensitivity analysis 2 assumes that data are MAR. The basic SAS code is as follows:

```
     PROC MI DATA=<data set name> OUT=<output data> seed=1306528
                    NIMPUTE=100;
        CLASS <treatment group> <strata > ;
        VAR <treatment group>  <strata >  <resp>;
       MONOTONE REG (/details);
    RUN;
```

The sensitivity analysis 3 assumes that data are MNAR. The basic SAS code is as follows:

```
     PROC MI DATA=<data set name> OUT=<output data> seed=1306528
                    NIMPUTE=100;
       CLASS <treatment group> <strata > ;
       VAR   <strata >  <resp>;
       MONOTONE REG (<resp>=<treatment group>  <strata> /details);
       MNAR MODEL (<resp>/modelobs=(<treatment group>=<placebo variable value>));
    RUN;
```

For each sensitivity analysis, the imputed datasets will then be analyzed by imputation using the analysis method for each endpoint as described in Table 7, and the PROC MIANALYZE procedure will be used to generate valid statistical inferences for each endpoint. The basic SAS code is as follows:

```
     PROC MIANALYZE DATA=<data set name>;
        MODELEFFECTS <estimated treatment effect>;
```

STDERR <estimated standard error >;

    RUN;

Transformations are needed depending on the nature of the statistics to be summarized. For example, Wilson-Hilferty transformation is needed for the Chi-square test statistics.

6.4.2. SAS Code for Exploratory Endpoints Analyses

For some exploratory endpoints, the analysis of changes over time involves an MMRM analysis. The basic SAS code for this analysis is as follows:

PROC MIXED DATA=<data set name> METHOD=reml;

   CLASS <patient id> <visit> <treatment group> <strata > ;

   MODEL <change> =<treatment group> <visit> <treatment group*visit> <strata >

                       <base>/ddfm=kr solution;

   REPEATED <visit>/type=un subject=<patient id>;

   LSMEANS <treatment group>*<visit>/CL DIFF;

RUN;

6.5. Details of Statistical Analyses to Address COVID-19 Impacts

6.5.1. Patients Who Were Impacted by COVID-19

Patients who were impacted by COVID-19 as follows will be identified:

    a. Patients who had a COVID-19-related AE
    b. Patients who missed 2 consecutive scheduled doses of study drug due to COVID-19-related disruptions
    c. Patients who terminated early due to COVID-19-related disruptions
    d. Patients who received concomitant treatments for COVID-19 that could be used as GBS medication

6.5.2. Efficacy Assessments

The planned analyses in Sections 5.3 and 5.4 will be repeated with the efficacy data to assess the impact of COVID-19 using the while-on-treatment strategy as follows:

    a. Efficacy assessments for patients who had COVID-19 impact will be censored at the date when patients had their first COVID-19-related events or disruptions.

This strategy is used to evaluate the treatment effect prior to the occurrence of the intercurrent COVID-19 events.

6.5.3. COVID-19-Related Analyses

The following analyses will be included to address COVID-19-related impact on the data:

    a. A summary of patient disposition will include COVID-19-related screen failure reasons and COVID-19-related discontinuations/withdrawals.

b. A summary of the number and percentage of patients with pretreatment and treatment-emergent known exposure to COVID-19 will be provided using SS.

c. A summary of COVID-19-related important protocol deviations will be provided.

d. A summary of the number and percentage of patients who missed a study visit and/or who had a modified study visit, along with the reasons (COVID-19 related/not), will be provided by treatment group and visit using the FAS. For patients who had a modified study visit, the method for the different assessments will be summarized.

e. A summary of the total number and percentage of patients with COVID-19-related missed doses, the reason for missed doses, and the total number of missed doses will be provided. Similarly, the total number of patients with any COVID-19-related unscheduled infusions, the reason for unscheduled infusions, and the total number of unscheduled doses will be provided.

f. The primary and key secondary efficacy endpoint analyses will be repeated using the while-on-treatment strategy on FAS.

g. A summary table of AEs with onset on or after the first dose of the study drug by SOC and PT will be provided for patients who had COVID-19 related AEs using the SS.

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