A PROSPECTIVE, MULTI-CENTER, PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN SUBJECTS WITH GUILLAIN–BARRÉ SYNDROME

(JET-GBS - Japanese Eculizumab Trial for GBS)

Tracking Number: 100069

Statistical Analysis Plan

Coordinating Investigator：
Chiba University Hospital, Department of Neurology
Satoshi Kuwabara, MD, PhD.
Approved on 6/December/2016

Statistical Analysis Supervisor：
Chiba University Graduate School of Medicine, Department of Global Clinical Research
Yasunori Sato, PhD.

Revision history
23/June/2015 Version 1.0
6/December/2016 Version 1.1

1. STUDY OBJECTIVES

The purpose of this study is to characterize the overall efficacy, safety, and tolerability of eculizumab in GBS patients.

1.1. Primary Endpoint

【Safety】

Frequencies and severity of adverse events/serious adverse events after treatment with investigational product

【Efficacy】

Proportion of patients who reach Hughes functional grade (FG) 2 or lower at Week 4 (Response Rate)

1.2. Secondary Endpoint

【Efficacy】

1. Proportion of patients with improvement of 1 or more Hughes functional grades from baseline at each visit
2. Proportion of patients who are able to walk unaided (FG 2 or lower) at each visit
3. Duration required for improvement by at least 1 Hughes functional grade*[1]
4. Proportion of patients who reach FG 1 or 0 at Week 24
5. Change in the FG score between peak disability score and the scores at each visit
6. Proportion of patients with a clinically relevant improvement in the R-ODS score. An increase in the R-ODS score (0-48) converted to the centile metric score (0-100) by at least six points at each visit
7. Proportion of patients with a clinically relevant improvement in ONLS (a decrease in the ONLS score from baseline by at least 1 point) at each visit
8. Proportion and number of patients who require ventilatory support (FG 5)
9. Duration of ventilatory support
10. Occurrence of relapse during the trial *[2]
11. Overall survival during the trial (OS)
12. Change in grip strength from baseline at each visit
13. Change in results of the manual muscle test (MMT) score from baseline at each visit
14. Change in the rate and results of below measures on median and ulnar nerve conduction test parameters from baseline: CMAP amplitude, distal latency, motor nerve conduction velocity, F wave latency, SNAP amplitude, and sensory nerve conduction velocity
15. Change in vital capacity and % vital capacity from baseline at each visit
16. Proportion of patients who undergo readministration of IVIg

*1: Investigators will determine the duration required for improvement by at least 1 Hughes functional grade according to clinical assessments and the patient's diary.
*2: Investigators will assess the clear relapse of GBS observed after four weeks from the onset of GBS with reference to the NINDS diagnosis criteria. Treatment related fluctuations will not be included.

2. GENERAL CONVENTIONS IN STATISTICAL ANALYSIS

2.1. Interim Analysis

No interim analysis will be performed in this trial.

2.2. Data Monitoring Committee

A Data Monitoring Committee will be set up to ensure the safety of the trial patients in accordance with a separate set of operating procedures.

2.3. Handling of Missing Data

Unless otherwise noted, any data of dropouts that are unavailable or missing will not be replaced with substituted values created by statistical imputation.

2.4. Data Transformation

In the case of changes in variables such as square roots or logarithms, the specific procedures will be described in the statistical analysis plan.

2.5. Significance Level and Confidence Interval

Unless otherwise noted, all statistical tests will be two-sided and performed at the significance level (α) of 0.05 and 95% confidence intervals (CI) will be provided. However, the primary efficacy analysis will be tested with a one-sided significance level of $\alpha = 0.05$.

2.6. Multiplicity Adjustment

Unless otherwise noted, statistical adjustments for multiplicity will not be performed in this trial.

2.7. Data Processing Conventions

Definitions of days and period

- Number of days will be calculated by subtracting the beginning date from the final date and 1 day will be added afterwards.

Examples:

- Number of days dosed: If dosing ends on the first day of administration, the dosing period will be counted as 1 day.
- Number of days until the occurrence of an adverse event (AE): If an AE occurs on the next day after the first day of administration, the period until the onset of the AE will be counted as 2 days.
- Survival period: If death occurs on the next day after the first day of administration, the survival period will be counted as 2 days.

- Number of days are calculated for year, month, and week as follows:
  - 1 year: 365.25 days
  - 1 month: 30.4375 days
  - 1 week: 7 days

- The number of days after the initial date of administration or the number of days before an event will be described as follows:
  - The first date of administration is set as the initial date: day (1)
    The days following will be counted up one by one.
  - The date 1 day before the initial date of administration is set as day (-1)
    The days before day (-1) will be counted backwards one by one.

- The assessment visit will be specified as “Screening, Baseline, Week 1-24, Early termination, and Follow-up” visit. When simply denoted as each visit, analyses will be made for all visits where data exists.

Handling of digits after the decimal point

- For means, standard deviations, and medians, the significant figures will be displayed with 1 additional decimal place than those of allotted in the Case report form (CRF). The calculated results will be displayed with 1 additional decimal place than the significant digits and the last digit in the value will be rounded.
- All percentages should be rounded to 1 decimal place and the results will be reported (e.g. 12.3%).
- When calculating means, standard deviations, and/or medians for statistical analysis, the numbers will be rounded only after the final results are obtained and not during the calculation.

Confidence Interval of the frequencies of events

Confidence interval (CI) of the proportion of patients (or incidence rates) and response proportion (or response rates) will be calculated by exact method based on F distribution.

The number of population for analysis will be defined as N, and the number of patients who experience events, or the number of responders to the treatment will be defined as X. The response rate (p), the upper limits (p_U), or lower limits (p_L) of the confidence interval of 100 (1 – α) % at a two sided-test, will be calculated by the following equations. 95% confidence interval reflects α of 0.05.

$$p = \frac{X}{N},$$

$$p_U = \left(1 + \frac{N - X}{(X+1)F\left(1 - \frac{\alpha}{2}, 2(X+1), 2(N-X)\right)} \right)^{-1},$$

$$p_L = \left(1 + \frac{N - X + 1}{X\,F\left(1 - \frac{\alpha}{2}, 2X, 2(N-X+1)\right)} \right)^{-1}.$$

2.8. General Conventions for Figures, Tables and Listings

Analysis results will be presented using A4 sized sheets, and figures or summary tables will be described in portrait mode, whereas tables or data listings in landscape mode in general. However, depending on specific requirements, any modification will be employed for each figure or table.

3. ANALYSIS

3.1. Definitions of Population

3.1.1. Full Analysis Set (FAS)

The FAS will include all patients who were randomized and received one dose of investigational product. However, patients who have a major protocol violation (such as no consent, or enrollment before the issuance of the contract or after the expiry of the contract) will be excluded.

3.1.2. Per Protocol Set (PPS)

The PPS will exclude all patients in the FAS population who fail to satisfy major criteria of the protocol such as follows:

- Inclusion criteria
- Exclusion criteria
- Prohibited concomitant drug criteria
- Prohibited concomitant therapy criteria
- Adherence to administration of study drugs with 75% and/over
- Adherence to treatment regimen of the protocol

3.1.3. Safety Analysis Set (SAF)

Safety analyses will be performed on the SAF population patients who were randomized and received at least one dose of the investigational product. Patients will be analyzed according to the treatment that they have actually received.

3.2. Analysis Principles

The primary analysis for all efficacy endpoints will be performed on the FAS while the analyses on the PPS will be treated as reference data. Safety analyses will be performed on the SAF.

4. POPULATIONS AND GENERAL ANALYSIS PLAN

4.1. Patient Disposition

The following patient data will be summarized with the number and the proportion of the patients for each treatment group. The data will be presented in figures or tables.

- Patients randomized
- SAF
- Patients who were not administered the investigational product
- FAS
- Patients who did not provided informed consent
- Patients who were enrolled in the trial outside the trial period
- PPS
- Patients in violation of inclusion criteria
- Patients in violation of exclusion criteria
- Patients in violation of prohibited concomitant drug usage
- Patients in violation of prohibited concomitant therapy
- Patients who withdrew from the trial prematurely

4.2. Handling of Withdrawal Data

The number and the proportion of all patients who withdrew prematurely will be tabulated with the reasons of withdrawal by assigned treatment group. The following data will be summarized in tables.

- Site name
- Patient identification code
- Treatment group
- Number of days between enrollment and withdrawal
- Primary reason for withdrawal
- Detailed description of reasons for withdrawal

The number and proportion of all patients with deviations will be tabulated with the reasons of deviation by assigned treatment group. The following data will be summarized in tables.

- Site name
- Patient identification code
- Treatment group
- Number of days between day of enrollment and occurrence of deviation
- Deviation code name
- Details of deviation

4.3. Patients Excluded from Analysis

A table will be created for the excluded patients from each analysis set, and will contain the following items:

- Site name
- Patient identification code
- Treatment group
- Inclusion or exclusion from each analysis set (FAS, PPS, and SAF)
- Reasons for exclusion (when needed)

4.4. Investigational Product Administration Adherence

A summary table will be created for investigational product administration adherence by assigned treatment group in SAF. The analysis variables and properties will be as follows;

Analysis variables:

- Total dose: Descriptive statistics of administered dose of the investigational product
- Treatment adherence and exposure (dose administered/dose planned in the protocol): Amount and dose rates

Property/command:

- Site name
- Patient identification code
- Treatment group
- Dose administered
- Administration adherence (Dose administered/Dose scheduled in the protocol)
- Temporary drug cessation

4.5. Immunoglobulin, Prophylaxis against *N.Meningitidis* Infection, Concomitant Medication and Treatment

A summary table describing IVIg administration by assigned treatment group in SAF will be created. The following properties will be listed in the table:

- Site name
- Patient identification code
- Treatment group
- Name of drugs
- Dose administered per day
- Unit of drugs dosed
- Duration of administration
- Readministration

A summary table will be created for prophylaxis against *N.Meningitidis* infection by assigned treatment group in SAF. The following properties will be included in the table:

- Site name
- Patient identification code
- Treatment group
- Name of drugs
- Dose administered per day
- Administration method
- Duration of administration

A summary table will be created for concomitant medication by assigned treatment group in SAF. The following properties will be included in the table:

- Site name
- Patient identification code
- Treatment group
- Name of drugs
- Dose administered
- Unit of drugs dosed
- Administration method
- Initial date of administration
- End date of administration
- Duration of administration (if possible)
- Reason for concomitant administration

A summary table will be created for concomitant treatment by assigned treatment group in SAF. The following properties will be included in the table.

- Site name
- Patient identification code
- Treatment group
- Name of treatment
- Initial date of treatment
- End date of treatment
- Duration of treatment (if possible)
- Reason for concomitant administration

5. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized according to assigned treatment groups with descriptive statistics. Continuous variables will be summarized with demographic statistics (number of patients [n], mean, standard deviation, minimum, maximum, and median).
Nominal variables or ordinal variables will be summarized by category frequencies and proportion according to assigned treatment groups. For a comparison of treatment groups, a t-test or Wilcoxon's rank-sum test will be used with continuous variables, while Fisher's exact test will be used with categorical variables.

All statistical tests will be two-sided and performed at the significance level (α) of 0.05. The following baseline demographics and clinical characteristics will be presented with nominal variables, ordinal variables, and continuous variables. A summary table will be created for medical history and complications.

Patient background

- Nominal variables

Gender, age (younger than 60 years or 60 years and older), complications and medical history (yes or no), medical history of GBS: antecedent infection (yes or no, specification), cranial nerve paralysis (yes or no), impairment of pain sensation (yes or no), impairment of vibratory sensation (yes or no), symptom progressive status for FG3 (yes or no, specification).

- Ordinal variables

Not applicable

- Continuous variables

Age, weight, height, cerebrospinal fluid (protein, number of cells)

- Summary table

Medical history and complications (properties: site name, patient identification code, treatment group, disease name, onset year of the disease, current status)

Baseline data

- Nominal variables

FG score (FG=3 or FG>=4), urine test (urinary protein, urinary glucose), pregnancy test (results), ECG evaluation, anti-ganglioside antibody

- Ordinal variables

FG, R-ODS score, ONLS score, MMT scale score (left and right)

- Continuous variables

Grip strength (left and right, and their average),
R-ODS score (total score),
ONLS score (total score),
MMT score (left and right, and total score),
Nerve Conduction Study [CMAP amplitude, distal latency, F wave latency, F wave latency (adjusted by height as follows ※) of median nerve and ulnar nerve. SNAP amplitude, sensory nerve conduction velocity],
Vital capacity and % vital capacity,
Blood pressure (systolic and diastolic), temperature, heart rate
Blood count [RBC, Hb, Hct, WBC, white blood cell differentiation (neutrophils, lymphocyte, monocyte, eosinophil, basophil), PLT]
Chemistry panel (total protein, albumin, urea nitrogen, creatinine, AST, ALT, γ-GTP, ALP, LDH, total bilirubin, glucose, Na, K, Cl, IgA, IgG, IgM)
Serum concentration of eculizumab
Serum hemolytic activities

※ F wave latency (corrected by height)= 165/height (cm) × F wave latency (actual measured value)

6. EFFICACY ANALYSIS

6.1. Analysis Plan for Primary Endpoints

The primary efficacy endpoint is the proportion of patients who reach FG2 or lower at Week 4 (response rate).

The main purpose of this study is to assess the response rate of FG= <2 at week 4.
The sample size was based on the results from the previous study and historical database of GBS patients at Chiba University Hospital. As H0 (null hypothesis) we estimated that a 4 week response threshold would be 50%, whereas the expected value would be 80% as H1 (alternative hypothesis).
The exact 90% confidence interval will be calculated by binomial distribution for the response rate of each assigned treatment group. For the primary analysis, a group comparison will not be performed between the eculizumab group and the placebo group. A 95% confidence interval will be provided as well.

6.2. Analysis Plan for Secondary Endpoints

The analyses of the secondary efficacy endpoints will be performed to support the discussion of the results of the primary analysis in this trial. A multiplicity adjustment will not be performed in this trial in assessing the secondary endpoints.

6.2.1. Secondary Efficacy Endpoints

(1) Proportion of patients with improvement of one or more Hughes functional grades from baseline at each visit

The number and proportion of patients who improve by 1 or more Hughes functional grades at each visit will be summarized. Changes in FG score at each visit from baseline will be described by the generalized linear mixed model (GLMM) (Breslow NE, Clayton DG, *J Am Stat Assoc* 1993; **88** (421): 9-25; Wolfinger RD, O'Connell MA, *J Stat Comput Sim* 1993; **48**: 233-243), to obtain point estimates of probabilities of improvement by each assigned treatment group and their 95% confidence intervals.
The correlation structure is assumed as unstructured, and the Toeplitz, Autoregressive, or Compound-symmetry structure will be used in order if a convergence is not obtained. Adjustment factors will be set as [FG (FG=3 or FG>=4) and age (younger than 60 years or 60 years and older)]. The proportion at each visit and its 95% confidence interval, as well as the differences will be presented to compare the treatment groups. When a generalized linear mixed model (GLMM) is not applicable, Fisher’s exact test will be performed. For reference, number

and proportion of FG distribution at each visit will be summarized.

(2) Proportion of patients who are able to walk unaided (FG2 or lower) at each visit

The number and proportion of patients who are able to walk unaided (FG2 or lower) at each visit will be summarized.

The point estimation of probabilities of gaining FG2 and the FG from the baseline will be described by the GLMM, to obtain point estimates and 95% confidence limits.

The correlation structure is assumed as unstructured, and Toeplitz, Autoregressive, or Compound-symmetry structure will be used in order if convergence is not obtained.

Adjustment factors will be set as [FG (FG=3 or FG>=4) and age (younger than 60 years or 60 years and older)]. The proportion at each visit and its 95% confidence interval, as well as the difference will be presented to compare the treatment groups. When a generalized linear mixed model (GLMM) is not applicable, Fisher's exact test will be performed.

(3) Duration required for improvement by at least one Hughes functional grade from baseline (days)

Improvement by at least one FG from baseline will be defined as an outcome event and days to event will be analyzed using the Kaplan–Meier method for the survival-time analysis.

Patients are treated as censored cases when follow-up information is not available for reasons other than the event occurrence before the last visit required of him/her by the study protocol.

Descriptive statistics values (events, censored events, the median survival time (MST) and its 95% confidence interval) will be presented. In order to compare groups, a log-rank analysis will be performed. The adjusted hazard ratio (using placebo as the reference category) and its two-sided 95% confidence interval will be presented using Cox proportional-hazards model. Adjustment factors will be set as [FG (FG=3 or FG>=4) and age (younger than 60 years or 60 years and older)] with a two-sided significance level of 5%.

(4) Proportion of patients who reach FG1 or 0 at week 24

The number and proportion of patients who have reached FG0 or FG1 at Week 24 (Day 169) will be summarized according to each assigned group.

The response rate will be calculated from binomial distribution with a 95% confidence interval for each assigned treatment group. Fisher's exact test will be two-sided for group comparison with a significance level of 5%. For reference, the number, proportion of FG0 or FG1, and its confidence interval at each visit will be summarized.

(5) Change in FG score at each visit in comparison with the peak disability score

The descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median) will be calculated for changes in the FG score at each visit compared to peak disability FG score after enrollment.

(6) Proportion of patients with clinically relevant improvements in the R-ODS score - Those who show an increase in the R-ODS score (0–48) converted to the centile metric score (0–100) by at least six points at each visit

The R-ODS score and its changes at each visit from baseline will be summarized. The number and proportion will be presented for patients who show an increase of at least 6 points in the R-ODS score, converted to the centile metric score.

The proportion of the 6 point increase in the converted centile metric score in each assigned treatment group will be presented with an exact 95% confidence interval by binomial distribution.

(7) Proportion of patients with a clinically relevant improvement in ONLS (a decrease in the ONLS score from baseline by at least 1 point) at each visit

The ONLS score and its change at each visit from baseline will be presented. The number and proportion will be summarized for patients whose score decrease at least one point in ONLS. The proportion of the responders will be presented with an exact two-sided 95% confidence interval by binomial distribution.

(8) Proportion and number of patients who require ventilatory support (FG5)

The number and proportion of patients who require ventilatory support from the start of the investigational product administration to the end of the trial, will be summarized. The proportion of the patients who require ventilatory support will be presented with an exact two-sided 95% confidence interval by binomial distribution.

(9) Duration of ventilatory support due to GBS

A survival-time analysis will be performed according to the Kaplan-Meier Model for the days between randomization and an event, which is defined as requirement for ventilatory support.

Patients are treated as censored cases when follow-up information is not available for reasons other than the event occurrence before the last visit required of him/her by the study protocol.

Descriptive statistics values (events, censored events, MST and its 95% confidence interval) will be presented.

In order to compare groups, a log-rank test will be performed with a two-sided 5% significance level. However, for the patients whose reasons for termination of ventilatory support are death,

a competitive risk model (Gray RJ. *Ann* Stat 1988; 16: 1141–1154.) will be used for estimation of cumulative incidence function.

(10) Occurrence of relapse during the trial

A survival-time analysis will be performed according to the Kaplan–Meier method for the days between randomization and an event, which is defined as relapse occurrence.

Patients are treated as censored cases when follow-up information is not available for reasons other than the event occurrence before the last visit required of him/her by the study protocol.

Descriptive statistics values (events, censored events, MST and its 95% confidence interval) will be presented.

In order to compare groups, a log-rank test will be performed with a two-sided 5% significance level.

The cox proportional-hazards model will be used to estimate the adjusted hazard ratio (using the placebo as the reference category) and a two-sided 95% confidence interval. The analysis will be adjusted for covariate as factors FG (FG=3 or FG>4) and age (younger than 60 years or 60 years and older).

(11) Overall survival during the trial (OS)

A survival-time analysis will be performed according to the Kaplan–Meier method for the days between randomization and an event, which is defined as death. Patients are treated as censored cases when follow-up information is not available for reasons other than the event occurrence before the last visit required of him/her by the study protocol.

Descriptive statistics values (events, censored events, MST and its 95% confidence interval) will be presented.

In order to compare groups, a log-rank test will be performed with a two-sided 5% significance level.

The Cox Proportional-Hazards Model will be used to estimate the adjusted hazard ratio (using the placebo as the reference category) and the two-sided 95% confidence interval. The analysis will be adjusted for covariate as factors FG (FG=3 or FG>4) and age (younger than 60 years or 60 years and older).

(12) Change in grip strength from baseline at each visit

Changes and the percentage of changes at each visit from baseline will be summarized as descriptive statistical values (*n*, mean, standard deviation, minimum, maximum, and median).

(13) Change in the manual muscle test (MMT score) from baseline at each visit

Changes and percentage of changes in the manual muscle test (MMT) from baseline at each visit for both sides of the following 6 muscle groups (deltoid muscle, biceps brachii, wrist extensors, iliopsoas muscle, quadriceps femoris, and tibialis anterior muscle) and neck anteflexion will be summarized as descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median).

In addition, the total MMT scores of the thirteen parameters will be summarized for changes in the rate and results from baseline at each visit as descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median).

(14) Change in nerve conduction study from baseline at each visit: median and ulnar nerve conduction test parameters (CMAP amplitude, distal latency, motor nerve conduction velocity, F-wave latency, SNAP amplitude, sensory nerve conduction velocity)

Changes and percentage of changes of median and ulnar nerve conduction test parameters (CMAP amplitude, distal latency, motor nerve conduction velocity, F-wave latency, SNAP amplitude, sensory nerve conduction velocity) against baseline at each visit will be summarized as descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median).

(15) Change in vital capacity and % vital capacity from baseline at each visit

Change and percent of change in vital capacity and % vital capacity from baseline at each visit will be summarized as descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median)

(16) **Proportion of patients who undergo readministration of IVIg**

The number and the proportion of patients who undergo readministration of IVIg during the trial will be summarized by each treatment group.

The proportion of the patients who undergo readministration of IVIg will be presented with an exact two-sided 95% confidence interval by binomial distribution.

Fisher's exact test will be two-sided and performed at the significance level (α) of 0.05 for treatment comparison.

7. SAFETY ANALYSIS

Primary analysis for safety is to determine the number of severity of adverse/serious adverse events after treatment with eculizumab and IVIg.

7.1. Analysis Plan of Adverse Events

・Frequencies of adverse events

Adverse events will be classified according to MedDRA/J terminology. The number of events, the number of the patients to whom the events occurred, and the incidence rates will be summarized by each treatment group. The incidence rates will be presented with an exact two-sided 95% confidence interval by binomial distribution.

Fisher's exact test will be two-sided for treatment comparison with the significance level (α) of 0.05.

・Frequencies of serious adverse events

Serious adverse events will be classified according to MedDRA/J terminology. The number of events, the number of the patients to whom the events occurred, and the incidence rates will be summarized by each treatment group. The incidence rates will be presented with an exact two-sided 95% confidence interval by binomial distribution.

Fisher's exact test will be two-sided for treatment comparison with the significance level (α) of 0.05.

・Frequencies of adverse events whose causal relationship cannot be denied with investigational drugs

Adverse events whose causal relationship cannot be denied with investigational drugs will be classified according to MedDRA/J terminology. The number of those adverse events, the number of the patients with those events, and the incidence rates will be summarized in a table. The incidence rates will be presented with an exact two-sided 95% confidence interval by binomial distribution. Fisher's exact test will be used for treatment comparison against the significance level (α) of 0.05 at a two-sided test.

The following properties will be included in the table.

- Site name
- Patient identification code
- Gender
- Adverse events
- SOC (Japanese)
- PT (Japanese)

- Days between initial date of administration and events
- Seriousness
- Severity
- Classification of severity
- Causality relationship with investigational product
- Treatment after events
- Outcome
- Days between start of administration and outcome

7.2. Analysis Plan for Clinical Assessment Values and Vital Signs

Changes in clinical laboratory test and vital signs will be analyzed. Each measurement parameter will be calculated for descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median) and interval estimation for the parent population. For urinalysis parameters, the number and the incidence rate will be calculated by two-sided 95% CI. For each measurement parameter (except for urinalyses), changes of the average values by treatment group will be described in a box-and-whisker plot figure. The description of assessments is described below.

- Hematological Test
  RBC, Hb, Hct, WBC, WBC differentiation [neutrophils, lymphocyte, monocyte, eosinophil, basophil] , PLT
- Chemistry Panel
  Total protein, albumin, urea nitrogen, creatinine, AST, ALT, γ-GTP, ALP, LDH, total bilirubin, glucose (at investigator's discretion), Na, K, Cl, IgA, IgG, IgM
- Urinalysis
  Urinary protein, urinary glucose, hematuria
- Vital signs
  Blood pressure [systolic/diastolic], heart rate, temperature

A summary table for clinical laboratory test values and vital signs will be presented. An outlier for each reference data will be calculated.

8. ANALYSES OF OTHER PARAMETERS

Changes in the following measurement parameters will be analyzed. The numbers and the proportion of nominal variables will be summarized at each assessment visit. Continuous variables will be calculated for descriptive statistic values (*n*, mean, standard deviation, minimum, maximum, and median), and their changes will be presented in a box-and-whisker plot figure.

- Nominal variable
  Anti-ganglioside antibodies

- Continuous variables

Eculizumab concentration in serum, Hemolytic complement activity in serum

The association between antiganglioside antibodies (single antibodies, complex antibodies) and the subtype classification of AMAN or AIDP by nerve conduction study will be analyzed. A contingency table will be presented for the number and proportion of each viable, and Fisher's exact test will be used to compare them.

9. Subgroup Analysis

A subgroup analysis of the responder status will be conducted based on the following parameters for patients with FG 2 or lower at Week 4, and their predictive factors of responders will be explored with a significance level of $p<0.05$.

Subgroups:

- Antiganglioside antibodies (single antibodies, complex antibodies, single/complex antibodies),
- AMAN or AIDP by NCS
- Days to administration from onset of the disease (within 7 days or more than 8 days)
- Readministration of IVIg

  Treatment-by-subgroup (i.e. antiganglioside antibodies, classification of AMAN or AIDP, days to administration from onset of the disease, and readministration of IVIg) interactions will be evaluated by logistic regression models with FG 2 or lower at Week 4 as the dependent variable. The results will be presented with the *P*-value for the interaction term, regression coefficient, and its 95% confidence interval. Detailed sub-group analyses for all efficacy endpoints may be provided.

10. REVISION HISTORY

10.1. Changes According to Protocol Amendment

Date	Name	Distribution	Changes
NA	-	-	-

10.2. Revision History of Statistical Analysis Plan

Date	Name	Distribution	Changes
June 20, 2015	Kazue Nagai	None	Version 0
June 23, 2015	Kazue Nagai	Yasunori Sato Kengo Nagashima	Version 1.0 (Original version)
December 6, 2015	Kengo Nagashima	Yasunori Sato Nobuko Yamaguchi Michiko Hanawa	Version 1.1 Throughout the document, minor grammatical, spelling changes or improved revisions to English translation were made. Minor editorial changes in wording and addition of required information ・2.5. Addition of significance level ・2.7. Changes made in description of each visit ・3.1.2. PPS (updated to reflect current manual for data set: Ver. 1.0) ・4. Addition of missing information on sites and groups) and revision of misprints ・4.1.–4.3. Revisions and addition on analysis by treatment group ・4.4.–4.5. Addition of tables ・5. Addition of age and other required information ・6.2. Addition of required information and revision of misprints ・6.2.(1–2) Addition of details on how to handle data when an analysis method is not applicable ・7.1. Addition of tables and minor editorial changes

			・7.2. Addition of list/deviation tables and minor editorial changes ・8. Addition of figures and minor editorial changes ・9. Addition of detailed explanation for analysis Deletion of overlapping information ・2.7. Deletion of chapter on subgroup analysis

11. STATISTICAL ANALYSIS IMPLEMENTATION SYSTEM

11.1. Statistical Analysis Supervisor

Chiba University Graduate School of Medicine, Department of Global Clinical Trials
Yasunori Sato, PhD

11.2. Statistical Analyses

Chiba University Graduate School of Medicine, Department of Global Clinical Trials
Kengo Nagashima, PhD

Chiba University Hospital, Clinical Research Center
Kazue Nagai, PhD

11.3. Hardware System

The following hardware version will be used for statistical analysis.

- Microsoft Windows XP or following OS

11.4. Software System

The following software will be used for statistical analysis.

- SAS 9.4 or higher
- Microsoft Office 2013 or after
- Adobe Acrobat XI or higher

12. Approval

This statistical analysis plan for “A PROSPECTIVE, MULTI-CENTER, PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ECULIZUMAB IN PATIENTS WITH GUILLAIN–BARRÉ SYNDROME” was approved and fixed prior to the final data analysis.

6/December/2016

Satoshi Kuwabara