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)

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1. PROTOCOL SYNOPSIS

Title of Study: A prospective, multicenter, Phase II study to evaluate the safety and efficacy of eculizumab in subjects with Guillain-Barré syndrome
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Name of Investigational Product: (Code name: ECU-GBS-001), Eculizumab ,Placebo
Trial site(s): 13 trial sites in Japan
Studied period (years): July 2015 – March 2017 (Enrollment Period July 2015 - June 2016) Estimated date for first patient enrolled: Q3, 2015 Estimated date LPLV: Q3, 2016 Estimated data lock date: Q1, 2017 Estimated final report date: Q1-Q2, 2017
Phase of development (I/II/III etc.): Phase II, Exploratory (POC: Proof of Concept)
Background and Study Rationale: Guillain-Barré Syndrome (GBS) is an immune-mediated polyneuropathy that usually follows an antecedent infection and causes acute neuromuscular paralysis. GBS is currently classified into the two major subtypes: a classical demyelinating type and axonal variant type. Whereas in Europe and North America demyelinating GBS is the major subtype, in East Asia and Central and South America, axonal GBS is found in 30~65% of patients. Although the pathophysiology of GBS has not been fully understood, major advances have been made in understanding the pathophysiology particularly for the axonal form of GBS. It is now established that axonal GBS is caused by molecular mimicry of human gangliosides by the *Campylobacter jejuni* lipo-oligosaccharides. Autoantibodies bind to GM1 or GD1a at the nodes of Ranvier, activate complements, and disrupt sodium channel clusters and axo-glial junctions, resulting in the nerve conduction failure and muscle weakness. *C. jejuni* infection induces production of antibodies, which cross-react with gangliosides on the human nerve axolemma, and activate the complements, resulting in formation of membrane attack complex (MAC). The pathology leads to axonal degeneration. The standard treatments for GBS are plasma exchange and intravenous immunoglobulin and the disease progression reaches its nadir within 4 weeks. However, during the acute phase, 18-28 % of the patients require artificial ventilation and 4.1-6.3 % of the patients die of complications. Recovery takes several

months or years, and 16.7-19.7 % of the patients still require aid to walk one year after onset. Because of such serious disability of GBS patients, an alternative novel therapy that can prevent death during acute phase or severe sequelae is needed.

Eculizumab is a humanized monoclonal antibody of murine anti-human C5 antibody and specifically binds to the final activation complement component C5 and inhibits MAC formation by suppressing the cleavage reaction of C5 into C5a and C5b. The efficacy of eculizumab against GBS has been shown in a model of axonal GBS. At present, there are no animal models of demyelinating GBS. However, autopsy studies have shown that C3d and C5b-9 (MAC) are deposited on the Schwan cells, and therefore eculizumab can be effective also for demyelinating GBS.

This clinical trial will be conducted to investigate the efficacy and safety of eculizumab for GBS to warrant future global clinical trials. Moreover, we also study the relationship between the efficacy and clinical subtypes of GBS, such as axonal or demyelinating form. Our trial will provide insights on whether the future global developmental plan should target the whole spectrum of GBS world-wide or focusing on Asia and South America.

Primary Objectives:

To characterize the overall efficacy, safety, and tolerability of eculizumab in GBS subjects。

Study Design:

Prospective, multi-center, placebo-controlled, double-blinded, and randomized Phase II study

Methodology:

This is a prospective, multi-center, placebo-controlled, double-blinded, and randomized Phase II study to investigate the efficacy of eculizumab and immunoglobulin in patients with severe GBS (progressively deteriorating F3 or FG 4–5 or) within less than 2 weeks from onset of weakness due to GBS. 33 eligible patients who are being considered for or are already administered immunoglobulin will be randomized to eculizumab infusion or placebo infusion at a 2:1 ratio respectively. The placebo is set as a reference, so we will not compare the placebo with eculizumab by statistical hypothesis testing as primary analysis. There will be three periods in this study: the screening period, IP administration period, and post-IP period. The primary endpoints are the incidence of AE/SAEs after treatment with eculizumab and IVIg and the percentage of patients who are able to walk unaided (FG 2 or lower) at 4 weeks. Safety and efficacy will be observed until 24 weeks.

Number of Subjects (planned):

33 subjects (eculizumab 22 subjects, placebo 11 subjects)

Enrollment and Randomization:

Enrollment is from July 2015 to June 2016. 33 (scheduled) patients with severe GBS (progressively

deteriorating FG3 or FG 4–5) who meet the inclusion criteria and do not fall under the exclusion criteria are to be enrolled. Subject allocation is 2:1 and is scheduled for administration of eculizumab to 22 subjects, and the placebo to 11 subjects.

Diagnosis/Case Definition and Main Criteria for Inclusion:

・Patients who have been diagnosed with GBS with reference to GBS NINDS diagnostic criteria (Table 3) and those who meet all the following inclusion criteria and do not fall under any of the exclusion criteria will be included in this trial.

Inclusion Criteria:

1. Subjects ≥ 18 years of age at the time of obtaining informed consent
2. Patients with onset of weakness due to GBS less than 2 weeks before the time of consent
3. Patients unable to walk unaided for ≥5 meters (progressively deteriorating FG3 or FG 4–5)
4. Patients who are already on IVIg or deemed eligible for and who will start IVIg (Generally, administration of 400mg/kg over 5 days)
5. Patients who can start their first dose of eculizumab within 2 weeks from onset of weakness and before the end of the IVIg treatment period
6. Female subjects of child bearing potential with a negative result in their pregnancy test. All subjects must be able to practice an effective, reliable, medically approved method of contraception during the IP administration period and up to 5 months after IP administration is ended.
7. Patients who can be hospitalized during IP administration period.
8. Patients who have signed the informed consent form.

Exclusion Criteria:

1. Patients who are being considered for or are already on plasmapheresis
2. Patients who are pregnant or lactating
3. Patients showing clear clinical evidence of peripheral polyneuropathy other than GBS, e.g. diabetic (except for mild sensory disturbance) or severe vitamin B1 deficiency related
4. Patients who have received immunosuppressive treatment (e.g. azathioprine, cyclosporine, tacrolimus, or >20 mg prednisolone daily) during the 4 weeks prior to providing consent
5. Patients who are known to have severe concurrent disease (such as malignancy with uncontrolled primary tumors or metastatic lesions, severe cardiovascular disease, severe COPD, or TB)
6. Patients who are unable to comply with study procedures and the treatment regimen
7. Patients who have received rituximab within 24 weeks prior to providing consent
8. Patients with unresolved *Neisseria meningitidis* infection or a history of meningococcal infection.
9. Patients with active infectious diseases determined to be clinically severe by the Investigator or Subinvestigator that are not being appropriately treated with antibiotics
10. Patients who cannot be treated with antibiotic prophylaxis due to allergies
11. Patients who are allergic to eculizumab
12. Patients who are known to have or are suspected of having hereditary complement deficiencies
13. Patients who have been administered another investigational product within 12 weeks prior to

providing consent or are currently participating in another trial.

14. Patients with any condition that, in the opinion of the Investigator or Subinvestigator, could increase the patient's risk by participating in the study or confound the outcome of the study
15. Patients who have a history of Eculizumab treatment for GBS

Investigational Product (IP), Dosage and Mode of Administration:

Intravenous administration of eculizumab 900 mg (3 vials) or matching placebo once a week for a total of 4 times.

Duration of treatment: 4 weeks

Control Therapy, Dosage and Mode of Administration: None
Concomitant Medications: None
Restricted Medications : Rituximab/Plasmapheresis/ Steroid Pulse Therapy (more than 500mg/day of methylprednisolone)/Other investigational drugs

Preventive Measures against *Neisseria Meningitidis*

All subjects enrolled in this trial must receive a preventive measure against *N.menigitidis*, either one of the following measures. In this trial, because GBS is an acute disease and administration of IP must be started as soon as possible after the GBS diagnosis is given, and preventive measures against the *N. meningitidis* should also be conducted as quickly as possible. All cases are presupposed to receive option 1 and option 2 will only be possible for individual cases in which the Investigator/Subinvestigator determines that the positive effects of administering the meningococcal vaccine outweigh the potential dangers of long-term administration of antibiotics. If it is so determined, the Investigator/Subinvestigator should refer to local immunization practice guidelines and the product labels of locally available meningococcal vaccines.

1. Prophylactic Antibiotics
   A suitable antibiotic should be administered starting from Day 1. Because of complement recovery due to eculizumab's half-life, the antibiotics should continue to be administered until 8 weeks from the last dose of eculizumab.
   Example: ciprofloxacin 500mg /day ,oral intake once a week

2. *N. Meningitidis* Vaccine and Prophylactic Antibiotics
   Vaccine against *N. Meningitidis* should be administered promptly right after Day1. In the event that vaccine is chosen, prophylactic antibiotics will be administered concurrently starting from Day1 for 3 weeks after vaccination. The Meningococcal vaccine Menactra® has been approved in Japan as of July 2014, and its use is under consideration.

Endpoints:
The safety and efficacy of eculizumab will be assessed by the below endpoints. The baseline for assessment will be set as the first day of administration.

Primary endpoints:

・[Safety] Expressed frequency and severity of incidence of AE/SAEs after treatment with investigational product.

・[Efficacy] Proportion of subjects who reach a score of FG2 or lower on the Hughes functional grading scale at week 4（Response Rate）

Secondary Endpoints:

1. Proportion of subjects with improvement of one or more scores on the functional grading scale at each visit
2. Proportion of subjects who are able to walk unaided (FG2 or lower) at each visit
3. Duration required for improvement by at least one grade on the Hughes functional grading scale
4. Proportion of subjects 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 subjects 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 subjects with a clinically relevant improvement in ONLS. (a decrease in the ONLS score from baseline by at least 1 point) at each visit
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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, sensory nerve conduction velocity
15. Change in vital capacity and % vital capacity at each visit from baseline

Exploratory endpoints:

・Antiganglioside antibodies (Antibodies to GM1, GD1a, GalNAc-GD1a, GQ1b, and their ganglioside complexes)

・Concentration of eculizumab in serum

・Hemolytic complement activity in serum

Statistical Methods:

Statistical analysis and reporting of this trial will be conducted in accordance with the CONSORT guidelines, with the primary analyses based on the intent-to-treat principle without imputing any missing observations. All efficacy analyses are primarily based on the full analysis set (FAS), which includes all patients who have received one dose of the study treatment. The baseline demographic and clinical characteristics are summarized with frequencies and proportions for categorical data and means

and SDs for continuous variables. Patient characteristics are compared using Fisher's exact test for categorical outcomes and t-tests or the Wilcoxon Rank Sum Test for continuous variables, as appropriate.

The main purpose of this exploratory study is to assess the 4-week response proportion of FG= <2. Although we will not compare the placebo and eculizumab by statistical hypothesis testing as primary analysis, the response proportion of each group is calculated along with corresponding one-sided, exact binomial 90% confidence intervals (CIs). All statistical analyses are performed using SAS software version 9.4 and the R statistical program, version 2.13. Furthermore, all statistical analyses are described in the statistical analysis plan (SAP), and the SAP is fixed prior to database lock.

Sample Size Considerations:

The sample size is determined based on our epidemiological analysis in our data for the patients treated with IVIg. We assumed that a 4-week response threshold is 50% as H0 (null hypothesis), whereas we have predicted that the expected response rate will be 80%, as H1 (alternative hypothesis) from the point of clinical significance, health economics, and feasibility. With these assumptions, a sample size of approximately 20 subjects provides 80% power with one-sided α of 5%. Considering the probability of discontinuation, the number of patients in the eculizumab group is set at 22.While we will not compare it to the eculizumab group, in order to collect efficacy and safety data in the placebo group, 11 patients will be randomly assigned to the placebo. In this study, the total sample size is set at 33 patients.

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Attachment 1: JET-GBS Group

Appendix1: Overall Neuropathy Limitations Scale (ONLS)

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 1 . Abbreviations and Special Terms

Abbreviation or Special Term	Explanation
AG	Arm Grade
aHUS	Atypical Hemolytic Uremic Syndrome
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
ALT	Alanine aminotransferase
AMAN	Acute motor axonal neuropathy
Cmax	Maximum concentration
Cmin	Minimum concentration
EIU	Exposure in utero
FG	Functional Grade
GCP	Good Clinical Practice
GBS	Guillain-Barré Syndrome
ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IP	Investigational Product
IVIg	Intravenous Immunoglobulin
MAC	Membrane Attack Complex
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Miller Fisher syndrome
MHLW	Ministry of Health, Labour, and Welfare
MMT	Manual muscle testing
MRC	The Medical Research Council of Great Britain
ONLS	Overall Neuropathy Limitations Scale
PD	Pharmacodynamics
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal hemoglobinuria
POC	Proof of Concept
PMDA	Pharmaceuticals and Medical Devices Agency
R-ODS	Rasch-built Overall Disability Scale

Definition of Terms

Terms	Definition
Investigational product	Eculizumab and/or placebo
Active product	Eculizumab
Relapse	A clear exacerbation of GBS after 4 weeks of first showing symptoms. Therapy dependent exacerbation is not included.
Discontinuation of IP	Cessation of IP administration at a certain dose. Said dose will not be re-administered later.
Suspension of IP	Temporary halting of IP administration at a certain dose. Said dose may be re-administered later.
Withdrawal of subject	Early discontinuation of subject's participation in the trial.

5. INTRODUCTION

5.1. Guillain-Barré Syndrome (GBS)

Guillain-Barré Syndrome (GBS) is an immune-mediated polyneuropathy that usually follows an antecedent infection and causes acute neuromuscular paralysis[1]. GBS occurs in the general population at a rate 1.15 cases per 100,000 persons per year and the gender ratio is 3:2, more common in males[2]. GBS occurs in all age groups and the average age of onset is fairly young at 39 ±20.0 years of age[2]. The paralysis reaches its nadir within 4 weeks and resolves over months or years[1].

GBS is classified into the two major subtypes: demyelinating type and axonal type. Whereas the demyelinating form is common in Europe and North America, the axonal form is comparatively more common in Asia and Central America[3]. Whereas the pathophysiology of GBS has not been fully understood, an autoimmune response directed against antigens in the peripheral nerves triggered by a preceding infection is assumed as a favored hypothesis[4]. Over the past two decades major advances have been made in the understanding the pathophysiology, particularly for the axonal form of GBS[3].

It is now established that axonal GBS is caused by molecular mimicry of human gangliosides by the *Campylobacter jejuni* lipo-oligosaccharides[5]. *C. jejuni* is the most frequent antecedent pathogen for GBS[3,6]. The terminal structures of *C. jejuni* LOS are identical to human gangliosides expressed on the surface of human peripheral axons[7]. *C. jejuni* infection induces production of antibodies which cross-react with gangliosides on the axolemma, such as GM1 or GD1a[7,8]. IgG antibodies deposited at the nodes of Ranvier of the axons activate the complement system and resulting the formation of membrane attack complex, which impairs voltage-dependent Na channels at the nodes and then, leads to axonal degeneration[3,9]. In demyelinating GBS, the target molecule(s) in the Schwann cell membrane or myelin sheath have not yet been identified, and therefore the mechanisms for demyelination have not been elucidated. However, autopsy studies of demyelinating GBS patients have shown C3d and C5b-9 are deposited along the outer surface of the Schwann cells, and suggest that antibodies that are directed against epitopes on the Schwann cells and resulting complement activation are also closely associated with myelin destruction[10].

5.1.1. Unmet medical needs for GBS

The standard treatment for GBS is plasma exchange or intravenous immunoglobulin[4,11]. The disease progression reaches its nadir within 4 weeks, but during the acute phase, 18-28 % of the patients require artificial ventilation and 4.1-6.3 % of the patients die of complications[12]. Recovery takes several months or years, and 16.7-19.7 % of the patients still require aid to walk one year after onset[12]. New treatment options are required to improve the survival and functional recovery.

5.1.2. Eculizumab

Eculizumab is a humanized monoclonal antibody of murine anti-human C5 antibody and specifically binds to the final activation complement component C5 and inhibits MAC formation by suppressing the cleavage reaction of C5 into C5a and C5b. The complement is activated by either the classical pathway, substitute pathway or lectin pathway, which all lead to C3. Later, this activation cascade produces C5 converting enzyme which activates C5 and C5 is cleaved into C5a and C5b. C5a is a strong anaphylatoxin, chemotactic factor and cell activation factor that induces multiple types of inflammation promoting activity. C5b produces C6-9, which forms MAC as C5b-9 and leads to cell disorders. Eculizumab binds to C5 and inhibits the degradation of C5 in this cascade and has been designed to inhibit subsequent production of inflammatory products.

At present, eculizumab is indicated for paroxysmal nocturnal hemoglobinuria[13] and atypical hemolytic uremia syndrome[14] which are both diseases with hemolysis due to complement activation as the main disease state. Development to target uremia syndrome caused by Shiga toxigenic Escherichia coli, prevention of antibody-related rejection in renal transplant recipient and systemic myasthenia gravis and recurrent optic neuromyelitis is currently in progress.

Regarding safety, an increase in susceptibility to infection due to inhibition of activation of the final complement has been indicated. In particular, susceptibility to infection by capsulated cocci (especially *N. Meningitidis*) increases. Therefore, patients in maintenance treatment against chronic disease are recommended to be vaccinated against *N. meningitidis* at 2 weeks prior to receiving eculizumab administration.

5.1.3. Eculizumab in GBS

The efficacy of eculizumab against Guillain-Barré syndrome has been shown in a model of axonal GBS[15]. Eculizumab effectively inhibited MAC formation and deposition on the axolemma and prevent respiratory paralysis and associated functional and morphological hallmarks of terminal motor neuropathy[15]. At the present, there are no studies which investigate the efficacy of eculizumab on demyelinating type of GBS. However, considering the fact that C3d and C5b-9 deposited on the Schwan cells, eculizumab can be effective also in demyelinating GBS[10].

So far, two clinical trials (Phase II) which investigate the safety and efficacy of eculizumab for GBS are currently in progress: The British study “Inhibition of Complement Activation (Eculizumab) in Guillain-Barre Syndrome Study (ICA-GBS)” and this study. However, because axonal form is extremely rare in UK, the ICA-GBS cannot study the efficacy of eculizumab for axonal GBS. The inhibition of disease progression by eculizumab was clearly shown only in the animal model of axonal GBS. Therefore, the purpose of our trial is not only to investigate the efficacy and safety of eculizumab in GBS and but also to investigate the relationship between the efficacy and clinical subtypes of GBS, because the frequency of axonal and demyelinating form of GBS are about the same in Japan. Our trial will provide insights that future global developmental plan should target the whole world or focus on Asia and South America.

5.2. Study Drug Clinical Data

5.2.1. Dose selection/Treatment Regimen/Administration for GBS

GBS is an acute disease and typically reaches its nadir within 2-4 weeks from the onset of symptoms, and being able to reliably inhibit compliment activation and prevent damage to the nervous system of the utmost importance when discussing treatment. It is, therefore, absolutely necessary the treatment be able to reliably inhibit complements starting from the first dose.

Eculizumab has been approved for the indication of PNH in Japan and several other countries. Based on a the recommended dosage of 600mg weekly for the first 4weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter, the serum eculizumab concentration level exceeds 35µg/ml and inhibits the activation of terminal complement complex. The target serum concentration of 35µg/mL brings about hemolytic improvement in the patient and allows for sufficient stoichiometric binding with C5.

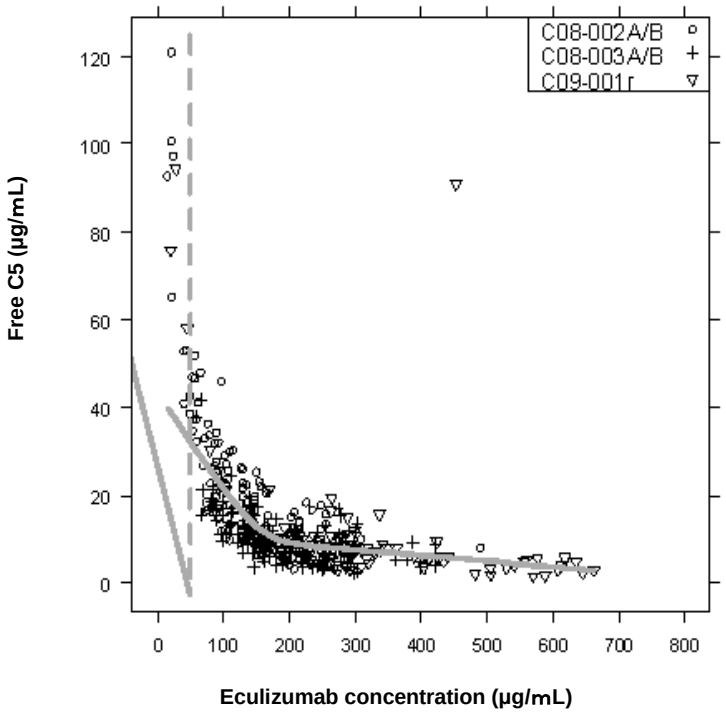
Empirical data from aHUS clinical trials using the currently approved aHUS dose regimen of 900/1200 mg indicate that serum eculizumab concentrations greater than 50 µg/mL and closer to at least 100 µg/mL were required to significantly reduce free C5 concentrations. Specifically, free C5 concentration was reduced significantly with increasing concentrations of eculizumab beginning at >50 µg/mL and was at near zero levels with eculizumab concentrations above 100 µg/mL. (Figure 1) Based on the free C5 PK/PD model, mean C_{max} and C_{min} values of eculizumab during the Induction Phase (900 mg dose weekly) would result in 92.9% and 91.8% inhibition of free C5, respectively. Similarly, mean C_{max} and C_{min} values of eculizumab during the Maintenance Phase (1200 every 14 days) would result in 93.4% and 92.8% inhibition of free C5, respectively. When hemolytic activity is measured by a validated PD assay, a significant and continuous final complement inhibition was confirmed for all patients who reached serum eculizumab concentrations of over 100 µg/mL. (Figure 2)

This trial's dosage and administration method are based on the analysis of the above PNH and aHUS clinical research data. With 50 to 100µg/ml set as the target concentration in order to reliably inhibit complement activation, a dosage of 900mg has been deemed appropriate.

Furthermore, in cases of Guillain-Barré syndrome, while complement activation is dependent on antiganglioside antibody deposits, the disease usually reaches its nadir within 4 weeks of onset, so the IP will be administered in the requisite minimum appropriate number of four doses at the start of treatment (Day 1, within two weeks of the onset of weakness), Day 8, Day 15, and Day 22.

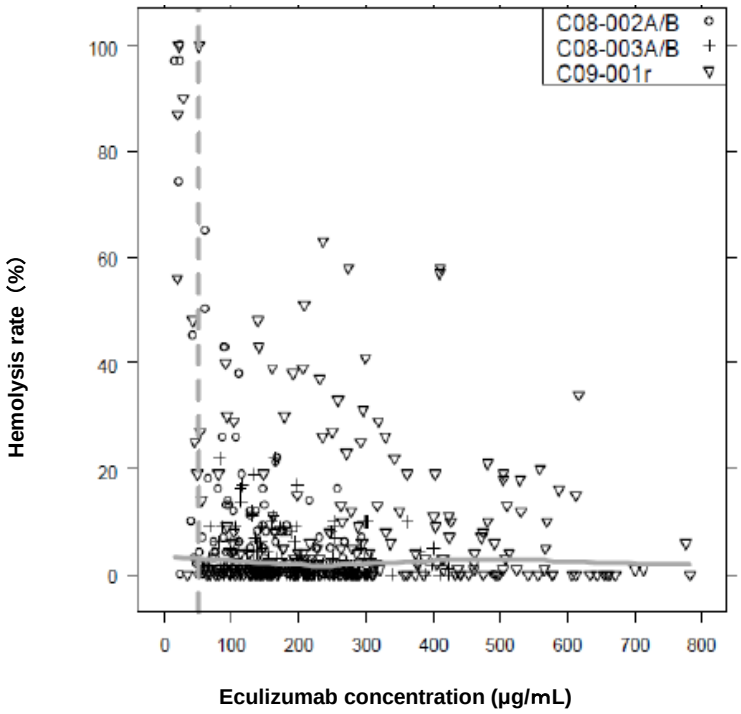
The subject will be admitted to the hospital and administered 900 mg of Eculizumab (3 vials) or placebo intravenously over the course of 4 weeks.

Figure 1. Relationship between Eculizumab and Free C5 Inhibition



- CO8-002A/B, Co8-003A/B
  Prospective, Phase II, Open-label Trial for Plasmapheresis Resistant aHUS (Adults and Adolescents)
- C09-001r
  Retrospective Study of Pediatric and Adults of aHUS

Figure 2. Relationship between Eculizumab Serum Concentration and Hemolysis Rate (Induction period and Maintenance period）



5.3. Possible Side Effects/ Benefits

5.3.1. Serious Side Effects

The following side effects have been reported to possibly occur with eculizumab administration:

1. *N. meningitidis*

An increase in susceptibility to infection due to inhibition of activation of the final complement has been indicated. In particular, susceptibility to infection by capsulated cocci (especially *N. Meningitidi*s) is increased. Therefore, patients who are administered eculizumab are required to receive preventive measures against *N. meningitidis*.

2. Infusion reaction

Administration of eculizumab may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. If anaphylaxis occurs, discontinue administration and administer the appropriate treatment.

5.3.2. Benefits

At present the benefits of eculizumab administration are unclear, but there is a possibility that with the inhibition of complement activation and membrane damage complex (MAC) formation by eculizumab, the level of severity at peak, the rate of sequelae, and the number of days until recovery could be reduced.

6. STUDY OBJECTIVES AND PURPOSE

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

6.1. Primary Objectives

6.1.1. Primary Safety Endpoint

・Expressed frequency and severity of incidence of AE/SAEs after treatment with investigational product.

[Rationale for Setting of Safety Endpoint]

Administration of eculizumab for the treatment of GBS has never been used as a treatment up to present. Therefore, it is necessary to collect safety information as widely as possible.

6.1.2. Primary Efficacy Endpoint

・Proportion of subjects who reach a score of FG2 or lower on the Hughes functional grading scale at week 4（Response Rate）

Table 2. Hughes Functional Grading Scale (From Hughes et al, Lancet 1978)

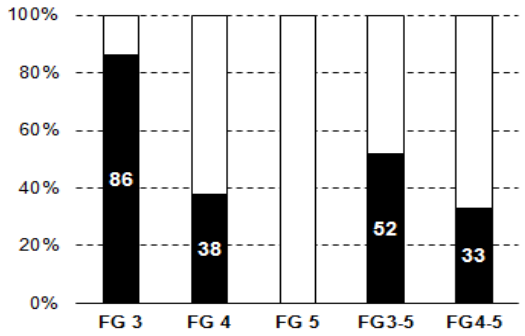
Score	Description
0	Healthy
1	Minor symptoms or signs, capable of running
2	Able to walk 5 meters independently
3	Able to walk 5 meters with a walker or support
4	Bed-ridden or chair-bound
5	Needing artificial ventilation
6	Dead

[Rationale for Setting of Primary Efficacy Endpoints]

Indicators used for primary efficacy endpoints should comprehensively assess clinical severity and be prevalent. FG can comprehensively assess the level of motor function, which is the main symptom of GBS, and is widely accepted as an evaluation scale for GBS. Furthermore, it has been used in numerous clinical trials as primary or secondary efficacy endpoints, and has been useful in meta-analysis. In recent clinical trials, an improvement of one grade on the functional outcome is often set as a primary endpoint. However, even in subjects at FG4-5 who show an improvement of one grade in functional outcome, FG1 disability (unable to walk/stand) still remains and the endpoint should be further reviewed. Considering the cost effectiveness of the study drug, in this trial we have set the primary efficacy endpoint as “The proportion of subjects who achieve a score of less than or equal to FG2 (able to walk) at Week 4”.

Figure 3 shows “the percentage of subjects who achieved a score of less than or equal to FG2 (able to walk) at Week 4” in patients with GBS of FG3 or higher at the start of treatment, examined at Chiba University Hospital from 1998 to 2014.

Figure 3. Percentage of subjects who achieved a score of FG2 or lower at Week 4 (n=64)



FG at Start of Treatment

6.2. Secondary Efficacy Endpoints

The efficacy of eculizumab will be assessed by the below endpoints. The baseline for assessment will be set as the first day of administration.

1. Proportion of subjects with improvement of one or more scores on the Hughes functional grading scale at each visit from baseline
2. Proportion of subjects who are able to walk unaided (FG2 or lower) at each visit
3. Duration required for improvement by at least one grade on the Hughes functional grading scale *1
4. Proportion of subjects 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 subjects 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 subjects 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 frequency of subjects who require ventilatory support (F 5)
9. Duration of ventilatory support
10. Occurrence of relapse from the start of the IP administration period until the end of the post IP period *2
11. Overall survival from the start of the IP administration period until the end of the post IP period (OS)
12. Change in grip strength at each visit from baseline
13. Change in results of the manual muscle test (MMT score) at each visit from baseline
14. Change in the rate and results of below measures on median and ulnar nerve conduction test parameter s from baseline: CMAP amplitude, distal latency, motor nerve conduction velocity, F wave latency , SNAP amplitude, sensory nerve conduction velocity
15. Change in vital capacity and % vital capacity at each visit from baseline

*1: Investigators will determine the duration required for improvement by at least one grade on the Hughes functional grading scale according to the subject's diary.

*2: After four weeks from date of onset the clear relapse of GBS diagnosed according to the NINDS diagnosis criteria. Therapy dependent exacerbation is not included.

[Rationale for Setting Secondary Efficacy Endpoints]

- 1–5, 7 and 13: Based on the comprehensive and temporal indicators of impaired motor function (the main symptom of GBS)
- 6: Indicator to measure the level of disability in daily life activities
- 8, 9, 15: Use of respirator due to decrease in respiratory function and bulbar paralysis are directly linked to the increase in death rate of GBS and hospitalization period

- 10: Relapse of GBS can affect prognosis
- 11: To evaluate the effect of eculizumab in decreasing the rate of severe GBS
- 12: Indicator to evaluate the severity of impaired motor functions in the upper extremities (main symptom of GBS)
- 14: Indicator that can objectively and quantitatively evaluate the degree of peripheral nerve disorder

6.3. Exploratory Endpoints (Central Clinical Laboratory)

To assess the following:

1. Presence of antiganglioside antibodies (Antibodies to ,GM1 GD1a, GalNAc-GD1a, GQ1b, and their ganglioside complexes)
2. Concentration of eculizumab in serum
3. Hemolytic complement activity in serum

[Rationale for Setting Exploratory Endpoints]

- 1: Antiganglioside antibodies act as factors of onset and neurological symptom definitions of GBS. By measuring the antiganglioside antibodies, subtypes of GBS can be assessed since IgG antigens against any gangliosides described above can be seen in axonal GBS.
- 2–3: By measuring the concentration of eculizumab in serum and hemolytic complement activity, the PK/PD characteristics of eculizumab in Japanese patients with GBS can be evaluated.

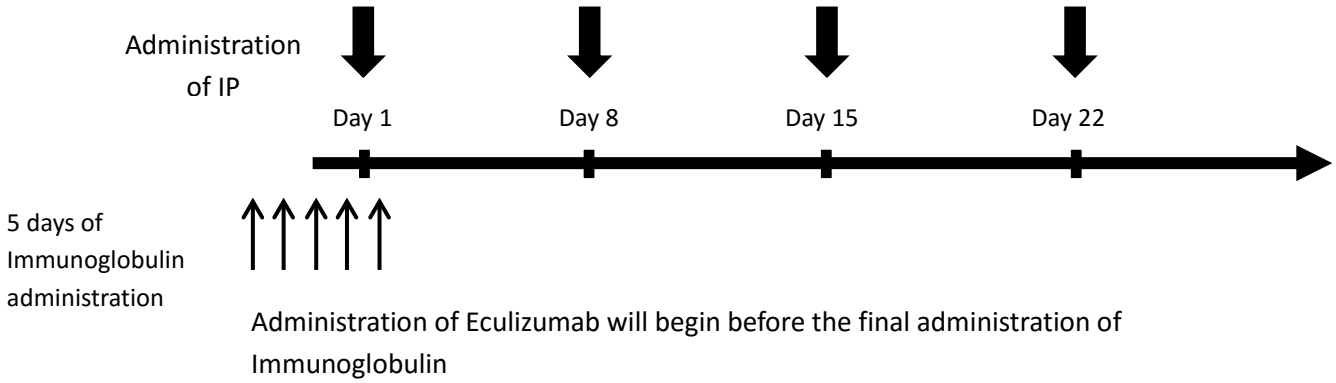
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a prospective, multi-center, placebo-controlled, double-blinded, and randomized Phase II study to investigate the efficacy of eculizumab and immunoglobulin in patients with severe GBS (progressively deteriorating FG3 or FG 4–5) within less than 2 weeks from onset of weakness due to GBS. Approximately 33 eligible patients who are considered for administration of or already are being administered immunoglobulin will be randomized on Day 1 at a 2:1 ratio to one of the two treatment arms— eculizumab infusion or placebo infusion.

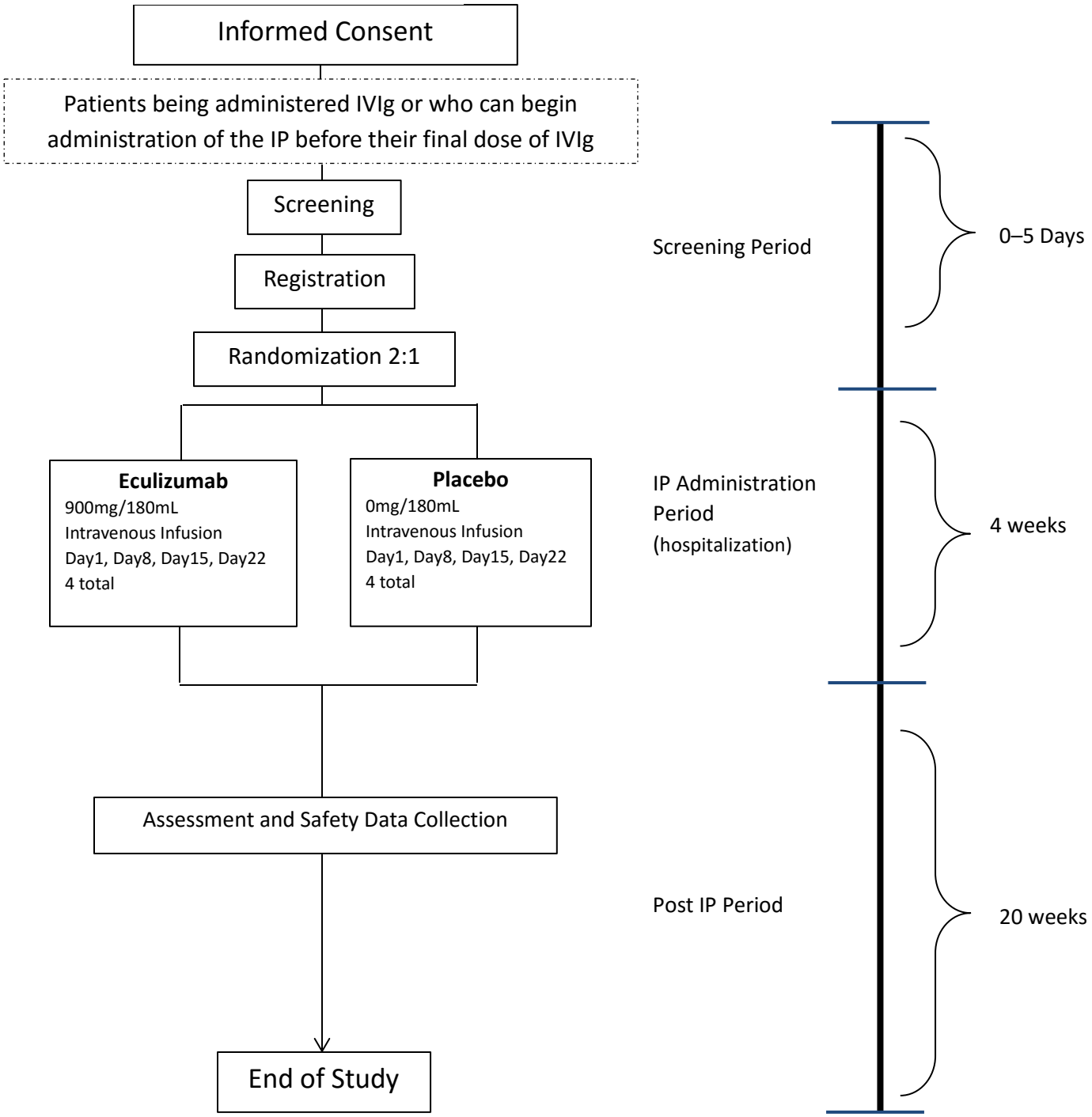
There will be three periods in this study: the screening period, IP administration period, and Post IP period. The IP administration schedule and an outline of the trial design are provided in Figures 4 and 5. The primary endpoints are the incidence of AE/SAEs after treatment with investigational product, and the percentage of patients who are able to walk unaided (FG 2 or lower) at 4 weeks. Safety and efficacy will be observed until 24 weeks. A schedule of assessments for the screening, IP administration, and Post IP periods is provided in Table 6.

Figure 4: Administration Schedule



7.2. Study Design Diagram

Figure 5. Study Design



7.3. Number of Subjects and Duration of the Study

33 subjects with GBS will be enrolled at 13 site hospitals (Eculizumab 22, Placebo 11).

Study duration period: July 2015~ March 2017 (Enrollment period: July 2015~June 2016)

7.4. Target

7.4.1 Target Subjects

Diagnosis/Case Definition and Main Criteria for Inclusion:
Patients who have been diagnosed with GBS with the reference to the NINDS (Table 3) and the following inclusion criteria, and do not conflict with the exclusion criteria will be included in this trial.

Table 3: NINDS Diagnostic Criteria for Guillain–Barré syndrome (GBS)

Features required for diagnosis	• Progressive weakness in both arms and legs (might start with weakness only in the legs) • Areflexia (or decreased tendon reflexes)
Features supportive of diagnosis	• Progression of symptoms over days to 4 weeks • Relative symmetry of symptoms • Mild sensory symptoms or signs • Cranial nerve involvement, especially bilateral weakness of facial muscles, autonomic dysfunction • Pain (often present) • High concentration of protein in Cerebrospinal fluid(CSF) • Typical electrodiagnostic features
Features that should raise doubt about the diagnosis	• Severe pulmonary dysfunction with limited limb weakness at onset • Severe sensory signs with limited weakness at onset • Bladder or bowel dysfunction at onset • Fever at onset • Sharp sensory level • Slow progression with limited weakness without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or CIDP) • Marked persistent asymmetry of weakness • Persistent bladder or bowel dysfunction • Increased number of mononuclear cells in CSF (>50 × 10E6/L) • Polymorphonuclear cells in CSF

Reference:

Adapted from Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 1990; 27 Suppl:S21–4.

[Rationale for setting of target subjects]

The GBS diagnostic criterion was proposed by Asbury et al. in 1978. It has been revised and currently the GBS diagnostic criteria used frequently is that of Asbury and Cornblath with some modifications. It has been also adopted as the diagnostic criteria for this trial. However, there are some aspects of the post-onset diagnosis that do not meet the diagnostic criteria listed above. We will, therefore, use the NINDS Diagnostic Criteria for GBS as reference.

7.4.2. Subject Inclusion Criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Subjects ≥ 18 years of age at the time of obtaining informed consent
2. Patients with onset of weakness due to GBS less than 2 weeks before the time of consent
3. Patients unable to walk unaided for ≥5 meters (progressively deteriorating FG3 or FG 4–5)
4. Patients who are already on IVIg or deemed eligible for and who will start IVIg (Generally, administration of 400mg/kg over 5 days)
5. Patients who can start their first dose of eculizumab within 2 weeks from onset of weakness and before the end of the IVIg treatment period
6. Female subjects of child bearing potential with a negative result in their pregnancy test. All subjects must be able to practice an effective, reliable, medically approved method of contraception during the IP administration period and up to 5 months after IP administration is ended.
7. Patients who can be hospitalized during IP administration period.
8. Patients who have signed the informed consent form

[Rationale for Setting Inclusion Criteria]

- 1, 6–7: In order to ensure the safety of the subjects.
- 2, 5: In order to set the criteria for patients that could expect efficacy from eculizumab.
- 3： In order to set the criteria for patients who would be considered desirable targets for a new treatment method, as treatment with only IVIg has a possibility of leaving a residual disability.
- 4, 5: In order to establish the efficacy and safety of simultaneous administration of IVIg and the IP.
- 8： Ethical considerations.

7.4.3. Subject Exclusion Criteria

For an eligible subject, all exclusion criteria must be answered “no”.

Exclusion Criteria:

1. Patients who are being considered for or are already on plasmapheresis
2. Patients who are pregnant or lactating
3. Patients showing clear clinical evidence of peripheral polyneuropathy other than GBS, e.g. diabetic (except for mild sensory disturbance) or severe vitamin B1 deficiency related
4. Patients who have received immunosuppressive treatment (e.g. azathioprine, cyclosporine, tacrolimus, or >20 mg prednisolone daily) during the 8 weeks prior to providing consent
5. Patients who are known to have severe concurrent disease (such as malignancy with uncontrolled primary tumors or metastatic lesions, severe cardiovascular disease, severe COPD, or TB)
6. Patients who are unable to comply with study procedures and the treatment regimen
7. Patients who have received rituximab within 24 weeks prior to providing consent
8. Patients with unresolved *Neisseria meningitidis* infection or a history of meningococcal infection.
9. Patients with active infectious diseases determined to be clinically severe by the Investigator or Subinvestigator that are not being appropriately treated with antibiotics
10. Patients who cannot be treated with antibiotic prophylaxis due to allergies
11. Patients who are allergic to eculizumab
12. Patients who are known to have or are suspected of having hereditary complement deficiencies
13. Patients who have been administered another investigational product within 12 weeks prior to providing consent or are currently participating in another trial
14. Patients with any condition that, in the opinion of the Investigator or Subinvestigator, could increase the patient's risk by participating in the study or confound the outcome of the study
15. Patients who have a history of Eculizumab treatment for GBS

[Rationale for Setting Exclusion Criteria]

- 2, 4–5, 7–12, and 14: Set under consideration of the safety of subjects.
- 1, 3, 6, 13, and 15: Set because it will affect the evaluation of the efficacy of the IP.

7.5. Enrollment and Randomization

7.5.1. Allocation of the IP

The drug allocation coordinator will create the randomization table using a reproducible randomization schedule, and the investigational product provider will conduct packaging and labeling of IPs based on that table. The IP randomization table will also be submitted to the Patient Registration Center.

The allocated IP will be delivered to the trial sites promptly after the start of the trial.

7.5.1.1 Blinding of IP in Allocation

The drug allocation coordinator will take measures to ensure that the blinding of the IP is maintained until the key -code opening. The blinding of the IP will be performed under the following procedures:

1. The drug allocation coordinator will verify that the external appearance and packaging of the eculizumab and placebo are both indistinguishable from each other.
2. The Investigator or Subinvestigator will not change the assessment of the subject before or after the emergency key has been opened in cases of SAE occurrence. Unblinded emergency key-codes will be handled as described in the section [12.2.8.4. Procedures to Unblind the Emergency Key-Code].
3. The drug allocation coordinator will verify at the time of key -code opening that the medication key-coded randomization table and envelope have been securely stored in a sealed condition.
4. At the time of key-code opening, the drug allocation coordinator will verify that the unadministered/unused IPs have been collected and sealed, and the sealed or unblinded condition of the emergency key.
5. For the blinded IP, the drug allocation coordinator will verify that the external appearance and packaging are both indistinguishable, and then proceed with the key-code opening.

7.5.2. Enrollment

After the signed informed consent is obtained and the screening is conducted, the patient will be registered for enrollment in the trial. Patients will be randomized using a web-based, centralized registration system. Online enrollment for this trial is possible 365 days a year 24 hours a day (excluding system maintenance hours of system), and will be done according to the below procedures:

1. After obtaining the signed informed consent, the investigator or Subinvestigator will perform a screening test and confirm that the subject must fulfill all the eligibility requirements of the inclusion criteria and do not fall under any of the exclusion criteria. For subjects who are determined to be eligible, the investigator, Subinvestigator, or study coordinator will enter the necessary information on the registration page of the web based registration system and complete the enrollment.
2. Upon receipt of the enrollment information, the patient registration center will verify the subject's eligibility with the inclusion/exclusion criteria, verify that there is no overlapped enrollment, and inform the trial site of the result of the subject's eligibility for enrollment per the web based registration system. If the subject is eligible for enrollment, the subject will be randomized and the medication code will be allocated.
3. After verifying that the subject is eligible for the trial and confirming the allocation number via the web based registration system, the investigator or Subinvestigator will administer the investigational product with the applicable allocation number.

The investigator and Subinvestigator may not administer the investigational product until the enrollment and randomization of the subject is complete.

7.5.2. 1 Handling of Unenrolled Subjects

If randomization is not performed due to reasons such as ineligibility before randomization, the patient will not be enrolled, and will not be included as an enrolled subject of this trial. In this case the investigator and Subinvestigator will explain to the subject that his/her enrollment in the trial is not possible.

7.5.3. Randomization

Eligible subjects assessed by the investigator or Subinvestigator will be randomized on Visit 1 in a 2:1 ratio of eculizumab infusion to placebo infusion. The randomization will be performed by the patient registration center using a program based on appropriate computer algorithm. Allocation to the eculizumab or placebo group will be performed via the web based registration system, and by a dynamic allocation based on Hughes Functional Grading score (FG=3 or FG≧4) and age (below 60 years of 60 years and older) as the adjustment factors.

[Rationale for Adjustment Factor]

As our retrospective data shown in the table4, we assigned FG score at the start of treatment and age at time of onset as adjustment factors because they affect the impact on FG score at Week 4.

Table 4. Adjustment factors (FG score at the start of treatment and age at time of onset) and impact on FG score at Week 4

	FG score at Start of Treatment		**P value**
	FG 3 (n=25)	FG 4・5 (n=42)	
FG score at 4 weeks after start of treatment (median, range)	2 (1–4)	4 (2–6)	<0.0001
Percentage of subjects with a score ≦FG2 at Week 4	86%	32%	<0.0001

	Age of onset		**P value**
	Below age 60 (n=40)	Over age 60 (n=27)	
FG at start of treatment (median, range)	3 (3–5)	4 (3–5)	0.002
FG at 4 weeks after start of treatment (median, range)	2 (1–5)	4 (1–6)	0.0002
Percentage of subjects with a score ≦FG2 at Week 4	70%	24%	0.0002

7.6. Study Procedures (At each research site)

7.6.1. Subject Background Information and Medical History

Subject identification code number, Gender, Birth date, Date of obtaining IC, Complications, Medical history (e.g. GBS, diabetes), current and concomitant medications, Weight, Height, Date of onset of weakness. If height and weight cannot be established, past values may be used.

7.6.2. Vital Signs

Vital signs will be measured at every visit and will include assessments of systolic and diastolic BP, temperature, and HR.

Systolic and diastolic BPs will be documented in mmHg. Temperature will be obtained in degrees Celsius. HR will be documented in beats per minute. Generally, each patient will have blood pressure tested in the same arm. Measurement device and measurement time will not be indicated.

7.6.3. FG (Functional Grade)

Mobility will be evaluated based on the 6 categories cited in Functional Grade (Table 2) guideline. In the FG guideline, larger numbers indicate more severe impairment. The Investigator/Subinvestigator will conduct evaluations. While subject Diaries are being recorded, FG will be evaluated based on subject self-reports and clinical assessments. After the Subject Diary has finished being recorded, FG will be evaluated based on clinical assessments. Subjects should be evaluated by the same person throughout the trial as much as possible.

7.6.3.1. Subject Diaries

From randomization each subject will be given a “subject diary” at each visit (treatment/examination days). The subject will record his/her FG score in the diary and return it at the next visit (treatment/examination day). The subject will evaluate his or her own FG score every day. If the subject has difficulty completing the diary due to muscular weakness, a family member or another person aside from the evaluating physician may record the score in the diary. The subject must continue writing in their subject diary until it has been determined that the patient’s FG score has improved at least one grade above the baseline.

7.6.4 ONLS (Overall Neuropathy Limitations Scale):

The subject’s symptoms will be evaluated using the ONLS (Interview of subject regarding subjective symptoms of arms and legs (numbness, hypoesthesia, muscle weakness)). A score will be given as well as a score for each individual limb. A higher score means that symptoms are more severe. Subjects should be evaluated by the same person throughout the trial as much as possible.

7.6.5 Manual muscle testing (MMT):

Evaluation of muscle strength of major muscles in the body: Both sides of Deltoid, Biceps brachii, wrist extension, Iliopsoas , Quadriceps muscle, and Tibialis anterior muscle as well as neck anteflexion. Assessment of muscle strength is based on the 5 parameters listed in table 5, and the grade of each muscle is totaled into a final score. Subjects should be evaluated by the same person throughout the trial as much as possible.

Table 5. MMT score by MRC

The patient's effort is graded on a scale of 0–5:	
Grade 0 zero	No visible contraction
Grade 1 trace	Visible contraction without movement of the limb
Grade 2 poor	Active movement of the limb but not against gravity
Grade 3 fair	Active movement against gravity over (almost) the full range
Grade 4 good	Active movement against gravity and resistance
Grade 5 normal	Normal strength

7.6.6. Grip Strength:

Over the course of the trial, grip strength will be measured using the same hand dynamometer (Smedley-spring type). When gripping the dynamometer, the handle of the dynamometer will be adjusted, so that the second joint of the index finger is bent straight at a right-angle, and the grip used during the initial examination should remain constant over the course of the trial. Grip strength will be measured in the right and left hands, three times each and the average will be recorded in kilograms.

<u>Grip Strength should be measured using the following procedure:</u>

Subjects that can stand with a steady posture: Stand with legs slightly spread, hold arms naturally at the side, and grip firmly.

Subjects that cannot stand with a steady posture: Sit upright, hold arms naturally at the side, and grip firmly.

[Try to prevent the hand dynamometer from touching the body, clothes, or chair (bed) as much as possible.]

Subjects that cannot remain in a stable sitting posture: lying horizontally, extend the arms horizontally over the bed (eliminating the force of gravity), and grip the dynamometer placed over the bed firmly.

7.6.7. R-ODS (Appendix 2)

Collect answers from subjects using the R-ODS questionnaire (see attached 2) regarding difficulty of movement in their daily activities. A low score indicates more severe symptoms.

7.6.8. Respiratory Function Test

Vital capacity will be measured by a spirometer and recorded in L（Litre）. If respiratory function cannot be measured due to ventilator support, the measured value will be treated as a missing value. % Vital capacity will be displayed automatically on the electronic data format using the predicted VC calculated by the VC-J Equation below.

*VC-J Equation (Predicted Vital Capacity)

Men: 0.045×height (cm) －0.023×age－2.258（L）
Women: 0.032×height (cm) －0.018×age－1.178（L）

7.6.9. Nerve Conduction Test

Nerve Conduction Study: Measure distal latency, CMAP amplitude, motor nerve conduction velocity, and minimum F-wave latency of the median, ulnar, fibular, and tibial nerves. Evaluate sensory nerve conduction amplitude and velocity of the median, ulnar, and fibular nerves. The tests for each individual patient should be conducted on one side of the body, and that side should remain the same throughout the trial period.

(Motor Nerve Conduction Study)

1. Recording electrodes

The active electrode will be placed over the belly of the muscle and the reference electrode placed over the muscle tendon. Generally skin temperature is to be maintained at a minimum of 32 ℃.

For each nerve that is stimulated, the action potential of the following muscles will be recorded:

- Median nerve: abductor pollicis brevis muscle
- Ulnar nerve: abductor digiti minimi muscle
- Peroneal nerve : extensor digitorum brevis muscle
- Tibial nerve: abductor hallucis muscle (1 cm below and 1 cm behind the navicular tubercle)

2. Stimulation points

The cathode of bipolar stimulating electrodes will be placed on the stimulation point described below and the anode will be placed proximally to the cathode. A single supramaximal stimulus will be given over the nerve and the CMAP will be recorded from a muscle innervated by the nerve.

- Median nerve:
  Distal: wrist (3cm proximal to the wrist crease)
  Proximal: elbow (cubital fossa)

- Ulnar nerve: elbow is bent at a right-angle when the study is being conducted
  Distal: wrist (3cm proximal to the wrist crease)
  Proximal: elbow (cubital tunnel)

・Peroneal nerve
Distal: anterior ankle
Proximal: medial biceps femoris tendon, lateral popliteal fossa

・Tibial nerve
Distal: behind the medial malleolus
Proximal: posterior popliteal fossa

3. Measurement of CMAP amplitude/latency and calculation of motor nerve conduction velocity

CMAP amplitudes will be measured from the baseline to the peak of negative deflection (negative-peak amplitude).

The motor nerve conduction velocity (NCV) will be calculated based on the distance and the latency difference between the two stimulation sites.

The formula for NCV is:

$$\text{NCV (m/sec)} = \frac{\text{Distance between two stimulation sites (mm)}}{\text{Latency (in msec) from the proximal stimulation site} - \text{Latency (in msec) from the distal stimulation site}}$$

4. F-wave Study

The F-wave study will be conducted following CMAP measurement.
The cathode of stimulating electrodes will be placed on the stimulation point described in Section2 and the anode will be placed distally to the cathode. A minimum of ten consecutive stimuli will be applied to each nerve to obtain the F-wave and the shortest F-wave latency will be measured with a sensitivity up to 200μV.

(Sensory Nerve Conduction Study)

1. Recording electrode

The sensory nerve conduction study will be performed antidromically by stimulating a nerve proximally and recording it distally. The recording electrodes will be placed over the nerves mentioned below. Skin temperature will be maintained at a minimum of 32 ℃. Any kind of electrode may be used (such as ring or dish electrodes).

・Median nerve
Active electrode: PIP (proximal interphalangeal) joint of the second finger
Reference electrode: 2cm distal to the active electrode

・Ulnar nerve
Active electrode: PIP joint of the fifth finger
Reference electrode: 2cm distal to the active electrode

・Sural nerve
Active electrode: midpoint between lateral malleolus and Achilles tendon
Reference electrode: 3cm distal to the active electrode

2. Stimulation points

The cathode of stimulating electrodes will be placed on the stimulation point described above and the anode proximal to the cathode. Record the action potential amplitude with the supramaximal stimulus.

・Median nerve: wrist (3cm proximal to the wrist crease)
・Ulnar nerve: wrist (3cm proximal to the wrist crease)
・*S*ural nerve: posterior part of a lower leg 14cm distal to the active electrode

3. Measurement of SNAP amplitude/latency and calculation of sensor nerve conduction velocity

Record the sensory nerve action potential. SNAP amplitudes will be measured from the baseline to the peak of negative deflection (negative-peak amplitude). The latency will be measured from the point of stimulation to the onset of the initial negative deflection of the SNAP.
The sensory nerve conduction velocity will be calculated based in the distance and the latency.

The formula for NCV is:

$$\text{NCV (m/sec)} = \frac{\text{Distance between two stimulation sites (mm)}}{\text{Latency (in msec)}}$$

7.6.10. ECG

A standard 12-lead ECG will be performed while the subjects are in supine position for at least 3 minutes.

7.6.11. Blood count

RBC, Hb, Hct, WBC, White blood cell differentiation (neutrophils, lymphocyte, monocyte, eosinophil, basophil), PLT

7.6.12. Chemistry panel

Total protein, albumin, urea nitrogen, creatinine, AST, ALT, γ-GTP, ALP, LDH, total bilirubin, glucose, Na, K, Cl, IgA, IgG, IgM

7.6.13. Urinalysis

Urinary protein, urinary glucose, hematuria

7.6.14 Pregnancy Test

A pregnancy test (urea or serum) must be conducted on all female subjects of child bearing potential during screening, on Day 169, Discontinuation Visit and the Follow up Visit after the discontinuation of the trial.

7.7. Study Procedures (Central Laboratory)

Antiganglioside antibodies and Eculizumab Serum Concentration/Serum Hemolytic Activity will be measured at a CRO central laboratory, and the test results for each subject will be stored in a location undisclosed to outside individuals (such as the Subjects, Investigator, Subinvestigator) from the start of IP administration until the key code-opening. After receiving contact from the Allocation Coordinator, the data will be disclosed to the Data Management Coordinator and the Statistician.

The residual samples will be handled according to section [16.5 Retention, storage and use of blood samples].

7.7.1. Antiganglioside Antibody
(Antibodies to GM1, GD1a, GalNAc-GD1a, GQ1b and their ganglioside complexes)

All patients must undergo a blood test to measure antiganglioside antibodies on Day 0 or Day 1 before administration of the IP. If for some reason a blood test cannot be conducted before administration of the IP, a blood test taken after administration may be submitted.

7.7.2 Eculizumab Serum Concentration/Serum Hemolytic Activity

Eculizumab Serum Concentration and Serum Hemolytic Activity will be measured in the first ten patients who are administered the IP. Serum for this measurement will be taken at Day 1, Day 8, Day 29 and Day 43.

Serum will be collected before and after IP administration on Day 1 and Day 8. Before administration, the serum will be collected at the baseline or trough value (0-90 min.), and after administration the serum will be collected at peak value (60 min ±10 min.).

Blood samples taken for measurements should be collected from a different line from that of IP administration.

7.8. Measurement Restrictions

7.8.1. CH 50

CH 50 measurements are restricted from being performed at each study site starting from Day 1 through the end of the trial period.

[Rationale for excluding CH 50]
Eculizumab administration is known to lower CH 50. Blinding cannot be maintained if CH 50 is measured, so it has been restricted in this trial.

8. Trial Implementation Schedule

8.1. Schedule of Assessment

Table 6 .Trial Flow Chart for Assessment

Period		Screening*8	IP Administration (In-Patient)					Post IP Administration (Out-Patient)						Follow-up Visit*12
Trial Visit		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	ET*11	8 weeks after the last IP administration
Study Days		Day 0	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 85	Day113	Day 169		
Study Weeks				Week1	Week 2	Week3	week4	Week6	Week8	Week12	Week16	Week24		
Time window(days)*1		-5		±2	±2	±2	+7	±7	±7	±7	±7	±7	+7	+7
Informed Consent		●												
Randomization*2		●												
Medical History		●												
Body Weight/Height*3		●												
IP administration*4			●	●	●	●								
Chemoprophylaxis against Infection*5			←						→					
Clinical assessments	FG	●	●	●	●	●	●	●	●	●	●	●	●	
	ONLS		●	●	●	●	●	●	●	●	●	●	●	
	MMT score		●	●	●	●	●	●	●	●	●	●	●	
	Grip strength		●	●	●	●	●	●	●	●	●	●	●	
	R-ODS		●				●		●	●	●	●	●	
Physiological Test	Vital capacity	●*9					●					●	●	
	Nerve conduction test	●*9					●			●		●	●	
	12-lead ECG	●		●								●	●	
Clinical Lab Test	Hematological test Blood biochemical test Urine test	●		●	●	●	●	●	●	●	●	●	●	●
Antiganglioside antibody*6		●												
Eculizumab concentration*6			●*10	●*10			●	●						
Hemolytic activation*6			●*10	●*10			●	●						
Pregnancy test (urine test)* 7		●										●	●	●
Vital signs		●	●	●	●	●	●	●	●	●	●	●	●	●
Concomitant drug/therapy review		←												→
AE assessment *8		←												→

Footnotes for Table 6:

*1: The time window for each visit is
Day 8, Day 15 to 22: ±2 days,
Day29: 0 to +7 days for clinical assessments, vital capacity and nerve conduction test, (while -4 to +7 days for other assessments).
Day 43 to 169: ±7 days,
At time of Early Termination (ET) and the last Follow-up Visit: +7 days (however, for Clinical Lab Test, ±3days).
There should be an interval of more than 6 days between Day29 and Day43, and also between Day43 and Day53.

*2: Enrollment will be completed after obtaining signed informed consent, and after eligibility is verified in the screening test.

*3: If the subject's height and weight cannot be measured, past patient data may be used.

*4: The IP will be administered after all tests and procedures are completed, except for the blood sampling at *10, which will be collected at IP pre-administration and post-administration.

*5: As prevention for infectious diseases, chemoprophylaxis will begin at the start of eculizumab infusion on Day1, and be continued till 8weeks from the last dose of eculizumab (if eculizumab has been administered 4 times, for a total of 11 weeks). If a vaccine is to be used concomitantly, the vaccine should be administered promptly, the administration of antibiotics will be started at Day1, and be continued until 3 weeks after the vaccine administration.

*6: Measurements for Antiganglioside antibodies, Eculizumab concentration, and hemolytic activation will be done at a central laboratory. See section [7.7. Study Procedures (Central Laboratory)].

7: A pregnancy test (urinalysis or serum β-HCG) must be performed on all women of child bearing potential at the specified time points and verified to have a negative result. A pregnancy test may also be performed at any visit at the investigator's discretion.

*8: If an Adverse Event occurs, the event will be followed up until it has stabilized or the subject has returned to the state they were in before administration of the IP or the laboratory results return to baseline or normalize. All AEs must be managed and SAEs must be reported according to section [12.2.8. Management of Adverse Events and Reporting of Serious Adverse Events].

*9: Blood samples for Physiological, Clinical, and Antiganglioside antibody assessments are to be taken once after obtaining informed consent and before IP administration on Day1. However, measurement values taken at the screening before obtaining informed consent can be used if

they are performed as part of a routine examination and the time of measurement falls within the established range. Vital capacity assessment and Nerve conduction test in particular should be done within 1 day prior to administration.

*10: Blood samples for eculizumab concentration and hemolytic activity on Day1 and Day8 are to be taken before and after IP administration.

Baseline and trough blood samples for eculizumab concentration and hemolytic activity are to be taken 5-90minutes before the IP administration. Peak blood samples for eculizumab concentration and hemolytic activity are to be taken 60 minutes (±10minutes) after IP administration.

*11: For subjects who withdraw early from the trial, an Early Termination (ET) Visit will be performed at time of termination.

*12: If a subject withdraws from the trial within 8 weeks after the last IP administration, a final follow-up visit will be performed for safety assessment.

8.2. Screening /Visit 1 (Day 0)

After obtaining consent, confirm the eligibility of the subject by conducting the following tests and evaluation. GBS Diagnosis/Case Definition and Main Criteria for Inclusion is to be done as described in section [7.4. Target].

1. Evaluate inclusion/exclusion criteria
2. Record patient information (Gender, birthdate, height, body weight, complications, past medical history, etc.)
3. Record FG
4. Measure vital capacity
5. Conduct nerve conduction test
6. Record 12-Lead ECG
7. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
8. Measure antiganglioside antibody
9. Conduct pregnancy test (urine or serum) on all female subjects with child-bearing potential
10. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
11. Record concomitant drug and/or treatment
12. Confirm that the patient fulfills all of the inclusion criteria and does not fall under any of the exclusion criteria and then register them in the Patient Registration Center.

8.3. IP Administration Period

Subjects will be admitted into hospital care for 4 weeks and receive a total of 4 doses of the IP (Day 1, Day 8, Day 15, Day22). The IP administration start time and end time will be recorded at each time of administration. The primary efficacy endpoint will be evaluated at Day29.

8.3.1. Baseline/Visit 2 (Day 1)

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Record R-ODS
6. Measure vital capacity*
7. Conduct nerve conduction test*
8. Record 12-Lead ECG*
9. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis) *

10. Measure eculizumab concentration in serum(both prior to and after IP infusion)
11. Measure hemolytic activity in serum (both prior to and after IP infusion)
12. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
13. Record concomitant drug and/or treatment
14. Administer IP (record administration start/end time)
15. Evaluate and record any adverse events
16. Begin prevention measures for *N. meningitidis* (See section [10.5.Warnings and Preventive Measures]) starting from Day 1

    *If each procedure of #6-10 is conducted on Day0, it will not be required on Day1.

8.3.2. Visit 3 （Day 8/Week1）

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Record 12-Lead ECG
6. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
7. Measure eculizumab concentration rate in serum (both prior to and after IP infusion)
8. Measure hemolytic activity in serum (both prior to and after IP infusion)
9. Measure vital signs such as systolic and diastolic BP, body temperature, and HR
10. Record concomitant drugs and/or treatments
11. Administer IP (record administration start/end time)
12. Evaluate and record any adverse events

8.3.3. Visit 4 (Day15/Week2), Visit 5 (Day 22/Week3)

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
6. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
7. Record concomitant drugs and/or treatments
8. Administer IP (record administration start/end time)
9. Evaluate and record any adverse events

8.3.4. Visit 6（Day 29/Week4）

Conduct the following tests and procedures:

1. Record FG(Primary efficacy endpoint)
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Record R-ODS
6. Measure vital capacity
7. Conduct nerve conduction test
8. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
9. Measure eculizumab concentration in serum
10. Measure hemolytic activity in serum
11. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
12. Record concomitant drugs and/or treatments
13. Evaluate and record any adverse events

8.4. Post IP Administration Period

The post IP administration observation period is set for the long-term evaluation of AEs and safety. It will start immediately after the IP administration period is ended and will continue up to Day 169 (Week 24).

8.4.1. Visit 7（Day 43/Week6)

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
6. Measure eculizumab concentration in serum
7. Measure hemolytic activity in serum
8. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
9. Record concomitant drugs and/or treatments
10. Evaluate and record any adverse events

8.4.2. Visit 8（Day 57/Week8）, Visit 10（Day 113/Week16）

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength

5. Record R-ODS
6. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
7. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
8. Record concomitant drugs and/or treatments
9. Evaluate and record any adverse events

8.4.3. Visit 9（Day 85/Week12）

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Record R-ODS
6. Conduct nerve conduction test
7. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
8. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
9. Record concomitant drugs and/or treatments
10. Evaluate and record any adverse events

8.4.4. Visit 11（Day 169/Week 24) or Early Termination

Conduct the following tests and procedures:

1. Record FG
2. Record ONLS
3. Record manual muscle testing (MMT) score
4. Measure gripping strength
5. Record R-ODS
6. Measure vital capacity
7. Conduct nerve conduction test
8. Record 12-Lead ECG
9. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
10. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
11. Record concomitant drugs and/or treatments
12. Evaluate and record any adverse events
13. Conduct a pregnancy test in all female patients of child-bearing potential (urinalysis or serum β-HCG)

8.4.5. Follow-up Visit

Subjects who have withdrawn from the trial within 8 weeks of the final administration will require a follow-up visit for safety assessment at 8 weeks after the final IP administration.

1. Conduct clinical lab tests (hematological testing, blood biochemical testing and urinalysis)
2. Measure vital signs (systolic and diastolic BP, body temperature, and HR)
3. Record concomitant drugs and/or treatments
4. Evaluate and record any adverse events
5. Conduct a pregnancy test in all female patients of child-bearing potential (urinalysis or serum β-HCG)

8.5. Definition of End of Study

This study is composed of a Screening period, IP administration period, and Post-IP administration period. After giving IC, the subject is considered to have completed the study when he/she completes the Day169 (Week24) visit. In the case of early withdrawal, the end of the study for the subject is either the day of the Early Termination visit or the follow-up visit 8weeks after the final IP administration, whichever is later.

9. Discontinuation/Withdrawal

The discontinuation of the IP administration and the subject's withdrawal are to be distinguished in this trial.

9.1. Suspension or Discontinuation of IP Administration at Visit

If an adverse reaction (e.g. infusion reaction) that cannot be denied its causal relation to the IP occurs during the administration of IP, the infusion may be suspended or discontinued. In the event of a subject's pregnancy, administration of the IP will be stopped and no further administration will be performed.

9.1.1 Re-administration after suspension or discontinuation of IP

For subjects who have had the IP administration suspended due to adverse events, such as an infusion reaction, it is possible to administer the IP at the next visit. However, there are no standards of determining whether or not re-administration of the drug is possible to patients who have experienced a serious infusion reaction. The possibility of re-administration will be determined by a risk benefit assessment of the administration. In addition, when restarting administration of the IP after a discontinuation caused by other adverse events, re-administration can only be conducted if the Investigator or Subinvestigator determines that it is viable.

9.1.2. Handling of Investigational Product Administration Discontinuation

If all four administrations of the IP cannot be carried out due to suspension or discontinuation of the IP, tests and assessments will still be performed on subjects according to the trial schedule, unless the subject meets the criteria as described in section [9.2. Subject Withdrawal Criteria].

9.2. Subject Withdrawal Criteria

If the following criteria apply, the subject's enrollment in the trial will be discontinued. The Investigator or Subinvestigator will record the reasons for discontinuation in the CRF:

1. The subject requests his/her withdrawal from the trial
   All patients can withdraw their consent of trial enrollment at any time. Maximum effort will be made to ensure the subject's will to enroll in the trial before the screening test is conducted. If any restrictions such as the change in concomitant medications arise for the enrollment in the trial, adequate explanation will be necessary.

2. The Investigator or Subinvestigator determines that the subject cannot continue his/her enrollment in the trial.
   e.g.) Event of an infusion reaction that is life-threatening or the event of a systemic infection where the risk of trial enrollment is higher than the subject's benefit of enrollment.

3. Reasons to determine that enrollment continuation is difficult.
   e.g.) subject does not visit the hospital, subject has changed hospitals.

4. Other cases where the Coordinating-Investigator determines the subject's withdrawal due to a major protocol deviation, etc.

The "day of withdrawal" for the above is defined as:
1. Day of event occurrence that is the reason of withdrawal
2-4. The day that the Investigator/Subinvestigator determines the subject's withdrawal

9.2.1. Handling of Subject Withdrawals

If a subject withdraws consent from the trial for a certain reason, the observation and tests planned for the time of withdrawal will be performed, but if the subject withdraws from the study before receiving any study treatment, the subject does not require further examination or tests.

If a subject withdraws from the trial within 8weeks after the last IP administration, a follow-up visit will be required for safety assessments.

If a subject withdraws consent from the trial after the study drug has been administered, the data obtained up to the withdrawal will be retained in the same way as the completion of the trial.

10. TREATMENT OF SUBJECTS

10.1. Treatment Compliance

The infusion of IP into subjects will be performed under the supervision of the Investigator/Subinvestigator or their designee, to ensure that the subject receives the appropriate dose at the appropriate time points during the trial.

10.2. IP Administration Dosage

Each vial of IP will contain either 300mg of eculizumab or matching placebo.

One dose of eculizumab (900mg) or matching placebo will be prepared according to section [11.4. Preparation of Investigational Product] and will be administered intravenously once a week, totaling four doses.

Table 7. Eculizumab Dosage

IP Administration Period	# of Vials	Eculizumab Amount
Day1	3	900mg
Day8	3	900mg
Day15	3	900mg
Day22	3	900mg

10.3. IP Administration Method

The first IP administration should be conducted within 2 weeks from the onset of weakness and before the final administration IVIg.

Do not administer the IP as an Intravenous Push or Bolus Injection.

The IP should be administered intravenously over 35 minutes (range 25-45 minutes). It is not necessary to protect the infusion bags from light while IP is being administered to the subject. At the site's discretion, the diluted IP may be administered via a syringe-type pump, or an infusion pump. The intravenous line should be flushed in order to ensure complete administration of the IP.

The subject will be monitored by the medical staff for at least 1 hour following infusion to monitor whether an infusion reaction occurs. IVIG infusion will be performed 1 hour after this observation period.

10.4. Treatment Procedures and Concomitant Medications

10.4.1. Concomitant Medication (IVIg)

400 mg/kg of immunoglobulin (IVIg) will be administered over the course of five days via intravenous injection as described in the packaged insert for IVIg.

If immunoglobulin is administered on the same day as the IP, the subject must be observed for the occurrence of an infusion reaction following the administration of eculizumab. The subject must be observed for at least one hour after the administration of eculizumab, after which the administration IVIg may begin.

Re-administration of IVIg (400 mg/kg over 5 days)should be considered after the start of IP administration and after Day 15 or Day22, only if the subject is monitored for progressive worsening of symptoms more than one grade on the Hughes functional grading scale compared to before the administration of the IP.

10.4.2. Prohibited Medications/Treatments

The following concurrent medications are prohibited after IC obtaining to Day169/Week24 (or to during the trial:

1. Rituximab
2. Plasmapheresis
3. Steroid Pulse Therapy (more than 500mg/day of methylprednisolone)
4. Immunosuppressive drugs
5. Other investigational drugs

10.5. Warnings and Preventive Measures

10.5.1. *N. Meningitidis* Infection

10.5.1.1 Warnings and Precautions

Inhibition of the terminal complement complexes predisposes subjects to infections with encapsulated bacteria. In particular, subjects treated with eculizumab are at increased risk for the development of infection caused by N.menigitidis, as infection with this organism is more frequent in subjects who have a terminal complement deficiency. Because eculizumab can directly inhibit complement activation, an increased susceptibility to infection is a potential adverse effect of eculizumab. Infection with *N.meningitidis* can be life-threatening or fatal. Therefore, to decrease the risk of such possible infection, all subjects who have been enrolled in this trial must receive the proper preventive measures against *N.meningitidis*.

10.5.1.2. Preventive Measures against *N. Meningitidis*

All subjects enrolled in this trial must receive a preventive measure against N.menigitidis, either option 1 or option 2 of the following measures. Prophylactic antibiotics should be prioritized over vaccination. Administration of the vaccine will only be possible for individual subjects whom the Investigator/Subinvestigator determines that the positive effects of administering the meningococcal

vaccine outweigh the potential risks of long-term administration of antibiotics. If it is so determined, the Investigator/Subinvestigator should refer to local immunization practice guidelines.

1. Prophylactic Antibiotics
   A suitable antibiotic should be administered starting from Day 1. Because of complement recovery due to eculizumab's half-life, the antibiotics should continue to be administered until 8 weeks from the last dose of eculizumab.
   Example: ciprofloxacin 500mg /day, oral intake once a week

2. *N. Meningitidis* Vaccine and Prophylactic Antibiotics
   Vaccine against *N. Meningitidis* should be administered promptly right after Day1. In the event that vaccine is chosen, prophylactic antibiotics will be administered concurrently starting from Day1 for 3 weeks after vaccination. The Meningococcal vaccine Menactra® has been approved in Japan as of July 2014, and its use is under consideration.

10.5.1.3. Participant ID Cards

During the study, subjects must carry a participant ID card describing the "alert" symptoms for *N. meningitidis* at all times. Development of the participant ID card will be the responsibility of the Investigator. The triggers for seeking immediate medical attention are any of the following symptoms:

- Headache with nausea or vomiting
- Headache with fever
- Headache with a stiff neck or back
- Fever of 39°C or higher with or without rash
- Onset of confusion
- Severe myalgia with flu-like symptoms
- Sensitivity to light

Any subject experiencing any of the above noted symptoms must see a physician as quickly as possible. For subjects that experience the onset of a systemic infection, if the Investigator or Subinvestigator examines the subject, appropriate cultures have been obtained, administration of antibiotics have begun, and it is deemed that the benefits exceed the risks IP administration may be continued with caution. The clinical trial will be conducted with careful monitoring of the subject. All AEs including any SAE or AE leading to discontinuation that occur during the study duration must be described in detail, fully evaluated by the Investigator, and reported in the appropriate CRF.

10.5.2. Warning and Precautions against Infusion Reaction

As with all protein products, administration of IP may result in infusion reactions. The Investigator/Subinvestigator should consider premedication with an antihistamine and anti-inflammatory

drug prior to dosing as is necessary. Medical treatment, slowing the infusion rate, or interrupting the infusion may be considered by Investigators /Subinvestigators following mild-moderate infusion reaction.

IP administration should be suspended or discontinued in all subjects experiencing severe infusion reactions and appropriate medical therapy such as oxygen therapy, vasopressor drug administration, bronchodilator administration, corticosteroid administration should be administered if signs of shock, anaphylaxis, cardiovascular instability, or respiratory compromise occur. There are no standards of determining whether or not re-administration of the drug is possible to patients who have experienced a severe infusion reaction. The possibility of re-administration will be determined by a risk benefit assessment of the administration.

10.5.3. Cautions for Pregnant or Lactating Females

The safety of eculizumab administration during pregnancy has not been established. Therefore, do not administer eculizumab to pregnant subjects. Female subjects of child bearing potential or subjects with a partner of child bearing potential must be practicing a medically approved contraceptive regimen [ex: Male condoms, female intrauterine device/ oral contraceptive (pill), tubal litigation]during the administration period and for at least 5 months following the final administration of eculizumab. If the subject becomes pregnant the administration of eculizumab will be stopped immediately. The Investigator/Subinvestigator will record the exposure during pregnancy of the subject or the subject's partner, and the progress of pregnancy will be monitored, and outcomes will be reported.

In addition, because the safety of eculizumab administration during lactation has not been established, breast-feeding to the infant should be suspended during the administration period and for at least 5 months following the final administration of eculizumab.

11. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

11.1. About the Investigational Product

Eculizumab is a recombinant humanized monoclonal IgG2/4κ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions (CDRs) grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Each active IP contains eculizumab 300 mg or matching placebo for intravenous administration.

Table 8 .Investigational Product Vial

Investigational Product	**ECU-GBS-001 10mg/mL, 30mL Vial**	
Product Name:	Eculizumab	Placebo
Dosage Form:	Concentrate for solution for infusion	Solution for infusion
Unit Dose:	300 mg	0 mg
Route of Administration:	Intravenous infusion	Intravenous infusion
Physical Description:	30 mL vial	30 mL vial
Manufacturer:	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.

11.2. IP Packaging and Labeling

The IP will be released to the study site of the Investigator according to the IP management SOPs. All medication provided to the study site will be prepared, packaged, and labeled by Alexion according to Standard Operating Procedures (SOPs), Good Manufacturing Practice guidelines, International Conference on Harmonization Good Clinical Practice guidelines (ICH GCP), and applicable local laws/regulations.

Each kit will have a single panel label on the vial and packaging describing the contents and a section for the pharmacist to record the subject ID code.

Label for Vial

ECU-GBS-001 Protocol :100069 / Code No. :

(Eculizumab 10mg/mL or Placebo, 30mL Vial) **Lot # :**

Storage : Store at 2°C-8°C, protected from light

Coordinating-Investigator and Address: **Expiry Date :**

Prof. Satoshi Kuwabara

Chiba University Hospital Department of Neurology

1-8-1 Inohana, Chuo-ku, Chiba 260-8677 Japan Prof.Satoshi Kuwabara

For clinical trial use only

Subject ID Code:_____

IP Packaging Label

For Clinical Trial Use Only **Protocol：100069 / Code No.：**

ECU－GBS－001

(Eculizumab 10mg/mL or Placebo, 30mL Vial) x Quantity

Lot # ： **Expiry Date：**

Administration Method: Subcutaneous injection

Storage： Store at 2°C-8°C, protected from light **Subject ID Code：**_____

Directions： Refer to protocol for drug handling instructions

Keep out of reach of children

Keep empty vials until collection

Coordinating-Investigator and Address:

Prof. Satoshi Kuwabara

Chiba University Hospital Department of Neurology

1-8-1 Inohana, Chuo-ku, Chiba 260-8677 Japan

11.3. Investigational Product Storage

The IP vials must be stored in the original carton until time of use under refrigerated conditions at 2-8°C and protected from light. Do not use beyond the expiration date stamped on the carton. Refer to section [11.5: Administration and Stability of Solution] below for stability and storage of diluted solutions of eculizumab. DO NOT FREEZE AND DO NOT SHAKE.

11.4. Preparation of Investigational Product

Investigational product should be prepared using aseptic technique. Each vial of IP contains 300 mg of active ingredient or indistinguishable placebo in 30 mL of product solution. Eculizumab is to be diluted to a final admixture according to the following steps:

Table 9. Eculizumab and Diluent Volumes

Volume of Eculizumab	Volume of Diluent [1]	Total Volume of Administration	Eculizumab Dose	IP Concentration
90 mL (3 vials)	90 mL	180 mL	900 mg	5 mg/mL

[1] Choose either of 0.9% sodium chloride or 5% dextrose in water

1. Remove any excess liquid from the infusion bag, and prepare 90 mL of diluent (either 0.9% NaCl Injection or 5% Dextrose in Water Injection).
2. Withdraw the 90mL of IP from the three vials into a sterile syringe
3. Inject the IP into the infusion bag (total 180mL of solution). Gently invert the infusion bag containing the diluted IP solution to ensure thorough mixing of the product and diluent.
4. Prior to administration, the admixture should be allowed to adjust to room temperature. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.
5. The admixture should be inspected visually for particulate matter and discoloration prior to administration.
6. The admixture should be used as soon as possible after preparation. However, if the IP is prepared more than 4 hours in advance of a subject's visit, the diluted material should be stored at 2°C to 8°C, and be allowed to return to room temperature before use.

11.5. Administration and Stability of Solution

Admixed solutions of IP are stable for 24 hours at 2-8°C and at room temperature. If the IP is prepared more than 4 hours in advance of a subject's visit, the diluted material should be stored at 2°C to 8°C for a maximum of 24 hours.

11.6. IP Accountability

1. The Coordinating-Investigator will deliver the Investigational Product to the Investigators at each site promptly after the start of the trial.

2. The Chief IP Management Pharmacist at each site will properly handle and store the IP in accordance with the IP Management SOP provided to the head of the site by the Investigator.

3. The Investigator at each site is responsible for creating an explanatory document (when applicable, the IP Management SOP, as described above) in regards to the handling of the IP (storage conditions, expiration date), and delivering the document to the head of the site, Subinvestigator, the study coordinators, and Chief IP Management Pharmacists.

11.7. Drug Management Precautions

All of the IP, both eculizumab and placebo, will use the same kits and labels and the outward appearance of the eculizumab and placebo will be indistinguishable. In this trial, an IP Management Pharmacist will be specifically assigned to manage and maintain the blinding of the IP (IP Management Personnel). The IP

Management Personnel will be uninvolved in the evaluation or the administration of the IP. The details of the IP Management Personnel's role and duties are described in the IP Management SOP.

11.7.1. Handling and Disposal of the Investigational Product

1. The IP Management Personnel will confirm the package contents upon receipt of all IP that is delivered to the site, and take care of all the necessary procedures for the receipt of the IP.
2. The IP Management Personnel will make records regarding the IP deliveries as soon as possible upon receipt.
3. The IP Management Personnel will keep the IP in a pharmacy or other locked and secure storage facility under controlled storage conditions.
4. Drug Accountability logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the IP. During the study, the following information must be noted in the accountability log: the subject identification code(s), drug allocation code, the date(s) and time that the IP is prepared and dispensed, and the initials of the pharmacist who prepared the IP.
5. The IP Management Personnel should manage all information regarding the IP as well as restrict other staff involved in the trial from accessing said information.
6. The Investigator and Subinvestigator will not administer the IP to any person other than the subjects of the study.
7. At the completion or termination of this study, the IP Management Personnel agrees to conduct a final drug supply inventory and to record the results of this inventory on the accountability log. Delivery records and records of used, returned or disposed of IP must be reconcilable.
8. The Monitor will verify the Drug Accountability Log and Inventory Log and once approval from the Coordinating-investigator is received, the IP Management Personnel will dispose of the used, unused, expired, or damaged IP as well as empty containers.
9. The IP management personnel will dispose of IPs according to the applicable guidelines for disposal of medicines.

12. ADVERSE AND SERIOUS ADVERSE EVENTS

12.1 Detection of Adverse Events (AE)

The Investigator and the Subinvestigator are responsible for detecting, assessing, documenting and reporting all Adverse Events directly observed by them or revealed by questioning of the patents and all Adverse Events self-reported by patients.

12.2. Adverse Events

12.2.1. Definition of Adverse Events

An Adverse Event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), or symptom or disease temporarily associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition, and abnormal laboratory findings that are considered to be of clinical significance are all to be considered as Adverse Events.

Situations where an untoward medical occurrences did not occur (social and/or convenience admission to a hospital), and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not Adverse Events.

The Investigator or Subinvestigator must obtain the appropriate information for all adverse events for the following aims:

1. Outcome of adverse events
2. Criteria for serious adverse event
3. Severity of adverse event
4. Causality of the adverse event.

For all adverse events, the terms recorded by the Investigator or Subinvestigator will be converted to the terms in the MedDRA/J edition.

12.2.2. Expectedness assessment of Adverse Events

The Investigator should establish the expectedness of AEs with reference to the latest Investigator's Brochure. If the occurrence of an AE (including the frequency and conditions of the AE) could not be predicted based on the relevant information in the Investigator's Brochure of the IP, it will labelled as "unknown"; otherwise, it will labelled as "known". However, if a safety information document is sent to the trial sites, it will be treated as a supplement to the Investigator's Brochure, and any relevant information can be used to establish the expectedness.

12.2.3. Serious Adverse Event (SAE) and SAE Criteria

Any adverse event that fulfills any one of the criteria listed below must be recorded as a Serious Adverse Event.

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization does not include the following:
    - Rehabilitation facility
    - Hospice facility
    - Nursing facility
    - Emergency Room
    - Same day surgery
    - Hospitalization or prolongation of hospitalization not associated with an adverse event is not an SAE, and examples include:
        - Admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE
        - Protocol-specified admission, pre-planned admission

4. Results in persistent or significant disability/incapacity
5. May lead to disability
6. Important medical event according to the above 1 to 5
7. Is a congenital anomaly/birth defect in later generations

NOTE: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

A non-serious adverse event is defined as any adverse event that does not fulfill any of the criteria listed above, and that the Investigator or Subinvestigator has determined as non-serious.

12.2.4. Severity Assessment

The Investigator or Subinvestigator will rate the severity of an AE as mild, moderate, or severe according to the following criteria:

Mild: Events that do not inconvenience daily life of the subject and the required treatment is minimal or no treatment is required.

Moderate: Event that causes mild inconvenience or concern for therapy. Moderate events may cause some functional disorder.

Severe: Event that prevents daily life of the subjects or may require systemic drug therapy or other therapy. Severe events impair normal physical functions.

12.2.5. Causality Assessment

The investigator or Subinvestigator must assess the causal relationship (cannot be ruled out, not related) of all AEs (serious and non-serious). This assessment must be recorded in the CRF and other SAE documents if required. The definition of causal relationship rating is as follows:

Causal relationship cannot be ruled out:
Regardless of the dose level, all reactions (including laboratory test value abnormalities) due to the administered IP that are harmful and not intentional. In other words, events that may at least have a logical possibility of causal relationship between this IP and adverse event and causal relationship cannot be negated. The following may be taken into account: disappearance after discontinuing administration, reoccurrence after starting administration again, previous establishment of causal relationship with this IP or similar drug, no confounding risk factor, consistency with exposure level/exposure period, almost certain explanation is possible for involvement of the target drug by accurate corroboration of medical history, no logical possibility that concomitant therapy is the cause, etc.

“Causality Unknown” will be also included in “cannot be ruled out”.

Not related: There is absolutely no relationship between the IP and reported event.

12.2.6. Outcome

The investigator or Subinvestigator must assess the outcome of the adverse events, and record the date of assessment.

Table 10. Outcome definition

	CDISC Submission Value	CDISC Definition
1	RECOVERED/RESOLVED	One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated.
2	RECOVERING/RESOLVING	One of the possible results of an adverse event outcome that indicates that the event is improving.
3	NOT RECOVERED/NOT RESOLVED	One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated.
4	RECOVERED/RESOLVED WITH SEQUELAE	One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.
5	FATAL	The termination of life as a result of an adverse event.
6	UNKNOWN	Not known, not observed, not recorded, or refused.

If a subject experiences an SAE with an outcome of death:

- The SAE resulting in death should have an outcome documented as death/fatal with an end date being the date of death
- If the subject had additional AE/SAEs that were ongoing at the time of death, these events would be documented as ongoing with no end date
- Only one event should have an outcome of death/fatal unless an autopsy report or Investigator states otherwise.

12.2.7. Exposure during Pregnancy and Lactation

Pregnancy data is to be collected from all subjects during this study.

If subjects that receive the IP in this study or the partner exposed to IP becomes pregnant or is revealed to be pregnant, the Investigator or Subinvestigator must report to the Coordinating -Investigator or IP provider, Alexion Pharmacovigilance:

Email：ClinicalSAE@alxn.com or
Fax: + 1-203-439-9347

Reports must be given three times from the moment the pregnancy is discovered to three months after the birth as taken place:

1. Before Delivery: The mother's condition and the state of the pregnancy
2. After delivery: A survey regarding the pregnancy and confirmation of natural miscarriage or termination, details of birth, absence/presence of congenital defects, and outcome of maternal or neonatal complications
3. Follow-up three months after birth: If the infant has experienced any AE following breastfeeding

Pregnancy in itself is not regarded as an AE unless there is a suspicion that investigational product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and many may meet criteria for a SAE. Complications of pregnancy and abnormal outcomes of pregnancy such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly would meet criteria of a serious AE and thus, should be reported as a serious AE. Elective abortions without complications should not be handled as AEs.

12.2.8. Reporting Obligations for Adverse Event(s) and Serious Adverse Event(s)

12.2.8.1. Adverse Events

In case of occurrence of any Adverse Event (AE), the Investigator or Subinvestigator must provide appropriate treatment and record the AE on medical record and CRF.

Any AEs should be observed during the reporting duration, defined in section [12.2.8.3. Reporting period], regardless of causal relations between the AEs and IP.

If an Adverse Event occurs, the event will be followed up until it has stabilized or the subject has returned to the state they were in before administration of the IP or the laboratory results return to baseline or normalize. However, certain cases can be excluded, e.g. when exacerbation of a primary disease or complication becomes a chronic condition, or any complicated situation occurs such as the patient's transfer to another hospital or follow up treatment is started.

The Investigator must tell patients when the Investigator decides to discontinue administration of IP, or any treatment is required for adverse events.

12.2.8.2. Serious Adverse Event(s)

1. In case of occurrence of a Serious Adverse Event (SAE), the Investigator or Subinvestigator must provide appropriate treatment regardless of causal relations between the SAE and IP.

2. The Investigator will immediately report the SAE to the head of the trial site as well as the Coordinating-Investigator and IP provider, regardless of causal relations between the SAE and IP.

3. The Coordinating-Investigator will verify the content of the SAE report obtained from the Investigator, and report the information of the SAE to the Investigators of the other trial sites.

4. The investigator of each trial site will verify the content of the SAE report obtained by the Coordinating-Investigator, discuss the content with the Coordinating-Investigator as necessary, and report his/her opinion as the Investigator to the Coordinating-Investigator (including the necessity of reporting the SAE to MHLW).

5. When the Investigators determine that there is a need to report the SAE to the Minister of MHLW, the Coordinating-Investigator will report the SAE.

6. In cases where SAEs that have occurred in other trial sites are reported to the Minister of MHLW, the Investigator will submit the AE report obtained by the Coordinating -Investigator and submit it to the head of the trial site as soon as possible.

7. When additional information related to the SAE is obtained, the Investigator of the trial site where the SAE has occurred will additionally report it to the head of the trial site immediately as well as to the Coordinating-Investigator and IP provider. Additional information will be treated according to 4–6.

The Investigator or Subinvestigator must report all SAEs to Alexion's Pharmacovigilance Delegate. The Investigator must send a copy of the SAE report prepared on RAVE to Alexion via Email or fax to the Alexion contact information provided below within 24 hours of their becoming aware of them:

Alexion Pharmacovigilance
Email: ClinicalSAE@alxn.com
Fax: + 1-203-439-9347

12.2.8.3. Reporting Period

For AEs and SAEs, the reporting period begins following the obtaining of informed consent and continues till the last trial visit. However, SAEs that are determined to have causal relationship with the IP are exempt from the reporting period.

12.2.8.4. Procedures to Unblind the Emergency Key-Code

The Investigator or Subinvestigator can break the emergency key-code when a SAE occurs which causal relationship with the IP cannot be ruled out, and the Investigator determines that it is necessary to secure the safety of the subject. In that case, the Investigator should notify the Coordinating-Investigator as soon as possible and record the reason and results for unblinding and submit them to the drug allocation coordinator. In deciding to break the key-code for the subject, the Investigator must stop administrating IP to the patient and decide upon the subject's withdrawal from the study. The opened emergency key-code will be resealed again and treated the same as unopened ones.

13. STATISTICS AND DATA ANALYSIS

13.1. General Considerations for Data Analysis

Statistical analysis and reporting of this trial will be conducted in accordance with the CONSORT guidelines, with the primary analyses based on the intent-to-treat principle without imputing missing observations. All efficacy analyses are primarily based on the full analysis set (FAS), which include all patients who have received one dose of the study treatment. Baseline demographic and clinical characteristics are summarized with frequencies and proportions for categorical data and means and SDs for continuous variables. Patient characteristics are compared using Fisher's exact test for categorical outcomes and t-tests or the Wilcoxon rank sum test for continuous variables, as appropriate.

All statistical analyses are performed using SAS software version 9.4 and the R statistical program, version 2.13. Furthermore, all statistical analyses are described in the statistical analysis plan (SAP), and SAP is fixed prior to database lock.

13.2. Efficacy Analysis

13.2.1. Primary Efficacy Variable and Analysis

The main purpose of this study is to assess the 4-week response proportion of FG= <2. H0 (null hypothesis) predicted a 4-week response rate of 50%, whereas H1 (alternative hypothesis) predicted the proportion of 80%, a type I error of 5% (one-sided) and 80.0% power. The response proportion of each group is determined along with corresponding one-sided, exact binomial 90% confidence intervals (CIs). As primary analysis, we will not compare the placebo and eculizumab by statistical hypothesis testing.

13.2.2. Secondary Efficacy Variables and Analyses

The secondary endpoints that are categorical will be analyzed in a manner same to that of the primary efficacy endpoint. Secondary efficacy endpoints that are continuous will be analyzed using t-tests or the Wilcoxon rank sum test, as appropriate. One-sided, 90% confidence intervals (CIs) will also be provided.

13.3. Safety Analysis

For this purpose, safety analyses will be conducted on the same population (FAS) and using the same evaluation period as for the efficacy analyses. All AEs recorded during the study will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

All summarized statistics will display, by treatment group, the overall frequency of patients with events. For each preferred term, a patient will be counted only once. For summaries on severe or drug-related AEs, for a given patient, the highest severity or relationship for a specific preferred term will be considered.

13.4. Sample Size and Power Considerations

The sample size is determined as follows by previous reports (REFs). In the eculizumab group, we assume that the expected value for the primary endpoint will be 80% and the threshold value will be 50%. In this situation, the sample size ensuring at least 80% power with one-sided α of 5% is 20. Considering the likelihood of some ineligible patients being enrolled, the number of patients in the eculizumab group is set at 22. On the other hand, to collect efficacy and safety data in the placebo control, 11 patients will be randomly assigned to the placebo control. In this study, the total sample size is set at 33 patients.

13.5. Interim Analysis and Premature Termination of the Trial

An interim analysis will not be held in this trial.

If additionally obtained information creates issues in safety and continuation of the trial, or if the efficacy of the conducted trial treatment cannot be expected further, premature termination of the trial will be considered. In addition, if the data monitoring committee issues a warning against trial continuation in terms of safety or efficacy, and if the Investigator determines to discontinue the trial, the trial will be terminated prematurely and the trial results will be presented immediately. However, in cases when the enrollment of subjects is terminated early the follow-up examination will be continued.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

The head of the clinical trial site and the Investigator must assure access to all source documents during monitoring by the monitor designated by the Coordinating-Investigator. The monitor will confirm that the study is appropriately conducted and the reliability of data is sufficiently ensured. The method of direct access and time period for monitoring are defined in the monitoring procedures.

The main responsibilities of a monitor are to:

1. Confirm that the clinical trial sites and Investigator meet the requirements to appropriately conduct the study.
2. Confirm that the IP is appropriately handled
3. Confirm that the study is appropriately conducted according to the protocol
4. Confirm that investigators, Subinvestigator, and investigational site personnel have obtained sufficient information regarding the study.
5. Verify the source documents and confirm that data is accurately described in the case report forms.
6. Verify that adverse events are appropriately reported according to the protocol, IRB, and GCP.
7. Confirm that documents to be retained at the clinical trial site are appropriately retained.
8. If there are any deviations from the GCP or protocol and procedures at the clinical trial site, the monitor should inform the Investigator and the head of the clinical trial site as necessary.

14.2. Audits and Inspections

The aim of audit is to assure the quality of the study and to systematically and independently validate whether the operations and documents related to the study are in accordance with GCP, protocol, and SOPs. The head of the clinical trial site and the Investigator must insure access to all source documents during audits and inspections of quality assurance as described in Section 15.2.

The Investigator must obtain consent from all related personnel before the start of the study to enable direct access for audits and inspections by regulatory agencies.

14.3. Materials approved by Institutional Review Board /Ethics Committee

The Investigator must obtain Institutional Review Board (IRB) / Ethics Committee (EC) approval for the trial. Initial IRB/EC approval and all materials approved by the IRB/EC for the trial including the subject ICF and recruitment materials must be maintained by the Investigator and made available for audit.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Quality Control

The Coordinating-Investigator will prepare a SOP for monitoring, and to have the monitor conduct monitoring according to the SOP. The Coordinating-Investigator will appoint a monitor with adequate scientific and clinical knowledge necessary for monitoring.

The monitor must conduct appropriate monitoring to ensure the study is properly conducted at clinical trial sites in accordance with the protocol and GCP and verify that the contents of case reports and other reports are accurate by directly evaluating access records related to the study such as source documents (source data). The monitor, data manager, and statistical analysis staff should each verify and confirm data handling at each stage.

15.2. Quality Assurance

The Coordinating-Investigator will prepare a plan and SOP for audit, and have the audits conducted according to the plan and the SOP. The Coordinating-Investigator will appoint as the auditor an individual who meets the requirements to appropriately conduct audits from experience in education and training. An auditor who is independent from all divisions conducting the trial (including but not limited to the Monitoring Division) will perform the audit of the clinical trial site and other sites involved with the clinical trial, and verify whether quality assurance is conducted appropriately.

16. ETHICS

16.1. Ethics Review

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP, applicable regulatory requirements, and the local institutional policy on Bioethics.

16.2. Ethics Committee/Institutional Review Board

Prior to the start of the study, the Institutional Review Board (IRB) will evaluate the ethical, scientific and medical appropriateness of this study. This study is conducted after obtaining approval from the IRB. If the evaluation results of the IRB are “approved with modification”, the study will be conducted after the protocol, case report, or consent forms are modified based on the review results. At the frequency of more than once a year, the IRB will continuously review whether the study is appropriately performed.

16.3. Data Monitoring Committee

Data Monitoring Committee will be established for this trial. The Data Monitoring Committee will be an independent body made of committee members possessing the qualifications necessary to make evaluations of the trial should that become necessary. The purpose of the Data monitoring committee is to ensure the safety of the trial subjects and, to this end, it will follow a separate set of operating procedures and give appropriate advice and recommendations in order to ensure that proper ethical and scientific clinical procedures are followed.

If an SAE is reported during this study from the Investigator, the Coordinating -Investigator may request the Data Monitoring Committee to discuss whether to continue the study and the modifications to the study protocol. The data monitoring committee will give the Investigator the results of the discussion in writing.

In cases where the Coordinating-Investigator may determine that preemptive emergency handling is required depending on the significance and range of effect of the content of the report, measures such as a suspension of enrollment and emergency contact to all participating sites regarding this content may be taken.

16.4. Written Informed Consent

The Investigator(s) or Subinvestigator(s) at each center will ensure that the subject is given full and adequate oral and written information, which has been approved by IRB, about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

Patients with Guillain-Barré syndrome are generally not administered antibiotics or vaccinations. However, in order to ensure the safety of subjects in the eculizumab group, it is absolutely necessary to take preventive measures against *N. meningitidis*, and because the placebo will be assigned based on blind randomization, implementing these preventative measures on both groups is inevitable. Because this may present an ethical problem for the control group, subjects must be given full and adequate written and oral information about the measures taken to prevent infection and provide their written consent.

However, if it is difficult for the subject to sign/seal due to progression of the underlying disease (such as paralysis), signed/sealed written consent can be obtained from a signatory. The signatory must meet the requirements of a legally acceptable representative, and he/she will write the name of the subject and his/her relationship with the subject in the space provided. If on a later date the subject is able to sign/seal the consent form, the written consent will be re-obtained from the subject.

If a study coordinator gives supplementary explanations to the subject, the study coordinator should also sign/seal and date the consent document together with the Investigator or Subinvestigator. A copy of the consent document and explanation document is given to the subject and the original copy of the consent document is retained at the clinical trial site.

The Investigator or Subinvestigator or study coordinator will confirm whether the subject who has given consent is consulting other clinics or hospitals. If the subject is consulting other clinics or hospitals, her/his, primary physician there must be notified about the subject's study participation.

When required, the Investigator will revise and update the consent form for approval of the IRB. If a patient is mid-trial, the Investigator must explain the revision of the consent form and re-obtain the subject's signature.

16.5. Retention of blood samples

The Central Laboratory blood serum test samples designated for the measurement of antibodies as described in Section 7.7.1., "Antiganglioside Antibodies", may be used in other research studies once this trial has been completed. Therefore, residual samples will be retained at the Chiba University Hospital School of Medicine Neurology Department and at the Kindai University Hospital Faculty of Medicine Neurology Department. Through the anonymizing of the test samples with identification codes, these samples will be handled so as not to allow the leak, mixing, theft, or loss of personal data. Signed informed consent should be obtained from the subjects for the storage of blood samples. The samples will be retained for no more than 20 years after the completion of the trial and all samples will be properly disposed of so as to preserve anonymity. Furthermore, in the event that the samples are used in future

research, the inclusion of these test samples must be documented in the new research protocol and submitted to an IRB for approval.

17. DATA HANDLING AND RECORD RETENTION

17.1. Retention of Records by the Clinical Trial Site

Documents and records related to the study that must be stored at the clinical trial site as ruled by the GCP, must be stored for a period by the head of the clinical trial site until whichever date is later among the following:

1. Marketing approval date of indication of trial drug (if development is discontinued, 3 years from the day that development was discontinued)
2. The date on which 5 years have passed after discontinuation or end of the study

The Investigator will notify the clinical trial site if the records that should be stored by the clinical trial site or IRB are not required to be stored any more.

17.2. Retention of Records by the Investigator

Documents or records that are related to the study and should be retained by the Investigator as designated in the GCP will be stored at a storage place deemed appropriate until whichever date is later among the following.

1. The date on which 5 years have passed from the marketing approval date for the indication of the drug (if development has been discontinued, the date on which 3 years have passed since the discontinuation of development). However, if the pharmaceutical product requires re-evaluation after approval in accordance with the Pharmaceutical Affairs Law, and the end of the re-evaluation period is more than 5 years, the date which the re-evaluation ends.
2. The date on which 5 years have passed after discontinuation or end of the study.

18. COMPLIANCEOF THE STUDY PROTOCOL AND DEVIATION

1. The Investigator or Subinvestigator will record all deviations from the study protocol, regardless of reason for the deviation.

2. If the reason for deviation from the study protocol is to avoid an emergency risk of the subject, or unavoidable medical treatment, the Investigator will immediately submit a documented report which lists

the details and reasons for the deviation to the head of the trial site, and promptly report the contents of the document to the IRB via the head of the trial site.

19. AMENDEMENTS

19.1. Amendments to the Study Protocol and Case Report Forms

Amendments to the study protocol and case report forms will follow the below procedures:

1. When amendments are considered to be necessary, the Coordinating-Investigator will provide to the Investigator the study protocol amendment draft, case report form amendment drafts, and the latest version of the investigator's brochure and other necessary material/information.
2. The Coordinating-Investigator will provide the Investigator with necessary time to adequately consider the aforementioned study protocol amendment draft and material/information and discuss the details with the Coordinating -Investigator.
3. After discussion with the Coordinating-Investigator, the Investigator will promptly submit the amended version of the study protocol or case report form to the head of the trial site, and receive approval of the IRB via the head of the trial site.
4. Within acceptable limits of the Coordinating-Investigator, the same procedures will apply to amendments to be made to the study protocol and case report forms according to instructions given by the head of the trial site based the opinions of the IRB.

19.2. Changes to Statistical Analyses

If any change is made to the statistical analyses planned in the protocol, the statistical analysis staff will describe all changes in the statistical analysis report and the clinical study report. A detailed account of changes of the statistical analysis plan should also be recorded.

20. TERMINATION, SUSPENSION, OR COMPLETION OF TRIAL

20.1. Standards of Suspension or Termination of Entire Trial

In situations where the below information is obtained and the continuation of the clinical trial is determined to be difficult, the Coordinating -Investigator will decide on the termination or suspension of the entire clinical trial upon discussion with the Investigator.

1. Occurrence of "unpredictable" Serious Adverse Event
2. Any information that indicates that the number, frequency, and condition of "predictable" Serious Adverse Events cannot be predicted from the investigator's brochure.

3. SAEs that have been determined to have no causal relations with the IP, but is later determined that the causal relations cannot be ruled out, due to the number, frequency, and condition of occurrences.
4. Research reports indicating the tendency of the number, frequency, and condition of occurrences of side effects having changed drastically.
5. Research reports indicating the possibility that cancer, other serious diseases, disabilities, or death may occur.
6. Information indicating that efficacy of the study drug cannot be expected in this clinical trial.
7. Information indicating that the IP does not have any efficacy or effect on the target disease of the clinical trial.
8. Information on any of the following related to over-the-counter drugs that include the same ingredients as the IP:
    - Termination of manufacturing, import, or retail
    - Collection or disposal
    - Any other measures taken against health and hygiene related risks

20.2. Procedures for Termination or Suspension of the Entire Clinical Trial

If the Coordinating-Investigator decides to terminate or suspend the entire trial upon discussion with the Investigator, the details and reasons for termination or suspension will promptly be reported to the head of the clinical site and the PMDA (Pharmaceuticals and Medical Devices Agency). Furthermore, all subjects undergoing administration of the IPs must be informed of the termination or suspension, and appropriate measures such as changes in proper treatment will be made.

20.3. Procedures for Termination or Suspension of the Clinical Trial in Respective Clinical Trial Sites

If the Investigator decides to terminate or suspend the clinical trial, she or he will inform this fact to the head of the clinical trial site via documentation, and will explain the details of the termination or suspension in the document.
Upon notice of the termination or suspension, the Study Coordinating-Investigator will inform this fact all to investigators involved in this clinical trial and the PMDA, via detailed documentation.

20.4. Report of Completion of the Clinical Trial

Upon completion of the clinical trial, the Investigator will report the completion to the head of the clinical trial site, and submit a summary of the results of the clinical trial via documentation.

21. CASE REPORT FORMS

21.1. Data Management

Detailed procedures of data management will be listed in the data management protocol.

21.2. Data Collection

The Investigator or Subinvestigator will prepare a case report form (CRF) that is compatible to the 21 CFR Part 11, GCP, and ER/ES (Electric record/Electric Signature) guidelines. The Investigator or Subinvestigator will make any changes or amendments in the written contents of the CRF in the software used to develop the CRF. If the Subinvestigator has prepared the CRF or the study coordinator has transcribed information from the source data into the CRF, the CRF will be checked for the contents and any issues by the Investigator before signing on the CRF. The Coordinating-Investigator will submit a copy of an electronic CRF (eCRF) in electronic format (e.g. CD-R) to the Investigator. The Coordinating-Investigator will secure the proper legibility and retention of the eCRFs.

21.3. Identification of Data Entered in the CRF

Source data is defined as follows for this clinical trial:

1. Data which is related to informed consent of the subject and information provided to the subject
2. Medical records, nursing records, clinical examination data, image data films, and other original data used to prepare the CRF. Data stored in electronic charts are also considered as source data.
3. Records related to IP administration
4. Documents or data related to this clinical trial that are deemed necessary by the GCP

The below are defined as source data when they are recorded in the CRF. However, if they are recorded in the medical records, the medical records will be considered as source data.

1. Purpose of the concomitant drug and concomitant therapy
2. Severity ,Seriousness and Outcome of adverse event/ Determination and reasons for determination of causal relations of the AE with the IP

3. Reason for the subject's discontinuation of the trial

4. Comments by the Investigator or Subinvestigator

22. HEALTH DAMAGE COVERAGE AND INSURANCE

If the subject's health is endangered due to the subject's participation in this clinical trial, the Investigator shall treat the subject for recovery and provide the appropriate medical care. This clinical trial is registered for clinical research insurance, and details on the coverage of any death or severe disabilities resulting from this trial will be defined in a separate SOP.

23. MONETARY COMPENSATION

If compensation is made for the reduction of the subject's financial burdens, they are to be made in accordance with the regulations of each medical institution.

24. PUBLICATION

The results of the clinical trial will be submitted as a report by the Investigator to the head of the clinical trial site upon completion of this clinical. Results that do not meet expected outcomes despite the proper conduct of the clinical trial must also be disclosed in publication. If the Investigator is to present information obtained by this clinical trial to external professional academic meetings, the Investigator must obtain approval beforehand from Co-chief Investigators, Coordinating-Investigator, and the IP provider via documentation. In case of disclosure of the results to the public, the subject's personal information must be kept confidential.

25. TRIAL FUNDS AND CONFLICT OF INTEREST

This trial is funded by the Japan Agency for Medical Research and Development (AMED) under the Agency's Early-phase/Exploratory or International-standard Clinical Research Program. The Investigator and Subinvestigator(s) at the clinical research sites are to conduct the trial with integrity.

The interest profile of this trial is to be reviewed and approved by the Conflict of Interest (COI) Committees of the participating sites, all in accordance with the applicable regulatory requirements and guidelines and properly dealt with through COI management and integrity assurance efforts.

26. PROVISION OF THE INVESTIGATIONAL PRODUCT AND INTELLECTUAL PROPERTY RIGHTS

In this study, the investigational product is provided by U.S.-based Alexion Pharmaceuticals, Inc. The ownership of the rights to any inventions, discoveries, or improvements of any nature (the "Inventions") derived from this study will be decided in accordance with the contracts with AMED and with Alexion.

27. JET-GBS IMPLEMENTATION GROUP (See Attachment 1)

28. LIST OF REFERENCES

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