TITLE PAGE

Protocol Title:	A Phase 3, Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Eculizumab in Patients With Guillain-Barré Syndrome (GBS)
Protocol Number:	ECU-GBS-301
Amendment Number	1.0
Compound:	Eculizumab (SOLIRIS®)
Study Phase	Phase 3
Short Title:	A Phase 3 Study to Evaluate the Efficacy and Safety of Eculizumab in Guillain-Barré syndrome
Sponsor Name:	Alexion Pharma GK (Alexion)
Legal Registered Address:	Alexion Pharma GK Ebisu First Square 1-18-14 Ebisu, Shibuya-ku Tokyo 150-0013, Japan
Regulatory Agency Identifying Number:	Not applicable
Approval Date:	**Original Version**: 15 September 2020 **Amendment 1.0**: 28 Oct 2021

Sponsor Signatory: [redacted]

01-Nov-2021 | 16:39:18 EDT

[redacted]

Date

Alexion Pharmaceuticals, Inc.

Medical Monitor Name and Contact Information can be found in the Study Contact List distributed to study sites.

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1.0	28 Oct 2021
Original Protocol	15 Sep 2020

Amendment 1.0 (28 Oct 2021)

Overall Rationale for the Amendment:

This amendment has been prepared to incorporate changes made in 4 Administrative Letters and to add a Safety Follow-up Phone Call or Visit to allow 8 weeks of follow-up for patients who discontinue study drug early or who terminate the study before Week 12. In addition, if intravenous immunoglobulin (IVIg) and study drug are administered on the same day, the requirement to administer study drug prior to IVIg was removed. Minor editorial updates were made for clarification and consistency.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Updated amendment number and approval date	Administrative change.
Section 1.1 Synopsis, Section 10.12 Abbreviations	Updated definition for abbreviation "AIDP" to "acute inflammatory demyelinating polyradiculopathy."	Correction.
Section 1.1 Synopsis, Section 6.3.2 Blinding, Section 9.6 Independent Data Monitoring Committee, Section 10.1.5 Committees Structure	Removed Independent Data Monitoring Committee (IDMC)	Clarified that there is no IDMC. Instead, an interim analysis will be performed by the Independent Analysis Center (IAC).
Section 1.3 Schedule of Activities, Section 7.2 Patient Discontinuation/Withdrawal From the Study	Added a Safety Follow-up Phone Call or Visit after early study drug discontinuation or early study discontinuation.	To provide safety follow-up for 8 weeks after the last dose of study drug for patients who discontinue the study drug early or who discontinue the study prior to Visit 10/Week 12.
Section 1.3 Schedule of Activities	The following footnotes were revised or added (**bold** text): • **b.** This is the **Early Termination (ET) Visit** for patients who permanently discontinue the study drug (see Section 7.1) or who permanently discontinue the study (see Section 7.2). • **c. Safety Follow-up Phone Call or Visit should be conducted 8 weeks after the last dose of study drug for patients who discontinue the study drug or who discontinue the study prior to V10/W12.** • i. In order to maintain good research practice, it is recommended that all	Updated for clarity and to incorporate changes per Administrative Letters 3.0 and 4.0.

Section # and Name	Description of Change	Brief Rationale
	efficacy assessments are performed by the same assessor. If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day or within 2 days, the efficacy assessments will not be repeated**, with the exception of the Hughes FG score**. • k. Targeted physical examination will be performed when deemed necessary by the Investigator. A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). **If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day, the targeted physical examination will not be repeated if already performed.** • **l. If height is unable to be obtained due to the patient's medical condition, measure and record it by knee height length method. If knee height length cannot be obtained, the patient should be asked about their latest height. If weight is unable to be obtained due to the patient's condition, the patient should be asked about their latest weight. If weight is unable to be measured directly, the Investigator should measure body weight as soon as possible. Height and weight, whether captured directly, indirectly, or historically, should be recorded.** • **m. If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day, vital signs will not be repeated unless deemed necessary by the Investigator.** • **o. If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day or within 2 days, clinical laboratory tests for hematology, chemistry, and urinalysis will not be repeated for Day 1.** q. **Women of childbearing potential should be enrolled only after a negative urine or serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site**	

Section # and Name	Description of Change	Brief Rationale
	policies, local regulation, or IRB and should be performed per the specified time points. A negative test result must be verified within 48 hours before the first dose of study drug. If the Screening/Enrollment Visit (V1) and Day 1 Visit (V2) occur within 48 hours, only 1 pregnancy test is required. A pregnancy test may also be performed at any visit at the Investigator's discretion.	
Section 1.3 Schedule of Activities, Section 5.1 Inclusion Criteria, Section 10.2 Appendix 2: Clinical Laboratory Tests	• Added text to clarify that women of childbearing potential should be enrolled only after a negative urine or serum pregnancy test result at Screening and that a negative pregnancy test result is required within 48 hours before the first dose of study drug.	To incorporate changes per Administrative Letter 1, which clarified that a negative urine or serum pregnancy test result is required for enrollment for women of childbearing potential, and to increase by 24 hours the timeframe for negative pregnancy test results prior to the first dose of study drug.
Section 5.1 Inclusion Criteria	Updated inclusion criterion 4 as follows: Patients with onset of weakness due to GBS ~~less than~~ ≤ 2 weeks before screening.	To enhance clarity.
Section 6.5.1 Allowed Medicine and Therapy	Removed the requirement for study drug administration to occur prior to or during the treatment period for intravenous immunoglobulin therapy. Clarified that if study drug and IVIg are given on the same day, they must be given at least 1 hour apart.	No pharmacokinetic reason exists for the restriction to require study drug administration prior to IVIg, so it was removed as a requirement. However, if both study drug and IVIg are given on the same day, they must be given at least 1 hour apart, so that the patient can be observed for immediate infusion reactions.
Section 6.5.3 Disallowed Testing	Clarified that measurements of 50% hemolytic complement activity and other serum complement pathway indicators, including anti-ganglioside antibody testing, are not allowed prior to database lock and study unblinding.	To enhance clarity.
Section 8.2.6 Nerve Conduction Test	Replaced the word "fibular" with "sural" as follows: The nerve conduction test measures distal latency, compound muscle action potential (CMAP) amplitude (proximal, distal), CMAP duration (proximal, distal), motor nerve conduction velocity, and minimum F-wave latency of the median, ulnar, fibular, and tibial nerves. It also evaluates sensory nerve conduction amplitude and velocity of the median, ulnar, and ~~fibular~~ **sural** nerves. s	Correction incorporating change per Administrative Letter 2.0.

Section # and Name	Description of Change	Brief Rationale
Section 8.6 Pharmacokinetics	Removed text stating that pharmacokinetic blood samples would be collected at unscheduled visits.	Correction
Section 8.7 Pharmacodynamics	Removed text stating that pharmacodynamic blood samples would be collected at unscheduled visits.	Correction
Section 9.2 Sample Size Determination, Section 9.5 Interim Analyses	Replaced the IDMC with the IAC, which will perform the interim analysis, and specified that details regarding statistical power calculations, sample size re-estimation, and blinding will be included in the Interim Analysis Plan (IAP).	Correction
Section 10.1.5 Committees Structure	Updated text to specify that details of the IAC will be provided in the IAP.	Clarification
Section 10.2 Appendix 2: Clinical Laboratory Tests	Updated text to clarify central and local laboratory sample collection. Specified that a fasting glucose test is preferred but not required.	Clarification
Section 10.11 Appendix 11 Work Productivity and Activity Impairment Questionnaire	Updated schedule to administer the questionnaire	To align with the Japanese version of the protocol
Section 10.13 Protocol Amendment History	Added section for protocol amendment history	Administrative change
Throughout	Minor grammatical, editorial, and document formatting revisions.	Clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Short Title:

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

Rationale:

Guillain-Barré syndrome (GBS) is a rare, but potentially fatal neuropathy, with rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system. It is preceded in two-thirds of cases by symptoms of infection. The symptoms may develop over hours to a few weeks. During the acute phase, the disorder can be life-threatening, with about 15% of people developing weakness of the breathing muscles and, therefore, requiring mechanical ventilation. The syndrome has a progressive, monophasic disease course, usually without relapse. It is the most common cause of acute flaccid tetraplegia worldwide with an annual global incidence of approximately 1 to 2 per 100,000 person-years.

Guillain-Barré syndrome is currently classified into 2 major subtypes:

- Acute inflammatory demyelinating form: Acute inflammatory demyelinating polyradiculopathy (AIDP)
- Acute motor axonal variant form: Acute motor axonal neuropathy (AMAN)

The treatment goal in GBS is to interrupt the immune-mediated nerve damage during the acute phase of the disease. The standard of care treatments in GBS are plasma exchange (PE) and IVIg.

Eculizumab (h5G1.1-mAb) (SOLIRIS®) is a humanized monoclonal antibody (mAb) derived from the murine anti-human complement component 5 (C5) antibody m5G1.1. Eculizumab specifically binds C5, thereby inhibiting its cleavage to C5a and C5b during complement activation and blocks membrane attack complex (MAC) formation. This strategic blockade of the complement cascade at C5 prevents the release of proinflammatory mediators and the formation of the cytolytic pore, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.

The potential efficacy of eculizumab against GBS has been shown in a murine model of Miller Fisher syndrome, a variant of GBS. In that model, eculizumab prevented axon-specific antiganglioside antibody-induced nerve damage.

The hypothesis of a causative link between complement activation and GBS pathology was further assessed in an Investigator-initiated study conducted in Japan. The efficacy and safety results from the Investigator-initiated study support further investigation in this Alexion-sponsored Phase 3 controlled clinical study, ECU-GBS-301. In this Phase 3 study, the

complement-mediated autoimmunity hypothesis for GBS will be tested in order to confirm the results observed in the Investigator-initiated study.

The primary objective of this Phase 3 study is to evaluate the efficacy of eculizumab in patients with GBS.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the efficacy of eculizumab in patients with Guillain-Barré syndrome (GBS)	• Time to first reaching a Hughes Functional Grade (FG) score ≤ 1
Key Secondary	
To further characterize the efficacy of eculizumab over time in patients with GBS	• Proportion of patients with a Hughes FG score ≤ 1 at Week 24 • Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24 • Proportion of patients with a Hughes FG score ≤ 1 at Week 8
Other Secondary	
To further characterize the impact of eculizumab on medical resource utilization in patients with GBS	• Hospital length of stay (LOS) • Intensive care unit (ICU) stay – LOS in the ICU – Proportion of patients admitted to the ICU • Disposition post hospital discharge
To evaluate the effect of eculizumab compared with placebo on respiratory function in patients with GBS	• Ventilator support – Duration of ventilator support – Proportion of patients requiring ventilator support
To characterize the pharmacokinetic (PK)/pharmacodynamic (PD) attributes of eculizumab in patients with GBS	• Concentration of eculizumab in serum • Free complement component 5 (C5) in serum • Hemolytic complement activity in serum
To assess the formation of antidrug antibodies (ADAs) in response to eculizumab treatment	• Incidence of ADAs
Safety	
To characterize the overall safety and tolerability of eculizumab in patients with GBS	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to study drug discontinuation

Objectives	Endpoints
Tertiary/Exploratory	
To characterize the functional status of patients with GBS post-acute phase	• Change from baseline in the functional scales of GBS (Rasch-built Overall Disability Scale [R-ODS], and Overall Neuropathy Limitations Scale [ONLS]) • Change from baseline in strength measurements (Medical Research Council [MRC]-sumscore, and Manual Muscle Testing [MMT]) • Change from baseline in the Hughes FG score over time
To evaluate the effect of eculizumab compared with placebo on pain in patients with GBS	• Change from baseline in the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) scores
To evaluate the effect of eculizumab compared with placebo on mood in patients with GBS	• Change from baseline in the Depression, Anxiety and Stress Scale, Short form, 21 questions (DASS-21) score
To evaluate the effect of eculizumab compared with placebo on fatigue in patients with GBS	• Change from baseline in the Chalder Fatigue Scale (Chalder) score
To evaluate the effect of eculizumab compared with placebo on quality of life (QoL) in patients with GBS	• Change from baseline in the European Quality of Life (EuroQoL) – 5 Dimensions – 5 Levels (EQ-5D-5L) score • Change from baseline in the Work Productivity and Activity Impairment (WPAI) score
To evaluate complement, inflammation, and neurodegeneration biomarkers in patients with GBS	• Change from baseline in biomarker levels in blood

Overall Design

Study ECU-GBS-301 is a Phase 3, prospective, multicenter, placebo-controlled, double-blind, randomized study to investigate the efficacy and safety of eculizumab in patients with severe GBS, defined using the Hughes Functional Grade (FG) scale (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997) as progressively deteriorating FG3 or FG4/FG5 within 2 weeks from onset of weakness due to GBS. Eligible patients will be randomized to receive intravenous (IV) infusion of eculizumab or placebo at a 2:1 ratio. All patients will be on concomitant IVIg therapy as per standard of care (400 mg/kg body weight daily for 5 days). Randomization will be stratified by FG score (progressively deteriorating FG3 or FG4/FG5) and diarrhea (present or absent < 4 weeks prior to onset of neurological symptoms).

An interim analysis is planned for the unblinded sample size re-estimation when approximately 60% (ie, at least 12 events) of the planned events are observed.

Disclosure Statement:

This is a double-blind, randomized, parallel group intervention study with 2 treatment arms (eculizumab arm and placebo arm).

Number of Patients:

Approximately 57 eligible patients will be randomized in a 2:1 ratio (eculizumab = 38 and placebo = 19).

Intervention Groups and Duration:

Eligible patients will be randomized in a 2:1 ratio to receive IV eculizumab or placebo. Treatment allocation will be blinded to patients, study site, the Sponsor, and the Sponsor's delegates throughout the study.

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

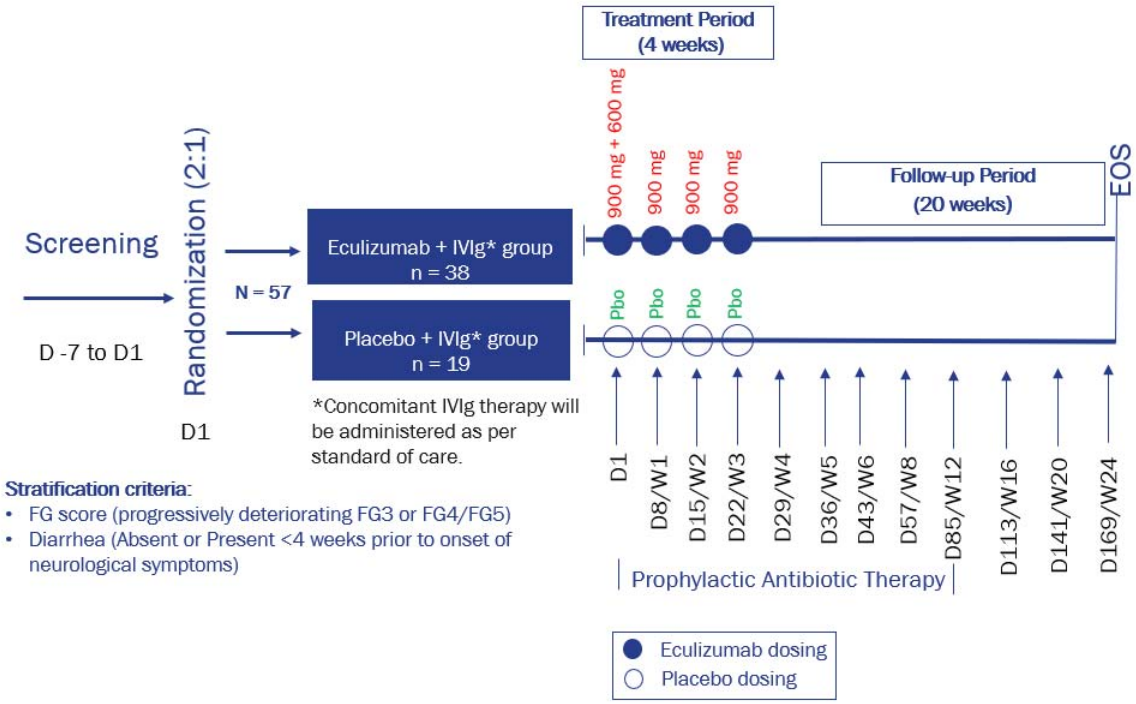
Placebo will be administered via IV infusion once a week for 4 weeks. Placebo is a matching sterile, clear, colorless solution with the same buffer components but without active ingredient, in an identical 30 mL vial. A supplemental dose of placebo will be administered with the first dose on Day 1 to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

For each patient, the total duration of study participation will be up to 25 weeks, including the Screening Period (up to 1 week), the Treatment Period (4 weeks), and the Follow-up Period (20 weeks). Efficacy and safety will be monitored through 24 weeks after the first dose of the study drug. The end of the study for each patient is defined as their last visit at Week 24.

Independent Data Monitoring Committee: No

1.2. Schema

Figure 1: Study Design Schematic



Abbreviations: D = day; EOS = end of study; FG = Functional Grade; IVIg = intravenous immunoglobulin; n = number of patients in each treatment group; Pbo = placebo; W = week.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Period	Screening/ Enrollment[a]	Treatment Period					Follow-up Period							ET[b]	Safety Follow-up Phone Call or Visit[c]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**		
Week[d]			**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24[e]**		
Day	**D -7 to D1**	**D1[f]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D57**	**D85**	**D113**	**D141**	**D169**		
Time window (day)			**±2**	**±2**	**±2**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**
General assessments/procedures															
Informed consent	●														
Medical/surgical/social history	●														
Confirmation of prior meningococcal vaccination[g]	●														
Prophylactic antibiotics[g]		Monitor prophylactic antibiotic therapy													●
Inclusion/exclusion criteria	●														
Randomization		●													
Study drug administration[h]		●	●	●	●										
Efficacy assessments[i]															
Hughes FG score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
R-ODS		●				●			●	●			●	●	
ONLS		●	●	●	●	●			●	●			●	●	
MRC-sumscore	●	●	●	●	●	●			●	●			●	●	
MMT score	●	●	●	●	●	●			●	●			●	●	
Nerve conduction test[j]	●					●									
SF-MPQ-2		●			●								●	●	
DASS-21		●			●								●	●	
Chalder Fatigue Scale score		●			●								●	●	
EuroQoL-EQ-5D-5L		●					●						●	●	
WPAI questionnaire		●					●						●	●	
Safety assessments															
Complete physical examination	●												●	●	
Targeted physical examination[k]		●	●	●	●	●	●	●	●	●	●	●			
Height and weight[l]	●														

Table 1: Schedule of Activities

Period	Screening/ Enrollment[a]	Treatment Period					Follow-up Period							ET[b]	Safety Follow-up Phone Call or Visit[c]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**		
Week[d]			**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24[e]**		
Day	**D -7 to D1**	**D1[f]**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D57**	**D85**	**D113**	**D141**	**D169**		
Time window (day)			**±2**	**±2**	**±2**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**
Vital signs[m]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
12-lead ECG	●												●	●	
Review of Patient Safety Card[n]		●	●	●	●	●	●	●	●	●	●	●	●	●	
Prior medications and procedures	●														
Concomitant therapy (including IVIg therapy) and physical therapy (including inpatient rehabilitation)		Monitor concomitant therapy and physical therapy (including both inpatient and outpatient rehabilitation)												●	●
Hematology[o] Chemistry[o] Urinalysis[o]	●	●		●		●		●		●			●	●	
Adverse events[p]	Continuous monitoring													●	●
Pregnancy test[q]	●					●			●	●	●	●	●	●	
Pharmacokinetic and pharmacodynamic assessments[h]															
Eculizumab concentration[r,s]		●	●		●	●	●			●			●	●	
Free C5[r,s]		●	●		●	●	●			●			●	●	
Hemolytic activation[r, s]		●	●		●	●	●			●			●	●	
Biomarker research															
Blood samples (plasma and serum) for biomarkers[t]		●		●		●				●			●	●	
Immunogenicity assessment															
Eculizumab ADA	●					●				●				●	

[a] Enrollment will be complete after obtaining signed informed consent and after eligibility is verified based on the inclusion/exclusion criteria.

[b] The end of treatment (ET) Visit should be conducted at the time of early discontinuation of the study drug (see Section 7.1) or early discontinuation from the study (see Section 7.2).

or Visitc Safety Follow-up Phone Call or Visit should be conducted 8 weeks after the last dose of study drug for patients who discontinue the study drug or who discontinue the study prior to V10/W12.

[d] Week designators denote end of the week.

[e] Week 24 is the end of the study for each patient. The end of study is defined as the date the last patient completes the Week 24 Visit (see Section 4.4).

[f] Assessments taken prior to administration of the study drug on Day 1 will be considered as the baseline assessment.

[g] Patients will not receive meningococcal vaccinations as part of the study. Patients who are not vaccinated within 3 years of study entry will receive prophylactic antibiotic therapy at the time of first dose of study drug and will continue on prophylactic antibiotic therapy throughout the duration of treatment and until 8 weeks post the last dose of the study drug. Prophylactic antibiotic therapy is not necessary if patients have documented meningococcal vaccination within 3 years of study entry and at least 2 weeks prior to the first dose of the study drug.

[h] Study drug infusions will be done in a hospital or clinic setting. Except on the days when blood samples are collected for PK and PD assessments, the study drug will be administered after all tests and procedures are complete. On the days of PK and PD assessments, blood samples will be collected predose and postdose. Pharmacokinetic/pharmacodynamic assessment results will not be provided to the Investigator until the end of the study.

[i] In order to maintain good research practice, it is recommended that all efficacy assessments are performed by the same assessor. If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day or within 2 days, the efficacy assessments will not be repeated, with the exception of the Hughes FG score.

[j] The nerve conduction test is performed at Screening and Week 4 to determine the GBS subtype (AMAN versus AIDP versus "indeterminate"). An independent expert assessor for GBS-variant determination will be appointed by Alexion. The assessor will review the clinical history of patients and analyze their nerve conduction test results to assign the GBS variants of AIDP, AMAN, and "indeterminate."

[k] Targeted physical examination will be performed when deemed necessary by the Investigator. A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day, the Day 1 targeted physical examination will not be repeated if already performed.

[l] If height is unable to be obtained due to the patient's medical condition, measure and record it by knee height length method. If knee height length cannot be obtained, the patient should be asked about their latest height. If weight is unable to be obtained due to the patient's condition, the patient should be asked about their latest weight. If weight is unable to be measured directly, the Investigator should measure body weight as soon as possible. Height and weight, whether captured directly, indirectly, or historically, should be recorded.

[m] If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day, vital signs will not be repeated unless deemed necessary by the Investigator.

[n] The Patient Safety Card is provided to increase patient awareness of the risk of infections, especially meningococcal infection, and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced by patients during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

[o] If Screening/Enrollment Visit (V1) and Day 1 Visit (V2) are on the same day or within 2 days, clinical laboratory tests for hematology, chemistry, and urinalysis will not be repeated for Day 1 (V2).

[p] If an AE occurs, the event will be followed up until it has stabilized, or the patient has returned to the state he/she was in before administration of the study drug, or the laboratory results return to baseline or normalize. All AEs must be managed and SAEs must be reported according to Section 10.3.

[q] Women of childbearing potential should be enrolled only after a negative urine or serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB and should be performed per the specified time points. A negative test result must be verified within 48 hours before the first dose of study drug. If both the Screening/Enrollment Visit (V1) and Day 1 Visit (V2) occur within 48 hours, only 1 pregnancy test is required. A pregnancy test may also be performed at any visit at the Investigator's discretion.

[r] Measurements for eculizumab concentration, free C5, and hemolytic activation will be done at a central laboratory.

[s] Blood samples for eculizumab concentration, free C5, and hemolytic activity on Day 1, Day 8, and Day 22 will be collected predose and postdose. Baseline and trough blood samples for eculizumab concentration and hemolytic activity will be collected 5 to 90 minutes before infusion of the study drug. Peak blood samples for eculizumab concentration and hemolytic activity will be collected 60 minutes (± 10 minutes) after end of infusion of the study drug.

[t] Blood samples for biomarker analyses will be collected predose at designated time points.

Note: Given the ongoing COVID-19 pandemic, Alexion, in consultation with Investigators and local regulatory agencies, may modify some of the out-patient assessments with proper social distancing measures and good clinical and laboratory practices. Samples for planned PK/PD assessments may be collected as appropriate following guidance from Alexion.

Abbreviations: AIDP = acute inflammatory demyelinating polyradiculopathy; AE = adverse event; ADA = antidrug antibody; AMAN = acute motor axonal neuropathy; C5 = complement component 5; COVID-19 = coronavirus disease 2019; D = day; DASS = Depression, Anxiety and Stress Scale, Short form, 21 questions; ECG = electrocardiogram; EDC = electronic data capture; ET = early termination; EuroQoL-EQ-5D-5L = European Quality of Life-5-Dimensions-5-Levels; FG = Functional Grade; GBS = Guillain-Barré Syndrome; HCG = human chorionic gonadotropin; IRB = Institutional Review Board; IVIg = intravenous immunoglobulin; MMT = Manual Muscle Testing; MRC = Medical Research Council; ONLS = Overall Neuropathy Limitations Scale; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QoL = quality of life; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SF-MPQ-2 = Short Form McGill Pain Questionnaire 2; V = visit; W = week; WPAI = Work Productivity and Activity Impairment.

2. INTRODUCTION

Guillain-Barré syndrome is a rare, but potentially fatal neuropathy, with rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system. It is preceded in two-thirds of cases by symptoms of infection. The syndrome has a progressive, monophasic disease course, usually without relapse (Leonhard, 2019). It is the most common cause of acute flaccid tetraplegia worldwide. The initial symptoms are typically changes in sensation or pain, often in the back along with muscle weakness, beginning in the feet and hands, often spreading to the arms and upper body, with both sides being involved (Guillain-Barré Syndrome Fact Sheet). The symptoms may develop over hours to a few weeks. During the acute phase, the disorder can be life-threatening, with about 15% of people developing weakness of the breathing muscles and, therefore, requiring mechanical ventilation (Ferri, 2016). The disease has an annual global incidence of approximately 1 to 2 per 100,000 person-years. (Leonhard, 2019).

Guillain-Barré syndrome is currently classified into 2 major subtypes:

- Acute inflammatory demyelinating form: AIDP
- Acute motor axonal variant form: AMAN

In Asia and Central and South America, axonal GBS is found in 30% to 65% of patients, while in Europe and North America, demyelinating GBS is the major subtype (69% to 90%) (Kuwabara, 2013).

Advances in understanding of the pathophysiology of AMAN have revealed that the binding of antibodies against ganglioside antigens and the activation of complement leads to nerve conduction block and eventually to axonal degeneration. In particular, the MAC, the terminal product of complement activation, could directly cause axonal degeneration in AMAN. Activation of complement and deposition of the MAC on Schwann cell membranes have also been identified in autopsies of patients with AIDP which suggests that AIDP is caused primarily by myelin disruption. However, secondary axonal loss also frequently occurs in AIDP and is the main cause of long-lasting disability (Misawa, 2018).

The treatment goal in GBS is to interrupt the immune-mediated nerve damage during the acute phase of the disease. The standard of care treatments in GBS are PE and IVIg (Willison, 2016). While PE and IVIg are effective immunotherapies for patients with GBS if given during the first few weeks of disease, the prognosis of GBS varies. Approximately 5% of patients die of pneumonia, pulmonary embolism, or cardiac arrhythmia attributed to severe respiratory or limb muscle weakness and autonomic involvement. Up to 20% of patients cannot walk independently a year after disease onset. In addition to incomplete recovery of motor function, many patients have a long disease course, often with pain and fatigue, and the long-lasting neurological sequelae result in great social and physical loss (Misawa, 2018).

2.1. Study Rationale

The potential efficacy of eculizumab (SOLIRIS®) against GBS has been shown in a murine model of Miller Fisher syndrome, a variant of GBS. In that model, eculizumab prevented axon-specific antiganglioside antibody-induced nerve damage (Halstead, 2008). At present, there are no animal models of demyelinating GBS. However, autopsy studies involving patients with AIDP have shown that C3d and C5b-9 (MAC) are deposited on the Schwann cells, and,

therefore, eculizumab may also be an effective treatment for demyelinating GBS (Hafer-Macko, 1996).

The hypothesis of a causative link between complement activation and GBS pathology was further assessed in an Investigator-initiated study conducted in Japan. In this study, 34 patients with GBS were assigned to receive either eculizumab (n = 23) or placebo (n = 11). The primary outcome measure did not reach the predefined response rate (lower 90% confidence interval [CI] boundary exceeds 50%). At Week 4, the proportion of patients able to walk independently (FG ≤ 2) was 61% (90% CI [42 – 78]; n = 14) in the eculizumab group, and 45% (90% CI [20 – 73]; n = 5) in the placebo group. However, the secondary endpoint, the proportion of patients with an FG score of 0 (healthy) or 1 (able to run) at Week 24, was shown to favor eculizumab treatment (74%; 95% CI [52 – 90]; n = 17) over placebo (18%; 95%CI [2 – 52]; n = 2) (p=0.004) groups (Misawa, 2018). No deaths or meningococcal infections occurred during the study.

The efficacy and safety results from the Investigator-initiated study support further investigation in this Alexion-sponsored Phase 3 controlled study, ECU-GBS-301. In this Phase 3 study, the complement-mediated autoimmunity hypothesis for GBS will be tested in order to confirm the results observed in the Investigator-initiated study.

2.2. Background

2.2.1. Unmet Medical Need in Patients With Guillain-Barré Syndrome

The standard treatments for GBS are PE and IVIg. Both treatments are considered in patients with disease severity of ≥ FG4 and in patients who are considered to have progressive disease of FG3 during the first 2 weeks after onset of neuropathic symptoms (Guillain-Barré syndrome and Fisher syndrome treatment guideline, 2013).

In treatment of severe GBS during the first 2 weeks after onset of neuropathic symptoms, both treatments are considered equally effective as monotherapies, and combination treatment with IVIg and PE has not been shown to be more effective than each treatment alone (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). In Japan, IVIg is selected as the first treatment in most cases. The approved regimen of IVIg is 400 mg/kg body weight per day for 5 days.

In mild cases, GBS symptoms may spontaneously decrease within several months, leading to a perception that GBS is a disease with a benign prognosis. However, in severe cases (peak severity of FG3 or more), 16.4% to 23.1% of the patients require assisted ventilation and 4.1% to 6.3% of the patients die of complications despite treatment with standard of care during the acute phase. Recovery takes several months or years, and 13.7% to 16.7% of the patients still require aid to walk 1 year after onset. Because of the serious risk of disability, an alternative novel therapy that can diminish severe sequelae and expedite recovery is needed (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).

2.2.2. Eculizumab and Complement Inhibition

A detailed description of the chemistry, pharmacology, and toxicology data available for eculizumab is provided in the Investigator's Brochure (IB).

Eculizumab (h5G1.1-mAb) is a humanized mAb derived from the murine anti-human C5 antibody m5G1.1. Eculizumab specifically binds C5, thereby inhibiting its cleavage to C5a and C5b during complement activation and blocks MAC formation. This strategic blockade of the complement cascade at C5 prevents the release of proinflammatory mediators and the formation of the cytolytic pore, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.

Eculizumab has been approved in Japan for the treatment of the following complement-related disorders:

- Hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) in 2010.
- Thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) in 2013.
- Refractory generalized myasthenia gravis (gMG) in patients whose symptoms cannot be managed by IVIg or apheresis in 2017.
- Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive in 2019.

The safety, tolerability, pharmacokinetics (PK), and dose-response of eculizumab in these conditions have been sufficiently investigated in clinical studies and postmarketing surveillances both in Japanese and non-Japanese patients.

2.3. Benefit/Risk Assessment

Eculizumab was first approved in Japan for the treatment of PNH in April 2010. Eculizumab has since been approved in Japan for the treatment of aHUS, refractory gMG, and NMOSD.

Eculizumab has been well tolerated across indications with a favorable benefit-risk profile. With over 10 years of postmarketing experience globally, the safety profile has remained stable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of eculizumab may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Identified risks of eculizumab treatment and specific risk mitigation measures are presented in Table 2.

Table 2: Identified Risks of Eculizumab

Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Neisseria meningitidis infection	Complement component 5 (C5) inhibition is known to increase the susceptibility to infections caused by *N. meningitidis.*	Patients who did not receive a meningococcal vaccination within 3 years of study entry will receive prophylactic antibiotic therapy at the time of first dose of study drug and will continue on prophylactic antibiotic therapy throughout the duration of treatment and until 8 weeks post the last dose of the study drug. Prophylactic antibiotic therapy is not necessary if patients have documented meningococcal vaccination within 3 years of study entry and at least 2 weeks prior to the first dose of the study drug.
Infusion reactions	As with all therapeutic proteins, administration of eculizumab may result in infusion reactions and could cause allergic or hypersensitivity reactions. Infusion reactions have been observed in clinical studies and in the postmarketing setting. Most events of infusion reactions have been nonserious.	Monitoring for infusion reactions will be conducted as part of routine safety assessments for this study.

2.3.2. Benefit Assessment

The results from a randomized study to assess the relative efficacy of PE and IVIg in patients with GBS showed that under the current standard of care, 4.1% to 6.3% of patients with GBS die and 13.7% to 16.7% cannot walk unassisted at 1 year after the onset of treatment (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). About 37.8% of patients have substantial difficulty in working and need to change professions due to GBS (Rajabally, 2012).

Based on the results from the Investigator-initiated study in Japan, potential benefits for GBS patients treated with eculizumab include clinical recovery and improved mobility compared to untreated patients (Misawa, 2018).

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the risks identified in association with eculizumab treatment are justified by the anticipated benefits that may be afforded to patients with GBS.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To characterize the efficacy of eculizumab in patients with Guillain-Barré syndrome (GBS)	• Time to first reaching a Hughes Functional Grade (FG) score ≤ 1
Key Secondary	
To further characterize the efficacy of eculizumab over time in patients with GBS	• Proportion of patients with a Hughes FG score ≤ 1 at Week 24 • Proportion of patients with a Hughes FG score improvement of ≥ 3 at Week 24 • Proportion of patients with a Hughes FG score ≤ 1 at Week 8
Other Secondary	
To further characterize the impact of eculizumab on medical resource utilization in patients with GBS	• Hospital length of stay (LOS) • Intensive care unit (ICU) stay – LOS in the ICU – Proportion of patients admitted to the ICU • Disposition post hospital discharge
To evaluate the effect of eculizumab compared with placebo on respiratory function in patients with GBS	• Ventilator support – Duration of ventilator support – Proportion of patients requiring ventilator support
To characterize the pharmacokinetic (PK)/pharmacodynamic (PD) attributes of eculizumab in patients with GBS	• Concentration of eculizumab in serum • Free complement component 5 (C5) in serum • Hemolytic complement activity in serum
To assess the formation of antidrug antibodies (ADAs) in response to eculizumab treatment	• Incidence of ADAs
Safety	
To characterize the overall safety and tolerability of eculizumab in patients with GBS	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to study drug discontinuation

Objectives	Endpoints
Tertiary/Exploratory	
To characterize the functional status of patients with GBS post-acute phase	• Change from baseline in the functional scales of GBS (Rasch-built Overall Disability Scale [R-ODS], and Overall Neuropathy Limitations Scale [ONLS]) • Change from baseline in strength measurements (Medical Research Council [MRC]-sumscore, and Manual Muscle Testing [MMT]) • Change from baseline in the Hughes FG score over time
To evaluate the effect of eculizumab compared with placebo on pain in patients with GBS	• Change from baseline in the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) scores
To evaluate the effect of eculizumab compared with placebo on mood in patients with GBS	• Change from baseline in the Depression, Anxiety and Stress Scale, Short form, 21 questions (DASS-21) score
To evaluate the effect of eculizumab compared with placebo on fatigue in patients with GBS	• Change from baseline in the Chalder Fatigue Scale (Chalder) score
To evaluate the effect of eculizumab compared with placebo on quality of life (QoL) in patients with GBS	• Change from baseline in the European Quality of Life (EuroQoL) – 5 Dimensions – 5 Levels (EQ-5D-5L) score • Change from baseline in the Work Productivity and Activity Impairment (WPAI) score
To evaluate complement, inflammation, and neurodegeneration biomarkers in patients with GBS	• Change from baseline in biomarker levels in blood

4. STUDY DESIGN

4.1. Overall Design

Study ECU-GBS-301 is a Phase 3, prospective, multicenter, placebo-controlled, double-blind, randomized study to investigate the efficacy and safety of eculizumab in patients with severe GBS, defined using the Hughes FG scale (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997) as progressively deteriorating FG3 or FG4/FG5 within 2 weeks from onset of weakness due to GBS. Eligible patients will be randomized to receive IV infusion of eculizumab or placebo at a 2:1 ratio. All patients will be on concomitant IVIg therapy as per standard of care (400 mg/kg body weight daily for 5 days). Randomization will be stratified by FG score (progressively deteriorating FG3 or FG4/FG5) and diarrhea (present or absent < 4 weeks prior to onset of neurological symptoms).

There will be 3 periods in the study:

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

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

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

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

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

4.2. Scientific Rationale for Study Design

A double-blind, randomized, placebo-controlled study design is selected to provide the most robust evidence of the effectiveness of the intervention on disease progression and safety. Randomization minimizes the effects of baseline differences and confounding factors on the study population. The use of a placebo comparator allows for the true treatment effect of the intervention to be established while also allowing for study management, drug administration, and assessments to be conducted similarly between treatment groups, thus minimizing the potential for bias. An unequal (2:1) randomization scheme was chosen to decrease the number of patients receiving placebo. Patients will continue to receive IVIg therapy as per standard of care (400 mg/kg body weight daily for 5 days).

To ensure that factors which could affect the course of the disease are equitably distributed between treatment groups, a stratification scheme (FG score [progressively deteriorating FG3 or FG4/FG5] and diarrhea [present or absent < 4 weeks prior to onset of neurological symptoms]) has been implemented.

Rationale for primary endpoint and key secondary endpoints.

Hughes FG is a widely accepted evaluation scale for GBS. It comprehensively assesses the level of impairment of motor function, which is the main symptom of GBS. A score of FG ≤ 1 represents a status where only minor symptoms/signs remain and/or the patient has regained the ability to run.

4.3. Justification for Dose

It is crucial to effectively inhibit complement activation and progression of neuropathy in acute phase of the GBS (onset to 2 to 4 weeks during which the peak of severity is attained).

The proposed dosing regimen (ie, 4 weekly doses of 900 mg with a supplemental dose of 600 mg on Day 1) is modified from the labeled dosing regimen to account for the influence of extrinsic factors including administration of IVIg in patients with GBS. All patients in this study will receive IVIg therapy as per standard of care (400 mg/kg body weight daily for 5 days).

The eculizumab PK is dependent on the neonatal Fc receptor (FcRn) recycling. As stated in the Company Core Data Sheet, IVIg treatment is expected to interfere with the endosomal FcRn recycling mechanism of mAb and thereby decrease serum eculizumab concentrations. This is supported by the following:

- Eculizumab PK data in an open-label study in patients with multifocal motor neuropathy (Fitzpatrick, 2011), which indicated significantly lower median serum eculizumab concentration (approximately 30% lower) in patients receiving 1 g/kg IVIg compared with those not receiving IVIg (Eculizumab Dose Simulations for Protocol ECU-GBS-301, Report Number: CPR-0023.00).
- Eculizumab PK data in the Investigator-initiated study in Japan (Misawa, 2018) which indicated an approximately 30% lower eculizumab PK exposure resulting from 2 g/kg IVIg treatment (400 mg/kg body weight daily for 5 days), compared to the eculizumab PK data from the Japanese patients with gMG (Studies ECU-MG-301 and ECU-MG-302) (Eculizumab Dose Simulations for Protocol ECU-GBS-301, Report Number: CPR-0023.00).

A modeling and simulation approach based on the established exposure-response relationships was used to characterize the proposed supplemental dose of 600 mg on Day 1. Based on the PK/pharmacodynamic (PD) data from the gMG Phase 3 registration study (Study ECU-MG-301), a threshold eculizumab concentration of 116 µg/mL at trough is required for ensuring complete terminal complement inhibition (ie, serum free C5 levels < 0.5 µg/mL). When hemolytic activity is measured by a validated PD assay, a significant and continuous terminal complement inhibition has been confirmed for nearly all patients who reached serum eculizumab concentrations that exceed 116 µg/mL. The PK/PD data from the NMOSD Phase 3 registration study (Study ECU-NMO-301) also confirmed that this threshold concentration led to immediate, complete, and sustained inhibition of terminal complement, as demonstrated by

serum free C5 < 0.5 µg/mL throughout the entire Treatment Period in nearly all patients. Simulations using the established population-PK/PD model of eculizumab confirmed that the proposed dosing regimen in patients with GBS is expected to achieve the threshold eculizumab concentration at trough for nearly all patients (defined as 97.5 percentile of the population) who will be dosed with IVIg regimen (400 mg/kg body weight daily for 5 days) (Eculizumab Dose Simulations for Protocol ECU-GBS-301, Report Number: CPR-0023.00).

Therefore, all patients in the eculizumab treatment arm in this study will receive a total dose of 1500 mg (900 mg plus 600 mg supplemental dose) on Day 1 followed by 3 weekly doses of 900 mg.

4.4. End of Study Definition

A patient is considered to have completed the study if he/she has completed his/her last visit at Week 24 as shown in the Schedule of Activities (SoA; Section 1.3).

The end of the study is defined as the date the last patient completes the last visit at Week 24 as shown in the SoA.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Patients must be ≥ 18 years of age at the time of signing the informed consent form (ICF).

Type of Patient and Disease Characteristics

2. Patients who meet the 2019 consensus GBS criteria (Leonhard, 2019).
3. Patients who are able to run prior to onset of GBS symptoms.
4. Patients with onset of weakness due to GBS ≤ 2 weeks before screening.
5. Patients unable to walk unaided for ≥ 5 meters (progressively deteriorating FG3 or FG4 to FG5).
6. Patients who are already on IVIg or deemed eligible for and who will start IVIg.
7. Patients who can start their first dose of study drug before the end of the IVIg treatment period
8. Patients who have access to physical therapy care and are willing to undergo an optimized regimen of physical therapy care (including both inpatient and outpatient rehabilitation) as appropriate.

Sex

9. Male and female patients are eligible for this study.
10. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 5 months after last dose of study drug.

    a. Male patients:

Male patients must agree to use contraception as detailed in the protocol (Section 10.4) during the Treatment Period and for at least 5 months after last dose of study drug and refrain from donating sperm during this period.

    b. Female patients:

A female patient is eligible to participate if she is not pregnant, not breastfeeding, and meets at least 1 of the following conditions:

- Not a woman of childbearing potential (WOCBP).

OR

- Is a WOCBP and using an acceptable contraceptive method as described in Section 10.4 during the Treatment Period and for at a minimum of 5 months after the last dose of study drug.
  - The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum pregnancy test) at Screening and within 48 hours before the first dose of study drug. Additional requirements for pregnancy testing during and after study drug administration are described in Section 10.4. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

11. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Patients with history of peripheral polyneuropathy other than GBS, eg, diabetic (except for mild sensory disturbance) or severe vitamin B1 deficiency-related peripheral polyneuropathy.
2. Patients with unresolved *N. meningitidis* infection or a history of meningococcal infection.
3. Patients with active systemic infectious diseases determined to be clinically significant by the Investigator.
4. Patients who are unable to take at least 1 antimicrobial agent used to prevent *N. meningitidis*.
5. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
6. Patients who are known to have or are suspected of having hereditary complement deficiencies.
7. Any medical or psychological condition that, in the opinion of the Investigator, could increase the risk to the patient by participating in the study or confound the outcome of the study.

Prior/Concomitant Therapy

8. Patients who have previously received or are currently receiving treatment with complement modulators.
9. Patients who have received rituximab within 12 weeks prior to screening.
10. Patients who are being considered for or are already on plasmapheresis.

11. Patients who have received immunosuppressive treatment (eg, azathioprine, cyclosporine, tacrolimus, or > 20 mg prednisolone daily) during the 4 weeks prior to providing consent.

Prior/Concurrent Clinical Study Experience

12. Patients who have been administered another investigational product within 30 days or 5 half-lives (whichever is longer) prior to providing consent or are currently participating in another interventional study.

Other Exclusions

13. Patients who are unable to comply with study procedures and the treatment regimen.
14. Patients who are pregnant or lactating.

5.3. Lifestyle Considerations

There are no lifestyle restrictions for this study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any serious adverse events (SAEs) and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY DRUG

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1. Study Drug(s) Administered

Intervention name	Eculizumab	Placebo
Dose formulation	Sterile liquid	Sterile liquid
Unit dose strength	Eculizumab is supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial	Placebo is supplied in an identical 30 mL vial
Dosage level	900 mg once a week for 4 weeks*	Matching placebo once a week for 4 weeks
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization.	Provided centrally by Alexion or contracted manufacturing organization.
Packaging and labeling	Study drug will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.	Study drug will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.

* A supplemental dose of 600 mg will be given with the first dose on Day 1.

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients enrolled in the study may receive the study drug and only authorized site staff may supply or administer the study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to [redacted] within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or

performance of a product or clinical trial material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

4. Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Patients will be randomly allocated on Day 1 to one of two treatment groups after the Investigator and Medical Monitor have verified that they are eligible. Patients will be stratified by FG score (progressively deteriorating FG3 or FG4/FG5) and diarrhea (present or absent < 4 weeks prior to onset of neurological symptoms) and randomized in a 2:1 ratio to either eculizumab IV infusion or placebo IV infusion.

All patients will be centrally randomized using an Interactive Response Technology (IRT) system. Before the study is initiated, login information and directions for the IRT system will be provided to each site. Study drug will be given IV at the study visits summarized in the SoA (Section 1.3).

6.3.2. Blinding

Patients, study site, the Sponsor, and the Sponsor's delegates directly associated with the conduct of the study will be blinded to patient treatment assignments. The blind will be maintained by using identical study drug kits and labels for eculizumab and placebo. The placebo will have an identical appearance to that of eculizumab. The randomization code will be maintained by the IRT provider. A supplemental dose of placebo will be administered with the first dose on Day 1 to maintain the blind.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's study drug assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a patient's study drug assignment unless this could delay emergency treatment of the patient. If a patient's study drug assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

When unblinding is the result of an AE which is unexpected or related and serious, the blind will be broken for that specific patient only. The blind with regard to treatment allocation for that specific patient will be maintained for all persons (other than the Treating Physician) responsible for the ongoing conduct of the study (such as the Management, Medical Monitors, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities, PK/PD and biomarker data handling, and/or Institutional Review Boards (IRBs).

6.4. Study Drug Compliance

Patients will be dosed at the site where they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the institution will be recorded in the source documents and recorded in the eCRF. The dose of study drug and patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

For additional information on study drug compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medicine and Therapy

- Intravenous immunoglobulin therapy as per standard of care (400 mg/kg body weight daily for 5 days) will be administered. The first dose of study drug will be given before or during the 5-day course of IVIg therapy.
- If IVIg is administered on the same day as the study drug, the study drug and IVIg must be given at least 1 hour apart, so that the patient can be observed for immediate infusion reactions.

  After discussion with the Medical Monitor, a second treatment of IVIg may be allowed 4 or more weeks after the first dose of study drug.
- Optimized regimen of physical therapy including both inpatient and outpatient rehabilitation.

6.5.2. Disallowed Medicine and Therapy

The following medications and therapies are prohibited during the study:

- Rituximab
- Plasmapheresis

- Steroid pulse therapy (more than 500 mg/day of methylprednisolone)
- Immunosuppressive drugs
- Other investigational drugs
- Other complement inhibitory agent

6.5.3. Disallowed Testing

Eculizumab administration is known to lower 50% hemolytic complement activity (CH50). To maintain study blind, measurements of CH50 and other serum complement pathway indicators, including anti-ganglioside antibody testing, are not allowed prior to database lock and study unblinding.

If measurement of a serum complement pathway indicator is considered necessary by the Investigator, it should be discussed with the Medical Monitor and the procedures described for unblinding (see Section 6.3.2) and discontinuation of the patient from the study (see Section 7.2) should be followed.

6.6. Dose Modification

There will be no modification of the planned dose in this study.

6.7. Intervention After the End of the Study

Not applicable.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) the study drug. If the study drug is definitively discontinued, the patient should remain in the study to be evaluated for safety follow-up. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Patients should be considered for discontinuation from study drug if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Severe uncontrolled infection;
- Use of disallowed medication as defined in Section 6.5;
- Pregnancy or planned pregnancy;
- The Medical Monitor or the Investigator deems it is necessary for the patient; or
- Unblinding of study drug assignment during the Treatment Period.

7.2. Patient Discontinuation/Withdrawal From the Study

- All efforts should be made to ensure patients are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for patient discontinuation must be recorded in the source documents and eCRF.
- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an Early Termination Visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- A Safety Follow-up Phone Call or Visit should be conducted 8 weeks after the last dose of study drug for patients who discontinue the study drug or who discontinue the study prior to V10/W12 as shown in the SoA (Section 1.3).
- The patient will be permanently discontinued from the study drug and from the study at that time.
- If the patient withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.

- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

If a patient fails to return, or is otherwise unavailable, for a scheduled visit within the acceptable visit window (Section 1.3), the site study staff must make a reasonable attempt to contact the patient to determine the reason for missing the appointment.

As it is vital to obtain any patient's missing visit information to ensure the missed appointment was not due to an AE, every effort must be made to undertake protocol-specified safety follow-up procedures.

In the exceptional circumstance where a patient cannot or does not come to the study site for examination, the patient will be instructed to see his or her local neurologist or physician. In this event, if possible, the Treating Physician or designee will contact the local neurologist or physician to obtain as much information as possible about the patient's medical and neurological condition, and provide clinical guidance, if needed. The study site will obtain relevant medical records as documentation from the local physician's examination and enter relevant data in the AE form as appropriate.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. General Assessments and Procedures

8.1.1. Informed Consent

The Investigator or qualified designee must obtain a signed and dated ICF from each patient (or the patient's legally authorized representative, as applicable) prior to conducting any study procedures as described in Section 10.1.3. All efforts should be made to ensure patients are willing to comply with study participation prior to conducting the screening procedures.

8.1.2. Medical/Surgical/Social History

The Investigator will review and document the patient's medical/surgical/social history and diagnosis at the Screening Visit. Social history will include work status and mobility prior to hospitalization.

8.1.3. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of eculizumab increases the patient's susceptibility to meningococcal infection (caused by *N. meningitidis*).

Patients will not receive meningococcal vaccinations as part of the study. Patients who have not received a meningococcal vaccination within 3 years of study entry will receive prophylactic antibiotic therapy at the time of first dose of study drug and will continue on prophylactic antibiotic therapy throughout the duration of treatment and until 8 weeks post the last dose of the study drug.

Prophylactic antibiotic therapy is not necessary if patients have documented meningococcal vaccination within 3 years of study entry and at least 2 weeks prior to the first dose of the study drug.

8.1.4. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the patient qualifies for study participation.

Both the Investigator and the Sponsor must approve patient eligibility before enrollment.

8.1.5. Study Drug Administration

Eculizumab or matching placebo will be administered via IV infusion at a dose of 900 mg once a week for 4 weeks. A supplemental dose of 600 mg eculizumab or matching placebo will be given with the first dose on Day 1. At the scheduled dosing visits (Section 1.3), study drug infusion should be performed after all other tests and procedures have been completed, excluding the postdose blood sampling for PK and PD assessments.

Refer to Section 6 for additional information on study drugs including preparation, handling, storage, and accountability. For detailed instructions, refer to the Pharmacy Manual.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3). In order to maintain good research practice, it is recommended that all efficacy assessments are performed by the same assessor.

Additional details related to the efficacy assessments are provided in the relevant manuals.

8.2.1. Hughes Functional Grade Score

Mobility will be evaluated on a 7-point scale as listed in Table 3 (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). Higher numbers indicate more severe impairment.

Table 3: Disability Functional Grade Scale

Score	Description
0	Healthy, no signs or symptoms of Guillain-Barré syndrome.
1	Minor signs or symptoms and able to run.
2	Able to walk 5 m across an open space without assistance.
3	Able to walk 5 m across an open space with the help of one person and waist-level walking-frame, stick, or sticks.
4	Chairbound/bedbound: unable to walk as in 3.
5	Requiring assisted ventilation (for at least part of day or night).
6	Dead.

8.2.2. Rasch-built Overall Disability Scale Score

The Rasch-built Overall Disability Scale (R-ODS) score is a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients with neurological conditions like GBS (van Nes, 2011).

If the patient has difficulty completing the questionnaire due to muscular weakness, a family member/caregiver may record the patient's self-evaluation in the questionnaire. A low score indicates more severe symptoms.

A copy of the R-ODS scale is provided in Section 10.5.

8.2.3. Overall Neuropathy Limitations Scale

The Overall Neuropathy Limitations Scale (ONLS) consists of a checklist for interviewing patients regarding subjective symptoms in their hands or arms (numbness, tingling, or weakness) and legs (difficulty running or climbing stairs, difficulty with walking, etc.). A total score will be given as well as a score for each individual limb. A higher score means that symptoms are more severe (Graham, 2006).

A copy of the ONLS scale is provided in Section 10.6.

8.2.4. Medical Research Council-SumScore

The Medical Research Council (MRC)-sumscore is a summation of the strength of the following 6 muscle groups tested on both sides (right and left) according to the MRC scale (Table 4) (Nerve Injuries Committee, MRC Memorandum No. 45, 1976 and Kleyweg, 1991).

- Abduction of the arm
- Flexion of the forearm
- Extension of the wrist
- Flexion of the leg
- Extension of the knee
- Dorsal flexion of the foot

Table 4: Medical Research Council Scale

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

The assessment will give the ‘MRC-sumscore’ ranging from 0 (paralysis) to 60 (normal strength). The patient is investigated in sitting posture and/or lying supine.

8.2.5. Manual Muscle Testing

The Manual Muscle Testing (MMT) evaluates the 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 (based on Nerve Injuries Committee, MRC Memorandum No. 45, 1976).

Table 5: Manual Muscle Testing Score by Medical Research Council System

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

8.2.6. Nerve Conduction Test

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

The nerve conduction test measures distal latency, compound muscle action potential (CMAP) amplitude (proximal, distal), CMAP duration (proximal, distal), motor nerve conduction velocity, and minimum F-wave latency of the median, ulnar, fibular, and tibial nerves. It also evaluates sensory nerve conduction amplitude and velocity of the median, ulnar, and sural 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 study period.

An independent expert assessor for GBS-variant determination will be appointed by Alexion to review the clinical history of patients and analyze their nerve conduction test results (Section 9.7).

8.2.7. Short Form McGill Pain Questionnaire 2

The Short Form McGill Pain Questionnaire 2 (SF-MPQ-2), a shorter version of the McGill Pain Questionnaire, is a multidimensional measure of perceived pain in adults with chronic pain. The SF-MPQ-2 includes visual analogue and verbal rating scales of pain intensity as well as 15 pain descriptors that are each rated on a 4-point verbal scale (Dworkin, 2019).

A copy of the SF-MPQ-2 questionnaire is provided in Section 10.7.

8.2.8. Depression, Anxiety and Stress Scale, Short Form, 21 Questions Score

The Depression, Anxiety and Stress Scale, Short form, 21 questions (DASS-21) is a 42-item self-report instrument designed to measure the negative emotional states of depression, anxiety and stress (DASS, Psychology Foundation of Australia, 2018).

Each of the 3 DASS scales contains 14 items, divided into subscales of 2 to 5 items with similar content.

- The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia.
- The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect.

- The Stress scale is sensitive to levels of chronic nonspecific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient.

Patients are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items.

A copy of the DASS-21 questionnaire is provided in Section 10.8.

8.2.9. Chalder Fatigue Scale Score

The Chalder Fatigue Scale (Chalder) measures subjective symptoms of fatigue and covers physical fatigue (eg, lack energy, feel weak, less muscle strength, need to rest), and mental fatigue (eg, concentration, memory). It contains 11 items to produce a global score and 2 domains of physical and mental fatigue (Cella, 2010).

A copy of the Chalder score is provided in Section 10.9.

8.2.10. European Quality of Life – 5 Dimensions – 5 Levels Score

The 5 Dimensions – 5 Levels (EQ-5D-5L) is a well-known and widely used health status instrument. It was developed by the European Quality of Life (EuroQoL) Group in the 1980s to provide a concise, generic instrument that could be used to measure, compare, and value health status across disease areas (Devlin, 2017).

A copy of the EuroQoL-EQ-5D-5L questionnaire is provided in Section 10.10.

8.2.11. Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment (WPAI) questionnaire is used to measure the effect of general health and symptom severity on work productivity and regular activities. Function-related endpoints are assessed as part of this questionnaire which allow a measure of the economic impact of relative differences in either the safety or efficacy of therapeutic interventions (Reilly, 1993).

A copy of the WPAI questionnaire is provided in Section 10.11.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at each study visit.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.

8.3.2. Height and Weight

- Body weight will be measured in kilograms
- Height will be measured in centimeters.

8.3.3. Vital Signs

- Vital signs will be measured at every visit and will include assessments of systolic and diastolic blood pressure (mm Hg), temperature (°C), respiratory rate (RR), and heart rate (HR) (beats/minute). Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Ideally, the same arm for each patient should be used for measurements.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

8.3.4. Electrocardiograms

- A single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, interval between the start of the Q wave and the end of the T wave in an ECG (QT), and corrected QT interval (QTc) intervals.
- Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded on the eCRF.

8.3.5. Prior and Concomitant Medication Review

It is important for Investigators or a qualified designee to review each medication and therapy the patient is taking before starting the study and at each visit (Section 1.3).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior medications and therapy.

8.3.5.1. Prior Medications

Prior medications and/or vaccines and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) that the patient took or underwent within 30 days before the start of screening or during the Screening Period before the first dose of eculizumab, as well as any meningococcal vaccine administered within the last 3 years prior to study entry, will be recorded in the patient's eCRF. Additionally, all medications or therapies ever used for GBS before the first dose of eculizumab must be collected.

8.3.5.2. Concomitant Medications and Therapies

Use of concomitant medications and therapies (Section 6.5) will be evaluated during the study. At each visit, patients should be questioned about any new medication or therapies or changes to concomitant medications and therapies since the last visit. Concomitant medications and therapies should be recorded in the source documents and the patient's eCRF.

Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. When possible, concomitant medications will be recorded from the first infusion of study drug until the patient has discontinued or completed the study.

Antibiotics administered for prophylaxis of meningococcal infection will also be recorded.

8.3.6. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient

management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3.7. Pregnancy

- Pregnancy data from female patients and female spouses/partners of male patients will be collected at the time points specified in the SoA (Section 1.3). Any female patient who becomes pregnant while participating in the study will be discontinued from the study drug. If a pregnancy is reported, the Investigator must immediately inform the Medical Monitor within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.
- For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues the study drug or withdraws from the study. The corresponding infant must be followed up with for 3 months postpartum.
- Pregnancy is not considered as an AE (Section 10.4.3) unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.4). Elective abortions without complications should not be reported as AEs.

8.3.8. Patient Safety Card

A Patient Safety Card will be provided to the patients to carry with them at all times. The card is provided to increase patient awareness of the risk of infections, especially meningococcal infection, and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced by patients during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit, the study staff will ensure that the patient has the Patient Safety Card (Section 1.3).

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

Adverse events will be reported to the Investigator or qualified designee by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug (see Section 7).

Procedures for recording, evaluating, reporting, and follow-up of AEs and SAEs are outlined in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last Follow-up Visit.

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up on each patient at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and Investigators.
- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.4.5. Adverse Events of Special Interest

Meningococcal infections will be collected as adverse events of special interest (AESIs).

8.5. Treatment of Overdose

For this study, any dose of study drug greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose. Overdose must be reported by the Investigator within 24 hours to Alexion regardless of its association with or without an AE.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetics

- Blood samples for determination of serum drug concentrations will be collected before and after infusion of study drug at the time points specified in the SoA (Section 1.3).
- The predose blood sample may be drawn through the venous access created for the dose infusion, prior to infusion of the dose. The postdose blood samples will be drawn from the patient's opposite non-infused arm.
- Blood samples at a non-dosing visit can be collected at any time.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF and the central laboratory requisition form.
- Study drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.

8.7. Pharmacodynamics

- Blood samples for PD (free C5 and hemolytic complement activity) will be collected before and after infusion of study drug at the time points specified in the SoA (Section 1.3).

- The predose blood sample may be drawn through the venous access created for the dose infusion, prior to infusion of the dose. The postdose blood samples will be drawn from the patient's opposite non-infused arm.
- Blood samples at a non-dosing visit can be collected at any time.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF and the central laboratory requisition form.
- Pharmacodynamic assessments that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

All biomarker assessments that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.9.1. Biomarker Research

Blood sample (plasma and serum) for biomarker research will be collected predose from all patients at the time points specified in the SoA (Section 1.3). Refer to the Laboratory Manual for details on sample collection, including blood volume requirements.

Biomarkers to be measured may include, but are not limited to, assessments of the following:

- Complement pathway dysregulation eg, C5b-9, C5a, etc.
- Neurodegeneration eg, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP).
- Neuroinflammation, eg, proinflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α]), autoantibodies, etc.

8.9.2. Additional Biomarker Research

Remaining samples from PK, PD, immunogenicity, and biomarker testing will be stored for additional biomarker research and may be evaluated after the study is completed. Analyses may be performed on biomarkers thought to play a role in GBS activity/progression or treatment response to eculizumab. These samples may also be used to develop methods, prognostics and/or companion diagnostic assays related to the study drug target, disease process, pathways associated with disease state, other complement-related diseases, and/or mechanism of action of the study drug.

Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study at a facility selected by Alexion to enable further analyses.

8.10. Immunogenicity Assessment

Antidrug antibodies to eculizumab will be evaluated in serum samples collected from all patients according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the Early Termination Visit from patients who discontinued study drug or were withdrawn from the study. These samples will be tested by Alexion or designee.

Serum samples will be screened for antibodies binding to eculizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of eculizumab.

The detection and characterization of antibodies to eculizumab will be performed using a validated assay method by or under the supervision of Alexion. Samples collected for detection of antibodies to study drug will also be evaluated for eculizumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug(s).

8.11. Health Economics Data and Medical Resource Utilization

Health Economics and Outcomes Research (HEOR) measures the societal impact of the disease on patients.

In this study, the overall health-related quality of life (QoL) of patients with GBS will be assessed using the EuroQoL-EQ-5D-5L questionnaire (Section 8.2.10). The EQ-5D-5L is the preferred EQ-5D version of the questionnaire in Japan.

In addition, the impact of the disease on patient working status will be assessed using the WPAI questionnaire (Section 8.2.11).

Copies of the EQ-5D-5L and WPAI questionnaires are provided in Section 10.10 and Section 10.11, respectively.

9. STATISTICAL CONSIDERATIONS

Statistical methods described in this section will be further detailed in a separate statistical analysis plan (SAP). The SAP will be developed and finalized prior to the database lock. Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings and figures. Inference from efficacy analyses will be based on a 2-sided Type I error (α) = 5% unless stated otherwise. The summary statistics for continuous variables will include, but not be limited to, the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

All efficacy analyses will be based on the Full Analysis Set (FAS). Supplemental per protocol analyses for primary and secondary efficacy endpoints will be performed based on the Per Protocol Set (PPS) in the same manner as done for the FAS. Safety analyses will be performed on the Safety Set (SS).

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

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

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

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

9.1.2. Key Secondary Hypotheses

The null hypotheses associated with the key secondary objectives are that eculizumab is no different than placebo for the respective endpoints; the alternative hypotheses are described below:

- Proportion of patients with an FG score ≤ 1 at Week 24: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score ≤ 1 at Week 24.
- Proportion of patients with an FG score improvement ≥ 3 at Week 24: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score improvement ≥ 3 at Week 24.
- Proportion of patients with an FG score ≤ 1 at Week 8: The alternative hypothesis is that there is a treatment difference from placebo in favor of eculizumab in the proportion of patients with an FG score ≤ 1 at Week 8.

9.2. Sample Size Determination

The sample size for this study is based on results from the Investigator-initiated study in Japan (Misawa, 2018). Assuming a 2:1 randomization of patients with GBS to eculizumab and placebo,

a drop-out rate of approximately 10%, a cumulative probability of response at 24 weeks of 70% for eculizumab and 20% for placebo (corresponding to a true hazard ratio of 5.4), one-sided Type I error of 0.025, a fixed Follow-up Period of 24 weeks for each patient with approximately an average enrollment rate of 1 patient per week, a total sample size of 57 patients with approximately a total of 19 events (responders) would provide at least 90% power using a log-rank test for the primary endpoint, time to first reaching an FG score ≤ 1.

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

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

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

9.3. Populations for Analyses

The analysis sets are defined in Table 6.

Table 6: Analysis Sets

Analysis set	Description
Full Analysis Set (FAS)	All patients who receive at least 1 dose of study drug and have a baseline FG score and at least 1 postbaseline FG score. Patients will be analyzed according to the treatment group assigned by randomization.
Safety Set (SS)	All patients who receive at least 1 dose of study drug. Patients will be analyzed according to the study drug they actually received.
Per Protocol Set (PPS)	All FAS patients without any major protocol deviations.
Pharmacokinetic Analysis Set (PKAS)	All patients who receive at least 1 dose of eculizumab and who have at least 1 postdose PK sample.

Abbreviations: FG = Functional Grade; PK = pharmacokinetic(s).

9.4. Statistical Analyses

9.4.1. Enrollment and Disposition

The number of patients screened, screen failed, and randomized will be presented. Enrollment information will be presented by stratification factor and treatment group. Number of patients discontinued and reasons for discontinuation will be summarized.

9.4.2. Demographics, Baseline Characteristics, Inclusion and Exclusion Criteria, and Protocol Deviations

All demographic information and baseline characteristics will be reported by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups. The number and percentage of patients not meeting specific inclusion or exclusion criteria will be summarized. Similar summaries will be provided for major protocol deviations based on prespecified categories.

9.4.3. Medical/Surgical History and Physical Examination

The medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. Complete and targeted physical examination findings will also be summarized.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purpose, any medication started prior to first dose of study drug will be considered as prior medication and any medication taken by a patient that overlaps with the infusion of study drug will be considered as concomitant medication. All prior and concomitant medications including GBS-specific medications during the study, if any, will be summarized.

9.4.5. Efficacy Analyses

9.4.5.1. Primary Endpoint

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

The comparison of the treatment groups for the primary endpoint time to first reaching an FG score ≤ 1 will use a stratified Logrank test. Confidence intervals (95% CIs) will be presented for the estimated proportion of patients reaching the defined endpoint at various timepoints based on complementary log-log transformation. Hazard ratio and cumulative probability of improvement over 24 weeks from a stratified Cox proportional hazards model will be summarized with 95% CI. Kaplan-Meier curves for both treatment groups will be produced. The randomization stratification variables will be used in these analyses.

The study will be considered to have met its primary efficacy objective if the null hypothesis is rejected at a 2-sided statistically significant level of 0.05 in favor of eculizumab. (See Section 9.4.5.4 for Type 1 error control due to the interim analysis for sample size re-estimation.)

Patients who are discontinued prematurely without a response or complete 24-week Follow-up Period without a response will be censored for this analysis. Further details will be provided in the SAP.

9.4.5.2. Key Secondary Endpoints

Hypothesis testing comparing eculizumab treatment with placebo treatment for the key secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

1. Proportion of patients with an FG score ≤ 1 at Week 24
2. Proportion of patients with an FG improvement of ≥ 3 at Week 24
3. Proportion of patients with an FG score ≤ 1 at Week 8

The hypothesis testing will proceed from highest rank (1: Proportion of patients with an FG score ≤ 1 at Week 24) to lowest rank (3: Proportion of patients with an FG score ≤ 1 at Week 8).

The comparison of the treatment groups for the key secondary endpoints will be based on a logistic regression model with treatment and randomization stratification factors as covariates. The p-value and 95% CI of the Odds Ratio will be presented. In addition, the difference in the proportion of patients with response (FG score ≤ 1) and the 95% CI of the difference between the treatment groups, as well as the number and proportion of patients with response for each treatment will be presented.

Patients who discontinued prematurely from the study without a response will be considered as a non-responder in this analysis. Further details will be provided in the SAP.

9.4.5.3. Other Secondary and Tertiary/Exploratory Endpoints

Analyses of other secondary and tertiary/exploratory endpoints are supportive in nature with p-values and 95% CIs presented for descriptive purposes only.

The mixed-effects model with repeated measures will be used for the tertiary/exploratory efficacy endpoints involving change from baseline over time using all available longitudinal data. The model will include the appropriate endpoint at each prespecified time point as the response variable, fixed categorical effects of treatment, study visit, and treatment-by-study visit interaction, as well as fixed covariate of baseline value and the randomization stratification variables. The treatment effect will be evaluated via contrast for the treatment-by-visit term at Week 24 and other timepoints of interest. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs (details to be provided in the SAP). The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

In addition, summary statistics will be provided for all secondary and tertiary/exploratory endpoints. Missing data will not be imputed.

Further details will be provided in the SAP.

9.4.5.4. Multiplicity Adjustment

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

An unblinded interim analysis on at least 12 events (approximately 60% of the planned events) will be conducted for only the sample size re-estimation based on the conditional power. The Cui, Hung, Wang (CHW) method will be used for controlling the Type 1 error rate due to the interim analysis. Further details will be provided in the SAP.

Hypothesis testing associated with the key secondary endpoints will proceed only if the null hypothesis associated with the primary endpoint is rejected and will proceed from the highest rank (1: Proportion of patients with an FG score ≤ 1 at Week 24 to the lowest rank 3: Proportion of patients with an FG score ≤ 1 at Week 8). If statistical significance is not achieved at an

endpoint (2-sided p-value ≤0.05), then the endpoint of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all key secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure. Further details will be provided in the SAP.

9.4.6. Safety Analyses

The safety and tolerability of eculizumab versus placebo in GBS patients will be assessed based on AEs, clinical laboratory findings, physical examination findings, vital sign findings, and ECG abnormalities.

9.4.6.1. Analysis of Adverse Events

The analysis and reporting of AEs will be based on treatment-emergent adverse events (TEAEs), defined as AEs with onset on or after the first dose of study drug. The incidence of TEAEs will be summarized by SOC and Preferred Term, with additional summaries showing severity, relationship to study drug, TEAEs leading to study drug discontinuation, and TEAEs resulting in death. Summaries of treatment-emergent serious adverse events (TESAEs) will also be summarized by SOC and Preferred Term, with an additional summary showing relationship to study drug. These summaries will be presented by treatment group.

9.4.6.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, and Electrocardiogram Parameters

Laboratory measurements as well as their changes from baseline and shift from baseline, if applicable, will be summarized descriptively. Electrocardiograms, including ECG interpretation of HR, PR, QRS, QT, and QTc intervals, and vital signs will also be summarized using descriptive analyses.

9.4.7. Analyses of Pharmacokinetic and Pharmacodynamic Parameters

Individual serum concentration data for all patients who receive at least 1 dose of the study drug and have at least 1 postdose PK sample will be used to derive PK parameters for eculizumab.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of eculizumab and who have evaluable PD data.

Descriptive statistics will be presented for all eculizumab PD endpoints at each sampling time. The PD effects of eculizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of eculizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

9.4.8. Analysis of Antidrug Antibodies

For assessment of immunogenicity, the presence of confirmed positive ADAs will be summarized. Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies.

9.4.9. Analysis of Biomarkers

Biomarker testing, data and analyses will be performed after study completion and may not be included in the clinical study report. For biomarker analyses, summary statistics will be presented for observed values, change, and percentage change from baseline.

9.4.10. Other Analyses

Any other analyses will be detailed in the SAP.

9.5. Interim Analyses

An interim analysis for the unblinded sample size re-estimation to a maximum 72 patients to generate a maximum of 32 events will be performed by the Independent Analysis Center (IAC) when approximately 60% (ie, at least 12 events) of the planned events are observed, using the conditional power approach. Details of the conditional power calculations and the sample size re-estimation will be prespecified in the IAP.

The planned interim analysis for the unblinded sample size re-estimation will be performed by the IAC. Details of the IAC membership, roles and responsibilities as well as the calculations for the unblinded interim sample size re-estimation will be provided in the IAP.

To maintain study integrity and to prevent the potential introduction of bias, all study team members will remain blinded until the final analysis. Details of this process will be documented in the IAP.

9.6. Independent Data Monitoring Committee

There will be no independent data monitoring committee.

9.7. Independent Guillain-Barré Syndrome Variant Determination

An independent expert assessor for GBS-variant determination will be appointed by Alexion. The assessor will review the clinical history of patients and analyze their nerve conduction test results from Screening and Week 4 to assign the GBS variants of AIDP, AMAN, and “indeterminate”.

The specific electrophysiologic criteria for GBS-variant determination and the specific responsibilities of the assessor will be described in the GBS Variant Determination Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB, and all other applicable regulations.

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent from all study patients prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the patient's rights and responsibilities) to the patient or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent or a certified translation if applicable, that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the patient was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF during their participation in the study.
- A copy of the signed (written or electronic) ICF documentation (ie, a complete set of patient information sheets and fully executed signature pages) must be provided to the patient or the patient's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent forms must remain in each patient's study file and must be available for verification at any time.

Patients who are rescreened are required to sign a new ICF (see Section 5.4).

10.1.4. Data Protection

- Patients will be assigned a unique identifier by Alexion. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- Patients must be informed that their personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the patients who will be required to give consent for their data to be used as described in the informed consent.
- Patients must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Details of the IAC will be provided in the IAP.

10.1.6. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical trial databases (eg, the US website https://www.clinicaltrials.gov/ and the Japan Registry of Clinical Trials https://jrct.niph.go.jp/), as appropriate, and in accordance with national, regional, and local regulations.

10.1.7. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the study drug, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.8. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each patient.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the first patient is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all patients have completed the end of study or the Early Termination Visit, all data have been collected and entered into electronic data capture (EDC) system, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and to provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the

publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.

  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.

- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required if the central laboratory results are not available in time for either study drug infusion and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is also obtained for inclusion of results in EDC. (If a local sample is used, the sample does not need to have been collected at the same time as the central laboratory sample. In other words, if a local sample collected as part of routine clinical management is used, a second local sample does not need to be collected at the same time as the central analysis sample.) Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Women of childbearing potential should only be enrolled after a negative urine or serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB and should be performed per the time points specified in the SoA (Section 1.3).

Table 7: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • Red blood cell count • Hemoglobin • Hematocrit • Red blood cell (RBC) indices (MCV, MCH, %reticulocytes) • White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical chemistry	• Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Blood urea nitrogen (BUN) • Calcium • Creatinine • Glucose (fasting preferred) • Potassium • Sodium • Total and direct bilirubin • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive serum or urine human chorionic gonadotropin (HCG) pregnancy test (as needed for women of childbearing potential)

Investigators must document their review of each laboratory safety report.

Clinical laboratory tests listed in Table 7 will not unblind the Investigator. However, testing C5 levels would result in unblinding.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>Not</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • 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. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study drug are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

1. Results in death

2. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording and Follow-up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion or designee in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion or designee. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Alexion or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study drug caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study drug.
  - Related: There is a reasonable possibility the study drug caused the AE.
    - The AE has a temporal relationship to the administration of the study drug.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study drug.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion or Designee via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion or designee will be the electronic data collection tool.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  - Email: [redacted] or Fax: [redacted]
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS).
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Alexion Medical Monitor by telephone.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

10.4.2.1. Guidance for Female Patients

Female patients of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female patients is defined as any of the following:

1. Prior to first menses
2. Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 Visit and FSH serum levels consistent with postmenopausal status
3. Permanent sterilization at least 6 weeks prior to the Day 1 Visit:
4. Hysteroscopic sterilization
5. Bilateral tubal ligation or bilateral salpingectomy
6. Hysterectomy
7. Bilateral oophorectomy

Female patients of childbearing potential must use a highly effective method of contraception, including at least one of the following:

1. Intrauterine device (without copper) in place for at least 6 weeks.
2. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks.
3. Intrauterine progestogen releasing system for at least 6 weeks.
4. Bilateral tubal occlusion for at least 6 weeks.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 Visit. Estrogen-containing hormonal contraception may not be initiated during the study period.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months).
7. Sexual abstinence for female patients:

a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent female patients who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse for at least 5 months after last dose of study drug.
    a. Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female patients.

Other methods of contraception that are not considered highly effective for female patients:

1. Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are not acceptable.
2. Spermicides or spermicidal sponges, used alone or in combination with barrier methods, are not acceptable.

Withdrawal (coitus interruptus) is not acceptable.

Lactational amenorrhea is not acceptable.

Female patients must not donate ova from the Day 1 Visit until 5 months after the last dose of study drug.

10.4.2.2. Guidance for Male Patients

Contraception is the responsibility of the heterosexually active male patients, regardless of his female partner's method of contraception.

Male patients who have had a vasectomy > 6 months prior must use a condom during heterosexual intercourse. Male patients who have had a vasectomy < 6 months prior must use a condom and spermicide during heterosexual intercourse.

Male patients who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse.

10.4.2.2.1. Sexual Abstinence for Male Patients

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent male patients who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods for a female partner) is not considered a highly effective method of contraception for male patients.

Male patients must not donate sperm from the Day 1 Visit until 5 months after the last dose of study drug.

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female patients and female spouses/partners of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study drug via semen following paternal exposure. If a female patient or a male patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion Global Drug Safety (GDS) via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study drug during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Any female patient who becomes pregnant while participating in the study will be discontinued from study drug.

10.4.3.1. Male Patients With Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate Pregnancy Outcome/Breastfeeding form and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. Female Patients Who Become Pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a patient's pregnancy.
- The patient will be followed up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to Alexion as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

  Any female patient who becomes pregnant while participating in the study will discontinue study drug, and each pregnancy will be followed up to term and Alexion notified regarding the outcome.

10.5. Appendix 5: Rasch-built Overall Disability Scale Score

RODS for GBS – CIDP - MGUSP

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box ("x"). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If your situation fluctuates, your answer should be based on how you *usually* perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

Are you able to	Mark the best option with **"x"**		
Task	**Not possible to perform**	**Possible, but with some difficulty**	**Possible, without any difficulty**
	[0]	**[1]**	**[2]**
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14.	do the shopping?	☐	☐	☐
15.	catch an object (e.g., ball)?	☐	☐	☐
16.	bend and pick up an object?	☐	☐	☐
17.	walk one flight of stairs?	☐	☐	☐
18.	travel by public transportation?	☐	☐	☐
19.	walk and avoid obstacles?	☐	☐	☐
20.	walk outdoors < 1 km?	☐	☐	☐
21.	carry and put down a heavy object?	☐	☐	☐
22.	dance?	☐	☐	☐
23.	stand for hours?	☐	☐	☐
24.	run?	☐	☐	☐

SAMPLE

10.6. Appendix 6: Overall Neuropathy Limitation Scale

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? Yes ☐ No ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their bands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0= Normal
1= Minor symptoms in one or both arms but not affecting any of the functions listed
2= Disability in one or both arms affecting but not preventing any of the functions listed
3= Disability in one or both arms preventing at least one but not all functions listed
4= Disability in both arms preventing all functions listed but purposeful movement still possible
5= Disability in both arms preventing all purposeful movements

SCORE=____

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0= Walking/climbing stairs/running not affected
1= Walking/climbing stairs/running is affected, but gait does not look abnormal
2= Walks independently but gait looks abnormal
3= Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4= Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm, frame)
5= Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6= Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7= Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

SCORE=____

Overall Neuropathy Limitation Scale= arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability))

TOTAL SCORE=____

Is there any disorder, other than peripheral neuropathy, which affects the above functions Yes ☐ No ☐
If **yes**, please describe:

SAMPLE

10.7. Appendix 7: Short Form McGill Pain Questionnaire 2

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

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10.8. Appendix 8: Depression, Anxiety and Stress Scale, Short Form, 21 Questions Score

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

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

1 (s)	I found it hard to wind down	0	1	2	3
2 (a)	I was aware of dryness of my mouth	0	1	2	3
3 (d)	I couldn't seem to experience any positive feeling at all	0	1	2	3
4 (a)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5 (d)	I found it difficult to work up the initiative to do things	0	1	2	3
6 (s)	I tended to over-react to situations	0	1	2	3
7 (a)	I experienced trembling (e.g. in the hands)	0	1	2	3
8 (s)	I felt that I was using a lot of nervous energy	0	1	2	3
9 (a)	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10 (d)	I felt that I had nothing to look forward to	0	1	2	3
11 (s)	I found myself getting agitated	0	1	2	3
12 (s)	I found it difficult to relax	0	1	2	3
13 (d)	I felt down-hearted and blue	0	1	2	3
14 (s)	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15 (a)	I felt I was close to panic	0	1	2	3
16 (d)	I was unable to become enthusiastic about anything	0	1	2	3
17 (d)	I felt I wasn't worth much as a person	0	1	2	3

SAMPLE

18 (s)	I felt that I was rather touchy	0	1	2	3
19 (a)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3
20 (a)	I felt scared without any good reason	0	1	2	3
21 (d)	I felt that life was meaningless	0	1	2	3

DASS-21 Scoring Instructions

The DASS-21 should not be used to replace a face to face clinical interview. If you are experiencing significant emotional difficulties you should contact your GP for a referral to a qualified professional.

Depression, Anxiety and Stress Scale - 21 Items (DASS-21)

The Depression, Anxiety and Stress Scale - 21 Items (DASS-21) is a set of three self-report scales designed to measure the emotional states of depression, anxiety and stress.

Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale is sensitive to levels of chronic non- specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset / agitated, irritable / over-reactive and impatient. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items.

The DASS-21 is based on a dimensional rather than a categorical conception of psychological disorder. The assumption on which the DASS-21 development was based (and which was confirmed by the research data) is that the differences between the depression, anxiety and the stress experienced by normal subjects and clinical populations are essentially differences of degree. The DASS-21 therefore has no direct implications for the allocation of patients to discrete diagnostic categories postulated in classificatory systems such as the DSM and ICD.

SAMPLE

Recommended cut-off scores for conventional severity labels (normal, moderate, severe) are as follows:
Note: Scores on the DASS-21 will need to be multiplied by 2 to calculate the final score.

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

Lovibond, S.H. & Lovibond, P.F. (1995). Manual for the Depression Anxiety & Stress Scales. (2nd Ed.)Sydney: Psychology Foundation.

SAMPLE

10.9. Appendix 9: Chalder Fatigue Scale Score

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. Please tick only one box per line.

	less than usual	***no more than usual***	***more than usual***	***much more than usual***
Do you have problems with tiredness?				
Do you need to rest more?				
Do you feel sleepy or drowsy?				
Do you have problems starting things?				
Do you lack energy?				
Do you have less strength in your muscles?				
Do you feel weak?				
Do you have difficulties concentrating?				
Do you make slips of the tongue when speaking?				
Do you find it more difficult to find the right word?				
	better than usual	***no worse than usual***	***worse than usual***	***much worse than usual***
how is your memory?				

This scale can be scored "bimodally" with columns representing 0, 0, 1 & 1 and a range from 0 to 11 with a total of 4 or more qualifying for "caseness". Alternatively, it can be scored in "Likert" style 0, 1, 2 & 3 with a range from 0 to 33. Mean "bimodal" score for CFS sufferers was 9.14 (SD 2.73) and for a community sample 3.27 (SD 3.21). Mean "Likert" score was 24.4 (SD 5.8) and 14.2 (SD 4.6).

Total (0-33) =

SAMPLE

10.10. Appendix 10: European Quality of Life – 5 Dimensions – 5 Levels Score

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES

(e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

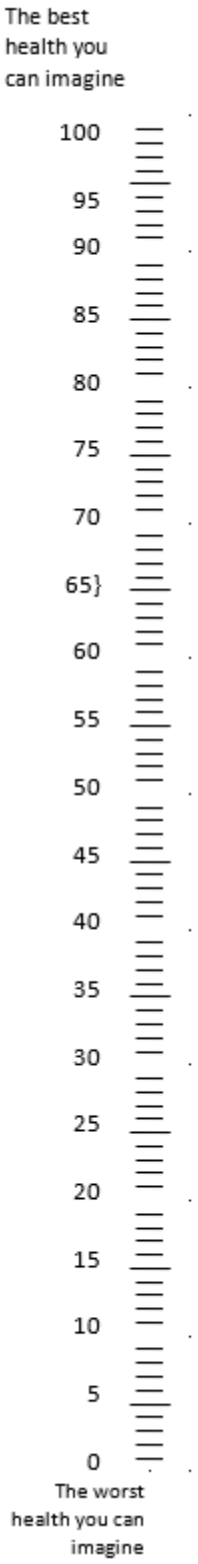
ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

10.11. Appendix 11: Work Productivity and Activity Impairment Questionnaire

HEOR questions for the ECU-GBS study

At Visit 2 (Day 1):

Question 0a: Are you currently employed (working for pay)? _____ NO ___ YES

("NO" answer covers unemployed, retired and housewife/husband patients)

If YES, check "YES" and then ask

Question 0b: Do you work full time in this paid job (40 hours by week)? ___NO__ YES

If NO, check "NO" and then ask

Question 0c: How many hours per week are you currently employed (working for pay)? _____ HOURS

If NO to question 0a, check "NO" and then ask

- Question 0d: Are you living in a retirement home or nursing home (use correct wording for Japan) _____ NO ___ YES
  (YES answered expected to come from some retired elderly patients or disabled patients not working)
- *And skip to question 6 of the WPAI questionnaire at Visit 7 (Week 5), Visit 13 (Week 24), and ET.*

At Visits 7, 13, and ET (Week 5, Week 24, and ET):

Ask the full WPAI questions to patients who answered "YES" to the Question 0 "currently employed"
Ask only the question 6 of the WPAI questionnaire to the ones who answered "NO" to the Question 0

Official English WPAI questionnaire available on next page

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems (Guillain-Barré Syndrome or GBS) on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of Guillain-Barré Syndrome? *Include hours you missed on sick days, times you went in late, left early, etc., because of GBS. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

SAMPLE

5. During the past seven days, how much did Guillain-Barré Syndrome affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If the GBS affected your work only a little, choose a low number. Choose a high number if the GBS affected your work a great deal.

Consider only how much Guillain-Barré Syndrome affected productivity while you were working.

GBS had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	GBS completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did Guillain-Barré Syndrome affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If GBS affected your activities only a little, choose a low number. Choose a high number if GBS affected your activities a great deal.

Consider only how much Guillain-Barré Syndrome affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365

SAMPLE

10.12. Appendix 12: Abbreviations

Abbreviations	Definition
ADA(s)	antidrug antibody (ies)
AE	adverse event
AESI	adverse event of special interest
AIDP	acute inflammatory demyelinating polyradiculopathy
aHUS	atypical hemolytic uremic syndrome
AMAN	acute motor axonal neuropathy
AQP4	anti-aquaporin-4
C5	complement component 5
Chalder	Chalder Fatigue Scale
CH50	50% hemolytic complement activity
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMAP	compound muscle action potential
CONSORT	Consolidated Standards of Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Events
DASS-21	Depression, Anxiety and Stress Scale, Short form, 21 questions
CHW	Cui, Hung, Wang
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EuroQoL	European Quality of Life
EQ-5D-5L	5 Dimensions – 5 Levels
ET	end of treatment
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FG	Functional Grade
FSH	follicle-stimulating hormone
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GDS	Global Drug Safety
gMG	generalized myasthenia gravis
GFAP	glial fibrillary acidic protein
HEOR	Health Economics and Outcomes Research
HR	heart rate
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IAC	Independent Analysis Center
IAP	Interim Analysis Plan
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IL-6	interleukin-6
IRB	Institutional Review Board
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
IRT	Interactive Response Technology
LOS	length of stay
mAb(s)	monoclonal antibody(ies)

Abbreviations	Definition
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
MMT	Manual Muscle Testing
MRC	Medical Research Council
NfL	neurofilament light chain
NMOSD	neuromyelitis optica spectrum disorders
ONLS	Overall Neuropathy Limitations Scale
PD	pharmacodynamic(s)
PE	plasma exchange
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPS	Per Protocol Set
QoL	quality of life
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
R-ODS	Rasch-built Overall Disability Scale
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System (software)
SF-MPQ-2	Short Form McGill Pain Questionnaire 2
SoA	Schedule of Activities
SOC	System Organ Class
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNF-α	tumor necrosis factor alpha
WOCBP	Woman/women of childbearing potential
WPAI	Work Productivity and Activity Impairment

10.13. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Original protocol	Not applicable	15 Sep 2020	Not applicable

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