Clinical Study Protocol

Protocol Title:	A Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in Symptomatic Subjects with Generalized Myasthenia Gravis
Investigational Product:	Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C)
Sponsor's Name and Address:	Grifols Therapeutics Inc. 4101 Research Commons 79 T.W. Alexander Drive Research Triangle Park, NC 27709
Sponsor's Telephone Number:	[redacted]
Study Number/Protocol Version Number/Date:	GTI1408/2.0/15 Jul 2015 Includes GTI1408/1.0/30 Sep 2014
EudraCT Number:	2014-003997-18
Development Phase:	Phase 2

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol:

Medical Monitor: [redacted]

Signature: [redacted] Date: 15 July 2015

Summary of Changes for Amendment 1

Protocol Version	Date of Approval
2.0 Amendment 1 + Integrated Protocol	15 Jul 2015
1.0 Original	30 Sep 2014

Amendment 1

The protocol for GTI1408 (Version 1.0, dated 30 Sep 2014) has been amended and reissued as Protocol Amendment 1, Version 2.0, dated 15 Jul 2015. See Appendix 9 for a summary of changes for Amendment 1.

Investigator Signature Page

The undersigned confirms that he/she agrees to conduct the study under the conditions described in this protocol and comply with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable regulatory requirements:

_____ _____

INVESTIGATOR NAME (Please Print) LOCATION

_____ _____

INVESTIGATOR SIGNATURE DATE

Protocol Synopsis

Title of Study:

A Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in Symptomatic Subjects with Generalized Myasthenia Gravis

Study Number

GTI1408

Phase:

2

Number of Subjects Planned:

Approximately 62 adult subjects will be randomized.

Study Centers Planned:

Approximately 40 study centers

Study Objectives:

The primary objective is to evaluate the efficacy of IGIV-C in subjects with generalized myasthenia gravis (MG) on standard of care treatment at study entry in terms of improvement in MG symptoms as measured by the mean change in Quantitative Myasthenia Gravis (QMG) score from Baseline (Week 0) to Week 24 as compared to placebo.

The safety objective of this study is to evaluate the safety and tolerability of IGIV-C loading dose of 2 g/kg followed by 7 maintenance dosages of 1 g/kg every 3 weeks through Week 21 in subjects with MG.

Target Population:

Eligible participants for this study will include adult subjects with a confirmed diagnosis of generalized MG who are receiving standard of care MG treatment, but continue to have symptoms of MG as demonstrated by a QMG $\geq$ 10 points.

Overall Study Description:

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of IGIV-C in subjects with MG who are symptomatic on standard of care treatment. Subjects will be randomly allocated in a 1:1 ratio to receive either IGIV-C or matched placebo every three weeks in double-blinded fashion. Randomization will be stratified by sentinel features of the subject's Baseline standard of care MG treatment regimen at the time randomization:

- Regimen includes **ONLY cholinesterase inhibitors**
- Regimen includes **corticosteroid (CS) as the ONLY IMMUNOSUPPRESSANT/IMMUNOMODULATOR**, alone or in combination with other MG medications (e.g., a subject on prednisone plus a cholinesterase inhibitor would be in this stratum)

- Regimen includes **ANY NON-CS IMMUNOSUPPRESSANT/IMMUNOMODULATOR** alone or in combination with other MG medications which may include CS (e.g., a subject on azathioprine, prednisone, and a cholinesterase inhibitor would be in this stratum)

For those subjects randomized to receive IGIV-C, an initial loading dose of 2 g/kg of body weight will be administered after the Baseline assessments are complete at Baseline (Week 0, Visit 1) followed by maintenance doses of 1 g/kg of body weight administered every third week through Week 21 (Visit 8). The initial loading dose (2 g/kg) will be divided on 2 consecutive days with extension of up to 4 consecutive days to account for tolerability/weight >80 kg. The subsequent 7 maintenance dosages (1 g/kg) will be infused on one day with an extension to 2 consecutive days (divided doses) to account for tolerability/weight >80 kg. For both loading and maintenance infusions the limit for blinded IGIV-C infusion is no more than 80 g/day, corresponding to an 80-kg body weight for a 1 g/kg per diem dosage.

For those subjects randomized to receive placebo, a sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent will be infused at the Baseline/Week 0 Visit (Visit 1) using the same volume as would be required for the IGIV-C loading dose. Subsequent placebo maintenance doses will be matched in volume to the IGIV-C maintenance doses and administered every third week until Week 21 (Visit 8).

The Investigators will hold the subjects' current background medical regimen constant from Screening through the end of the study (Week 24, Visit 9), unless there is a compelling emergent medical need to make medication adjustments, the subject discontinues the study because criteria for Treatment Failure are met as defined in Section 3.3.3 (after End of Study visit assessments are complete), or adverse effects due to other components of the subject's therapy become untenable; in such cases, the Medical Monitor must be contacted.

Week 21 (Visit 8) is the time of the last investigational product (IP) maintenance dosage. Week 24 (Visit 9) will constitute the primary endpoint time point for analysis because this timing allows an opportunity to assess the effect of the final IP infusion made at Week 21 (Visit 8). Week 24 (Visit 9) will serve as the final End of Study Visit.

Study Phases:

Screening:

During the three-week Screening Phase, assessments will be performed to determine subject eligibility.

Baseline:

Eligible subjects will have the Baseline assessments performed and will be randomized to receive either IGIV-C or placebo. After randomization, a loading dose of the blinded IP will be administered (Week 0, Visit 1).

IP Maintenance Phase:

Maintenance infusions of blinded IP will be given over 1 day every three weeks at Week 3

(Visit 2), Week 6 (Visit 3), Week 9 (Visit 4), Week 12 (Visit 5), Week 15 (Visit 6), Week 18 (Visit 7), and Week 21 (Visit 8).

End of Study/Early Termination:

Subjects will have an End of Study Visit at Week 24 (Visit 9).

Key Assessments and Procedures

During the course of the study, subjects will receive scheduled general physical examinations, neurological assessments of strength, functional ability and endurance, quality of life assessments, and laboratory evaluations.

Duration of Treatment:

Subjects will receive a loading dose of IP at the Baseline Visit (Week 0, Visit 1) in divided doses on two days and will then receive IP infusions every 3 weeks on one day from Week 3 (Visit 2) until Week 21 (Visit 8).

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Male or female, ages 18 to 85 years
2. Anti-acetylcholine receptor antibody positive
3. Confirmed diagnosis of generalized MG. Historically, subjects may have previously had the Myasthenia Gravis Foundation of America (MGFA) Class II, III, IV, or V.
4. MGFA classification of Class II, III, or IVa inclusive at Screening.
5. QMG score ≥ 10 at Screening. *Note: Subjects who only have a history of ocular MG may not enroll.*
6. Receiving standard of care MG treatment at a stable dose consisting of any one of the following for the time intervals delineated below (*time intervals apply to medications and maintenance of stable dose level*):
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and no immunosuppressants
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or *only one of the following*:
        - Prednisone (up to 60 mg/day or equivalent) for at least two months prior to Screening, or
        - Azathioprine for at least 6 months prior to Screening, or
        - Mycophenolate mofetil for at least 6 months prior to Screening, or
        - Methotrexate for at least 6 months prior to Screening, or
        - Cyclosporine or tacrolimus for at least 3 months prior to Screening
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or prednisone (up to 60 mg/day or equivalent) for at least one month prior to Screening and *only one of the following*:
        - Azathioprine for at least 6 months prior to Screening, or
        - Mycophenolate mofetil for at least 6 months prior to Screening, or

- Methotrexate for at least 6 months prior to Screening, or
- Cyclosporine or tacrolimus for at least 3 months prior to Screening

7. Subjects must be willing and able to provide written informed consent.
8. Subjects must be willing to comply with all aspects of the clinical trial protocol.

Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study:

1. Have received cyclophosphamide or any other immunosuppressive agent apart from the ones allowed per inclusion criteria within the past 6 months
2. Any change in MG treatment regimen between Screening (Week -3, Visit 0) and Baseline (Week 0, Visit 1)
3. *Greater than* two (>2) point change in QMG score, increased or decreased, between Screening (Week -3, Visit 0) and Baseline (Week 0, Visit 1)
4. Any episode of myasthenic crisis (MC) in the one month prior to Screening
5. Evidence of malignancy within the past 5 years (non-melanoma skin cancer, carcinoma in situ of cervix is allowed) or thymoma potentially requiring surgical intervention during the course of the trial (intent to perform thymectomy)
6. Thymectomy within the preceding six months
7. Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months
8. Have received immune globulin (Ig) treatment given by intravenous (IV), subcutaneous, or intramuscular route within the last 3 months
9. Current known hyperviscosity or hypercoagulable state
10. Currently receiving anti-coagulation therapy (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate, rivaroxaban, edoxaban, and apixaban], parenteral anticoagulants [e.g., fondaparinux]). Note that oral anti-platelet agents are allowed (e.g., aspirin, clopidogrel, ticlodipine)
11. Plasma exchange (PLEX) performed within the last 3 months
12. History of non-response to intravenous immunoglobulin (IVIg) when used in maintenance therapy of the subject's MG, as judged by the Investigator
13. Any comorbid condition that in the opinion of the Investigator would put the subject at undue safety risk or compromise the ability of the subject to participate in the trial or the scientific integrity of the study
14. Inadequate venous access to support repeated IV infusions
15. History of anaphylactic reactions or severe reactions to any blood-derived product
16. History of intolerance to any component of the IP
17. Documented diagnosis of thrombotic complications to polyclonal IVIg therapy in the past
18. History of recent (within the last year) myocardial infarction or stroke
19. Uncontrolled congestive heart failure; embolism; or historically documented (within the last year) electrocardiogram (ECG) changes indicative of myocardial ischemia or atrial fibrillation
20. History of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the Screening/Week -3 (Visit 0)
21. Active psychiatric illness that interferes with compliance or communication with health

care personnel
22. Females of child-bearing potential who are pregnant or have a positive serum pregnancy test (Beta-human chorionic gonadotropin [β-HCG]-based assay)
23. Females who are breastfeeding
24. Females of child-bearing potential who are unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence*) throughout the study.
    *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
25. Currently receiving, or having received within 1 month prior to the Screening/Week -3 (Visit 0), any investigational medicinal product or device. In the case of an investigational medicinal product trial, at least five half-lives (if known) must have elapsed prior to Screening.
26. Known Immunoglobulin A (IgA) deficiency and anti-IgA serum antibodies
27. Renal impairment (i.e., serum creatinine exceeds more than 1.5 times the upper limit of normal [ULN] for the expected normal range for the testing laboratory)
28. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory.
29. Hemoglobin (Hb) levels <9 g/dL
30. Any medical condition which makes the clinical trial participation unadvisable or which is likely to interfere with the evaluation of the study treatment and/or the satisfactory conduct of the clinical trial according to the Investigator's judgment. Any factor that in the opinion of the Investigator would compromise the ability of the subject to complete the trial.

Study Procedures:

Subjects deemed eligible based on Screening evaluations will complete the Baseline assessments, thereby initiating double-blind treatment. Subjects will continue with assessments for 24 weeks, with scheduled assessments at Week 0 (Visit 1) (Baseline and loading infusion divided on 2 consecutive days), followed by assessments and maintenance doses every 3 weeks through Week 21 (Visit 8). The time point for assessment of the primary endpoint is Week 24 (Visit 9). Visits/procedures and assessments should be scheduled within ± 3 days of the protocol-specified timing. The main protocol text and tabular summary Schedule of Study Procedures (Appendix 1) provide additional details. Tools for assessing MG are provided in Appendix 2 to Appendix 6.

The QMG score and MG Composite will be assessed at every visit. Therefore before each visit, subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the visit to assure accurate assessment of the QMG. The MG-Activities of Daily Living (MG-ADL) and the 15-item MG Quality-of-Life Instrument (MG-QOL 15) are assessed at Baseline, Week 9 (Visit 4), Week 15 (Visit 6), and Week 24 (Visit 9). Safety assessments include vital signs performed at each visit, clinical laboratory testing and physical examinations performed at Screening, Baseline, Week 9 (Visit 4), Week 15 (Visit

6), and Week 24 (Visit 9), assessments of adverse events (AEs) throughout the study, and targeted evaluations for potential thromboembolism risk and hemolysis at time points designated in Appendix 1 and Section 3.8 of the protocol.

Investigational Product, Dose, and Mode of Administration:

Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C)

Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified (IGIV-C) is the active IP for this study, which is a marketed product. IGIV-C glass vials may be supplied in the vial sizes of 10 mL, 25 mL, 50 mL, 100 mL, and 200 mL. The infusion solution will be visually masked to maintain the blind.

Administration of IP will be via the IV route, and will be administered in a double-blinded fashion. The unblinded pharmacist or designee will prepare the IP to maintain the blind for all parties during infusions and study assessments. Reference the Pharmacy Manual for additional details.

Placebo

Sterile 0.9% sodium chloride injection, USP (0.9% NaCl, USP) or equivalent will be used as placebo to maintain the blind. The infusion solution will be at a volume approximate to that required for the appropriate weight-based dose of IGIV-C and visually masked to maintain the blind.

Method of Assigning Subjects to Treatment Groups

This is a randomized, double-blind, placebo-controlled study. Subjects will be randomized in a 1:1 ratio via Interactive Web Response System (IWRS) into IGIV-C treatment group and Placebo treatment group to receive either IGIV-C or matching placebo every three weeks in a double-blind fashion via IV administration.

Preparation of Investigational Products

The volume (i.e., total infusion dose administered) of IP to be prepared for each IV infusion will be individualized for each subject based on body weight, and the protocol specified loading dose of 2 g/kg divided over 2 days starting after the randomization at Baseline (Week 0), followed by maintenance doses of 1 g/kg administered over 1 day every three weeks until Week 21 (Visit 8). The infusion solution will be visually masked to maintain the blind.

Note that the loading dosage is divided over 2 days as standard infusion time; however, extensions up to 4 days are allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight). Similarly, the maintenance dosage is infused on 1 day as standard; however, extension is allowed for divided dosage over 2 consecutive days for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight).

The unblinded pharmacist must inspect IGIV-C visually before preparing for administration to subjects. The solution must not be used if turbid or if it contains visible particles. Solution

which has been frozen should not be used.

Definition and Management of Treatment Failures Due to MG Worsening:

During the study, MG worsening will be defined as:

- QMG increase by ≥4 points relative to Baseline/Week 0

All subjects will remain in the study until at least Week 9 (Visit 4) is completed. No premature discontinuation of IP administration is to be made for reasons of Treatment Failure (QMG increase by ≥4 points relative to Baseline/Week 0) until the subject receives at least a total of 3 complete doses of the IP, which includes the initial loading dose and the first two maintenance doses irrespective of the QMG scores measured at Week 3 and Week 6 (Visit 2 and Visit 3) in order to allow time for the investigational medicinal product to potentially produce a beneficial effect.

At Week 9 (Visit 4) through Week 21 (Visit 8), if the subject suffers a worsening of his/her MG symptoms defined as a QMG increase ≥ 4 points relative to Baseline (Week 0), *and this worsening is confirmed at the next scheduled consecutive visit*, the subject will discontinue from the study. The earliest withdrawal for Treatment Failure will be at Week 9 and would occur only if QMG score is increased by 4 points or more (relative to Baseline) at both Week 6 (Visit 3) and Week 9 (Visit 4).

Safety Evaluation:

Safety will be assessed throughout the clinical trial for all individuals who have received at least one infusion of the IP. The following safety variables will be assessed in this study:

- Adverse events (AEs), suspected adverse drug reactions (Suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs (including myasthenic crisis)
- Vital Signs (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]); during infusions vital signs will be carefully monitored.
- Physical examinations: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Blood chemistry and Hematology
- Thromboembolic events (TEs) and hemolysis events

<u>Management and Recording of Adverse Events</u>

AEs (includes Suspected ADRs) occurring at any time between signature of the subject's informed consent form (ICF) and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's electronic case report form (eCRF) entry.

It is the Investigator's responsibility to ensure that all AEs are appropriately recorded.

AEs will be elicited by spontaneous reporting by the study individual or by a non-leading

inquiry or direct observation by the study staff.

This study will utilize an Independent Safety Review Committee (ISRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. The clinical trial team will remain blinded to subject treatment assignment. The ISRC will review relevant safety information from the study as outlined in the ISRC Charter. At a minimum, after the first 20 subjects are enrolled and have completed half of the treatment period, the ISRC will conduct a safety review of the following data at a minimum:

- AEs, SAEs, and discontinuations due to AEs and SAEs
- Vital signs
- Blood chemistry and hematology
- Assessing for TEs
- Assessing for hemolysis

During the study, the Medical Monitor will review all relevant safety information from the study in order to protect subject welfare and preserve study integrity. Data to be reviewed include but are not limited to the following: eCRFs, listings from the clinical and safety databases, AEs/SAE reports, concomitant medications, laboratory data, vital signs, and physical examinations data.

Clinical Outcome Measures:

Primary Efficacy Variable

The primary endpoint is improvement in MG symptoms as measured by the mean change in QMG score from Baseline (Week 0) to Week 24 as compared to placebo.

Secondary Efficacy Variables

- Percentage of subjects who experience a clinical improvement assessed by QMG score from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in QMG score
- Percentage of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in the MG Composite
- Percentage of subjects who experience a clinical improvement assessed by MG-ADL from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 2-point decrease in MG-ADL

Exploratory Variables

The exploratory objectives for this study are to evaluate the effect of IGIV-C on:

- Percentage of subjects who experience a clinical improvement in QMG score (defined above) at Weeks 6, 9, 12, 15, 18, and 21
- Time to first clinical improvement in QMG score (at least a 3-point decrease)
- Time to Treatment Failure based on QMG definition (Section 3.3.3)

- Change from Baseline (Week 0) in QMG score to Weeks 6, 9, 12, 15, 18, and 21
- Percentage of subjects who experience a clinical improvement in the MG Composite (defined above) to Weeks 6, 9, 12, 15, 18, and 21
- Change from Baseline (Week 0) in MG Composite to Weeks 6, 9, 12, 15, 18, 21, and 24
- Percentage of subjects who experience a clinical improvement in MG-ADL (defined above) to Weeks 9 and 15
- Change from Baseline (Week 0) in MG-ADL to Weeks 9, 15, and 24
- Change from Baseline in MG-QOL 15 to Weeks 9, 15, and 24
- MGFA postinterventional change in status at Week 24 relative to Baseline

Statistical and Analytical Methods:

Determination of Sample Size

Assuming that the IGIV treatment group is 50% better than the Placebo group, with alpha=0.05 and two-sided test, 28 subjects are needed for each treatment group (total 56 subjects) to have at least 80% power to detect the treatment difference. Assuming a 10% drop out rate, 62 subjects are planned to be randomized.

Subject Populations for Analysis

Intent-To-Treat (ITT) Population

The ITT population consists of all subjects who are randomized.

Safety Population

The Safety population consists of all subjects who received any amount of IP.

Per Protocol (PP) Population

The PP population consists of all subjects in ITT population without any major protocol deviation which has impact on the primary efficacy data. Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in the PP population will be assessed at a review meeting that will take place before finalizing the database. The review meeting will review the protocol deviation list, as well as data listings. If protocol deviations are identified which justify removing a subject from the PP population, then these decisions will be documented.

Primary Efficacy Analyses

The primary efficacy endpoint is the change in QMG score from Baseline (Week 0) to Week 24. The treatment comparison will be performed using analysis of covariance (ANCOVA) with change in QMG score as dependent variable, treatment and Baseline standard of care treatment regimen as fixed factors and Baseline QMG score as a covariate. The null

hypothesis (H0) and the alternative hypothesis (Ha) are:

$$H0: \mu1 = \mu2$$

$$Ha: \mu1 \neq \mu2$$

Where μ1 and μ2 represent the population mean in IGIV-C and Placebo group, respectively.

For subjects who discontinued the study early, the last observation carried forward (LOCF) method will be used to impute the change in QMG from Baseline to Week 24. A sensitivity analysis of completers with non-missing QMG score at Week 24 will be performed. For subjects who experience treatment failure (as defined in Section 3.3.3) or myasthenic crisis (as defined in Section 3.3.4) the value at time of failure will be employed.

For the longitudinal measurements of QMG score at various time points, the treatment effects will be explored by using the mixed-effect model repeated measures (MMRM) with change from Baseline as dependent variable; treatment, Baseline standard of care treatment regimen, protocol-specified visits, treatment by-visit interaction as fixed effects; Baseline QMG value as covariates; and measures within-subject at each visit as a repeated measure.

Primary Efficacy analyses will be based on the ITT population. For sensitivity analysis, the same analysis will be repeated using the PP population.

Secondary Efficacy Analyses

Treatment comparison will be performed by Cochran-Mantel-Haenszel (CMH) test adjusted for Baseline standard of care treatment regimen. Subjects who discontinued from the study early will be considered as not showing clinical improvement.

Exploratory Efficacy Analyses

For the time to event variables, Kaplan-Meier estimates will be provided and the treatment comparison will be performed using log-rank test. For change from Baseline variables, ANCOVA and/or MMRM methods similar to the primary efficacy endpoint will be used. For percentage variables, the CMH test adjusted for Baseline standard of care treatment regimen will be used.

MGFA postinterventional change in status at Week 24 relative to Baseline will be summarized by treatment group.

Safety Analyses

The safety analysis will be based on safety population.

The incidence of AEs, SAEs, suspected ADRs, and AEs by severity will be summarized by treatment, system organ class and preferred term using descriptive statistics. Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed.

Clinical laboratory results and the change from Baseline values will be summarized by treatment group using summary statistics. Shift tables will be provided to summarize values that fall outside the normal ranges.

Vital signs will be summarized by treatment using summary statistics at each time point and on the change from Baseline.

Physical exam data will be provided in data listings.

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GLOSSARY AND ABBREVIATIONS

AAN	American Academy of Neurology
AChR	Acetylcholine receptor
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
B19V	Parvovirus B19
BUN	Blood urea nitrogen
CBC	Complete blood count
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMH	Cochran-Mantel-Haenszel
CRO	Clinical research organization
CS	Corticosteroid
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
GBS	Guillain-Barré syndrome
H0	Null hypothesis
Ha	Alternative hypothesis
HAV	Hepatitis A virus
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator’s Brochure

ICF	Informed consent form
ICH GCP	International Conference on Harmonization Good Clinical Practice
ICU	Intensive Care Unit
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IgM	Immunoglobulin M
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
ISRC	Independent Safety Review Committee
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MC	Myasthenic crisis
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QOL 15	15-Item MG Quality-of-Life Instrument
MMRM	mixed-effect model repeated measures
NAT	Nucleic acid amplification technology
NINDS	National Institute of Neurological Disorders and Stroke
PE	Pulmonary embolism
PLEX	Plasma exchange
PP	Per protocol
QMG	Quantitative myasthenia gravis score
RBC	Red blood count
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SPC	Summary of product characteristics

Suspected ADR	Suspected adverse drug reaction
T	Temperature
TBL	Total bilirubin
TE	Thromboembolic event
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
USP	United States Pharmacopeia

1 INTRODUCTION

In addition to the information provided below, please also refer to the Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) Investigator's Brochure (IB) and any additional data supplied by the Sponsor.

1.1 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction and is clinically manifested as variable and fluctuating muscle weakness (1). In most cases, the disorder is associated with the production of antibodies against acetylcholine receptors (AChR) leading to the destruction of the postsynaptic motor end plate (2). Clinical symptoms of MG include muscle fatigue and weakness that can be localized, such as ocular, or generalized across multiple muscle groups (systemic). Manifest weakening during continued activity, quick restoration of power with rest, and dramatic improvement in strength following the administration of drugs inhibiting acetylcholinesterase such as neostigmine and pyridostigmine are other notable characteristics (3). The special vulnerability of the neuromuscular junctions in certain muscles gives myasthenia a highly characteristic clinical presentation. Usually the eyelids and the muscles of eye movement, and somewhat less often the face, jaws, throat, and neck are the first to be affected. Exacerbations of disease can lead to myasthenic crisis (MC) with severe respiratory weakness requiring intubation.

MG is a relatively rare disorder with an estimated prevalence of 1.7 to 10.4 per million depending on the location, and has been reported to be as high as 21 per million in Barcelona, Spain (4). While symptoms can be ameliorated with acetylcholinesterase inhibitors that prolong native acetylcholine activity, definitive therapy requires attenuation of the aberrant immune process. This can be achieved by treating patients with immunosuppressive medications, immunomodulation therapies or plasma exchange (5). Immunosuppressive medications used in the treatment of MG include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. B-cell targeted immunotherapies (e.g., rituximab, belimumab), and eculizumab have also been explored as investigational treatment modalities. Intravenous immunoglobulin (IVIg) is commonly used in the acute setting as an integral part of therapy (4, 6).

While there are a number of studies evaluating IVIg for the treatment of MG worsening or exacerbation (7, 8, 9, 10, 11), there are few prospective data from controlled trials in the public domain for IVIg treatment of chronic MG (12, 13). The latter 2 studies were in very small patient numbers 12 and 15 patients, respectively. The study by Wolfe and colleagues was terminated prematurely due to insufficient IVIg inventories, and that by Ronager and colleagues was a controlled crossover study wherein IVIg was given for 5 days with 16 weeks observation followed by plasma exchange every other day (5 interventions) with 16 weeks observation (or vice versa). Thus, there is a need for definitive, prospective clinical studies of IVIg in the chronic/maintenance setting.

Corticosteroids have generally been considered a fairly reliable and appropriate modality for immunomodulation of MG, mainly based on clinical experience rather than rigorously controlled studies (6). Prednisone (or prednisolone in Europe) is the initial

immunosuppressive treatment used in many MG patients, although the optimal dosage and schedule of administration have not been precisely defined (14). The long-term use of steroids is complicated by severe and often intolerable adverse effects, the cumulative burden of steroid side effects is high (15), and therefore there has been much clinical interest in approaches to CS dose reduction. The minimum effective CS dose is the clinical target (16).

1.2 Treatment of Myasthenia Gravis

Therapies for MG are based on two approaches, prolongation of the half-life of the neurotransmitter acetylcholine in the synaptic cleft, and reduction in the burden of pathologic antibodies inhibiting neuromuscular transmission.

Acetylcholinesterase inhibitors effectively prolong acetylcholine activity; neostigmine and pyridostigmine have been demonstrated to provide symptomatic improvement in muscle strength. Common adverse events (AEs) include diarrhea and abdominal cramps, whilst overdose symptoms show features consistent with acute cholinergic poisoning (4).

Down regulation of the production of antibodies through immune modulation is a complementary approach, and corticosteroids, azathioprine, cyclosporine, tacrolimus, and cyclophosphamide have been employed. Clinical observation and limited trial data support a number of medications using this approach, however all require close monitoring for frequent and sometimes serious adverse effects (17, 18, 19, 20, 21). Additionally, onset of of action is often reported to be slow with these agents, with the exception of corticosteroids (22). Although corticosteroids are the most common first-line immune suppressant employed in chronic MG, their adverse effect profile is considerable. Examples of adverse effects of systemic CS use include clinical adverse effects (e.g., adipose tissue redistribution, hypertension, cardiovascular risk, osteoporosis, peptic ulcer, adrenal insufficiency, infections, aseptic necrosis and pancreatitis as well as mood, ophthalmological, menstrual and skin disorders) and biological adverse effects (e.g., electrolyte homeostasis diabetogenesis, dyslipidemia and pregnancy-related AEs) (23, 24).

Additional therapies include complete thymectomy, an intervention that is the subject of an ongoing clinical trial supported by the National Institute of Neurological Disorders and Stroke (NINDS) (25) which presents an opportunity to reduce antibody production. Removal of an associated thymoma has shown benefit historically. In the setting of MC and exacerbations, plasmapheresis has been employed. However, a 2011 American Academy of Neurology (AAN) guideline update states that: “There is insufficient evidence to support or refute the use of plasmapheresis in myasthenia gravis” (26). Plasmapheresis requires highly specialized equipment, significant operator expertise, and often requires large gauge access to the central circulation.

IVIg derived from healthy donor plasma appears to mitigate immunologic events related to the pathologic antibodies in MG. While there are multiple theoretical mechanisms by which exogenous IVIg modulates the immune system, several generally accepted paths include competition with anti-idiotype antibodies, anti-complement effects, and Fc receptor saturation (27, 28, 29).

The mechanism by which IVIg exerts its clinical effect in MG remains to be elucidated but it is believed to improve symptoms by modulating the pathogenic autoantibody response. Other mechanisms of action postulated in other diseases include the Fc receptor blockade of the reticuloendothelial system, modulation of the idiotypic-anti-idiotypic network, enhancement of regulatory T cells, inhibition of complement deposition, modulation of cytokines, growth factors and adhesion molecules, modulation of apoptosis and macrophages, and immune regulation of both B-cell and T-cell immune function (30, 31). Improvement in MG symptoms typically occurs in about 70% of patients, beginning during treatment or within a few days of initiating IVIg treatment and lasting for weeks to months (32).

The Therapeutics and Technology Assessment Subcommittee of AAN recently released updated evidence-based guidelines that consider IVIg as an effective therapy for moderate-to-severe cases of MG, but also acknowledges the need for additional clinical trials (33).

1.3 Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C)

Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) is an intravenous (IV) product that is currently available commercially in a number of countries for the treatment of primary immunodeficiency, idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP) as well as other indications in some countries.

In addition to the information provided herein, please refer to the IGIV-C IB and any additional data supplied by the Sponsor.

1.4 Study Rationale and Dose Selection

1.4.1 Study Rationale

The general recommendation is that IVIg concentrates are a safe and effective treatment option as a short term treatment for acute exacerbation of MG. Moreover, IVIg has demonstrated a positive treatment effect in clinical studies of MG worsening or exacerbations (7, 9, 11), but further clinical data are needed to confirm the effectiveness of IVIg in the treatment of MG as a maintenance therapy (12, 13). In a recent Cochrane review (10) of IVIg for MG, controlled trials were generally of limited timeframe underscoring the need for longer term evaluation.

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in symptomatic subjects with generalized MG on standard of care treatment. The primary measure of efficacy for this study is the change in score of MG symptoms as measured by the Quantitative Myasthenia Gravis (QMG) score from Baseline (Week 0) to Week 24.

1.4.2 Dose Rationale

The optimal dose of IVIg for MG exacerbation is still unclear, but prior reviews reported a usual dose of 2 g/kg, which is administered over 3 to 5 days (32, 35). More recent studies in MG have evaluated the administration of a total IVIg dose of 2 g/kg over 2 consecutive days (1 g/kg daily) with no increase in side effects and a comparable benefit lasting up to 30 to 60 days post-treatment (7, 9, 11).

Likewise, in a study of subjects with Guillain-Barré syndrome (GBS), a total IVIg dose of 2 g/kg administered over 2 consecutive days (1 g/kg daily) was compared to the standard regimen of 0.4 g/kg daily for 5 days and there were no significant differences in the primary or secondary outcome measures (36).

Based on the above, subjects will receive a loading IGIV-C dose of 2 g/kg of body weight administered over two days followed by maintenance infusions at 3-week intervals at a dose of 1 g/kg of body weight administered over one day. The loading and maintenance dosage is the same as that used for IGIV-C in CIDP which has been well tolerated, and is approved for CIDP at this dosage both in North America and Europe.

2 STUDY OBJECTIVES

2.1 Efficacy Objectives

2.1.1 Primary Objective

The primary objective is to evaluate the efficacy of IGIV-C in subjects with generalized MG on standard of care treatment at study entry in terms of improvement in MG symptoms as measured by the mean change in QMG score from Baseline (Week 0) to Week 24 as compared to placebo.

2.1.2 Secondary Objectives

The secondary objectives of this study are to evaluate the efficacy of IGIV-C as compared to placebo from Baseline through Week 24 in the following:

- Percentage of subjects who experience a clinical improvement assessed by QMG score from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in QMG score
- Percentage of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in the MG Composite
- Percentage of subjects who experience a clinical improvement assessed by MG – Activities of Daily Living (MG-ADL) from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 2-point decrease in MG-ADL

2.1.3 Exploratory Objectives

The exploratory objectives for this study are to evaluate the effect of IGIV-C on:

- Percentage of subjects who experience a clinical improvement in QMG score (defined above) at Weeks 6, 9, 12, 15, 18, and 21
- Time to first clinical improvement in QMG score (at least a 3-point decrease)
- Time to Treatment Failure based on QMG score definition (Section 3.3.3)
- Change from Baseline (Week 0) in QMG score to Weeks 6, 9, 12, 15, 18, and 21
- Percentage of subjects who experience a clinical improvement in the MG Composite (defined above) to Weeks 6, 9, 12, 15, 18, and 21
- Change from Baseline (Week 0) in MG Composite to Weeks 6, 9, 12, 15, 18, 21, and 24
- Percentage of subjects who experience a clinical improvement in MG-ADL (defined above) to Weeks 9 and 15
- Change from Baseline (Week 0) in MG-ADL to Weeks 9, 15, and 24
- Change from Baseline in the 15-item MG Quality-of-Life Instrument (MG-QOL 15) to Weeks 9, 15, and 24
- Myasthenia Gravis Foundation of America (MGFA) postinterventional change in status at Week 24 relative to Baseline

2.2 Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of IGIV-C loading dose of 2 g/kg followed by 7 maintenance dosages of 1 g/kg every 3 weeks through Week 21 in subjects with MG.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of IGIV-C in subjects with MG who are symptomatic on standard of care treatment. Approximately 62 adult subjects will be randomized at approximately 40 global study centers.

Subjects who are on standard of care treatment for MG may enroll. Eligibility parameters allow monotherapy, dual treatment, or three-drug treatment (i.e., various combinations consisting of a cholinesterase inhibitor, CS, and an additional immunosuppressant). Subjects will be randomly allocated in a 1:1 ratio to receive either IGIV-C or matched placebo every three weeks in double-blinded fashion. Randomization will be stratified by sentinel features of the subject's *Baseline* standard of care MG treatment regimen *at the time randomization*:

- Regimen includes **ONLY cholinesterase inhibitors**
- Regimen includes **CS as the ONLY IMMUNOSUPPRESSANT/ IMMUNOMODULATOR,** alone or in combination with other MG medications

(e.g., a subject on prednisone plus a cholinesterase inhibitor would be in this stratum)

- Regimen includes **ANY NON-CS IMMUNOSUPPRESSANT/IMMUNOMODULATOR** alone or in combination with other MG medications which may include CS (e.g., a subject on azathioprine, prednisone, and a cholinesterase inhibitor would be in this stratum)

For those subjects randomized to receive IGIV-C, an initial loading dose of 2 g/kg of body weight will be administered *after the baseline assessments are complete* at Baseline (Week 0, Visit 1) followed by maintenance doses of 1 g/kg of body weight administered every third week through Week 21 (Visit 8). The initial loading dose (2 g/kg) will be divided on 2 consecutive days with extension of up to 4 consecutive days to account for tolerability/weight >80 kg. The subsequent 7 maintenance dosages (1 g/kg) will be infused in one day with an extension to 2 consecutive days (divided doses) to account for tolerability/weight >80 kg. For both loading and maintenance infusions the limit for blinded IGIV-C infusion is no more than 80 g/day, corresponding to an 80-kg body weight for a 1 g/kg per diem dosage.

For those subjects randomized to receive placebo, a sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent will be infused at the Baseline/Week 0 Visit (Visit1) using the same volume as would be required for the IGIV-C loading dose. Subsequent placebo maintenance doses will be matched in volume to the IGIV-C maintenance doses and administered every third week until Week 21 (Visit 8).

The Investigators will hold the subjects' current background medical regimen constant from Screening through the end of the study (Week 24, Visit 9), unless there is a compelling emergent medical need to make medication adjustments, the subject discontinues the study because criteria for Treatment Failure are met as defined in Section 3.3.3 (after End of Study visit assessments are complete), or adverse effects due to other components of the subject's therapy become untenable; in such cases the Medical Monitor must be contacted.

Week 21 (Visit 8) is the time of the last investigational product (IP) maintenance dosage. Week 24 (Visit 9) will constitute the primary endpoint time point for analysis because this timing allows an opportunity to assess the effect of the final IP infusion made at Week 21 (Visit 8). Week 24 (Visit 9) will serve as the final End of Study Visit.

A schematic of the overall study design and essential activities is shown in Figure 3-1. The Schedule of Study Procedures is provided in Appendix 1. Tools for assessing MG are provided in Appendix 2 to Appendix 6, and specific safety monitoring in Appendix 7 and Appendix 8.

Worsening of MG symptoms

The intent is that subjects will receive their original randomized treatment assignment of IP through the entire Treatment Period (i.e., through Week 21 [Visit 8]). Subjects will remain on IP until at least Week 9 (Visit 4). No premature discontinuations on the basis of the *a priori*

defined Treatment Failure (Section 3.3.3) are allowed until the subject receives a minimum of 3 complete doses of IP, which includes the initial loading dose and the first two maintenance doses irrespective of the QMG scores measured at Week 3 and Week 6 (Visit 2 and Visit 3), and the subject is assessed at Week 9 (Visit 4) with regard to continuation of worsening.

For example, a subject with a QMG increase of 4 points or more at Week 3 (Visit 2) or Week 6 (Visit 3) must have confirmation of this QMG increase at the next, subsequent scheduled visit (i.e., Week 6 [Visit 3] and Week 9 [Visit 4], respectively). *However, subjects will not be removed from study until at or after Week 9 for reasons of QMG score continuing to meet the criteria for Treatment Failure (Section 3.3.3) in order to allow time for the investigational medicinal product to potentially produce a beneficial effect.*

At Week 9 (Visit 4) through Week 21 (Visit 8), if the subject suffers a worsening of his/her MG symptoms with an increase in QMG of 4 points or more, as defined in Section 3.3.3 "**Definition of Treatment Failure Due to MG Worsening**", *and this worsening (increase in QMG of 4 points or more) is confirmed at the next scheduled consecutive visit,* the subject will be discontinued from the study.

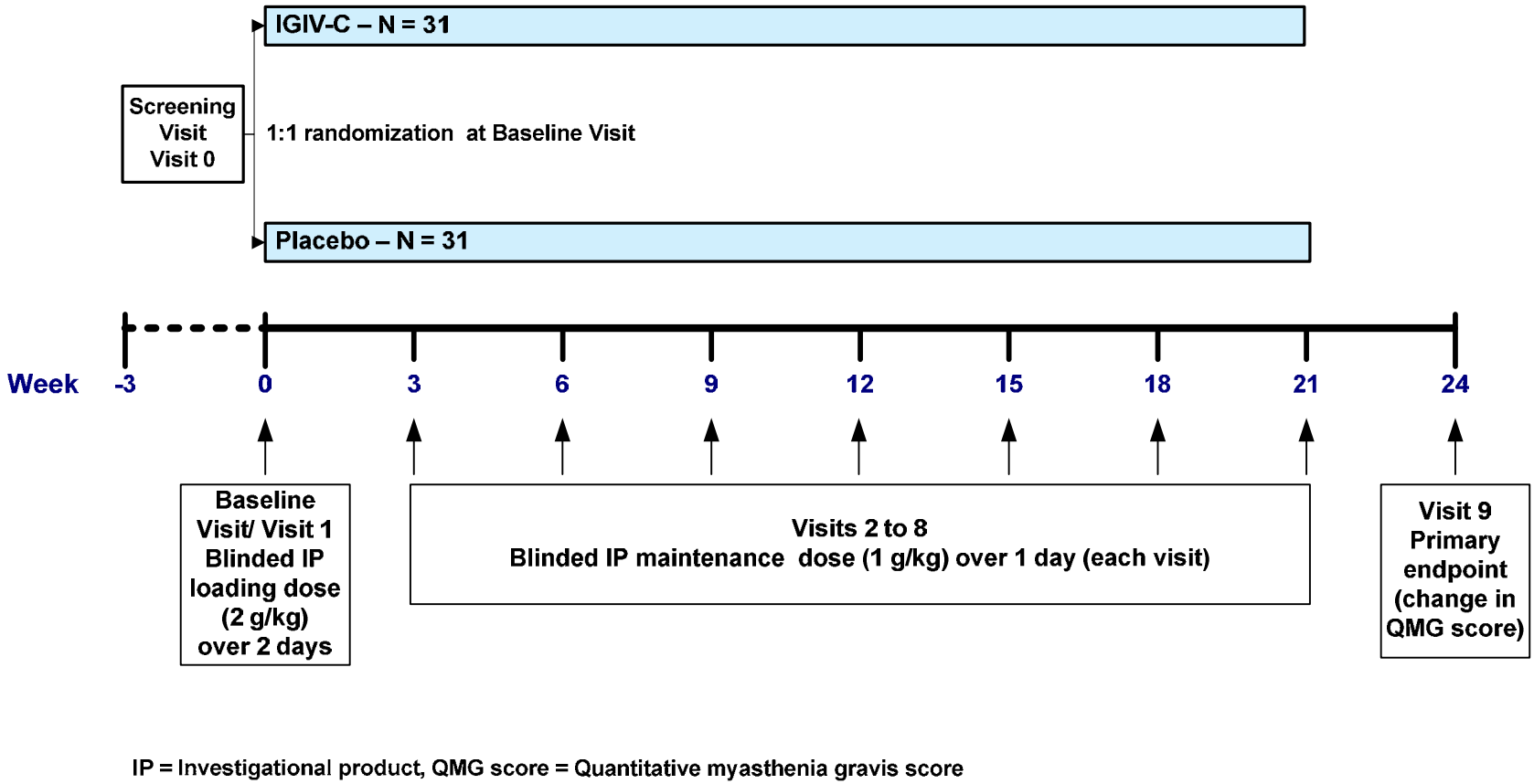


Figure 3-1 Overall Study Schema

3.2 Selection of Study Population

Eligible participants for this study will include adult subjects with a confirmed diagnosis of generalized MG who are receiving standard of care MG treatment, but continue to have symptoms of MG as demonstrated by a QMG ≥ 10 points. **There is a minimum time interval prior to Screening during which no change in dosage is allowed for MG medications predicated on medication class as delineated below (Inclusion #6). Following Screening, the subject's standard of care background regimen must not change in terms of medications used or dosage**. The only exception would be an urgent medical need.

3.2.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Male or female, ages 18 to 85 years
2. Anti-AChR antibody positive
3. Confirmed diagnosis of generalized MG. Historically, subjects may have previously had the Myasthenia Gravis Foundation of America (MGFA) Class II, III, IV, or V.
4. MGFA classification of Class II, III, or IVa inclusive at Screening.
5. QMG score ≥ 10 at Screening. *Note: Subjects who only have a history of ocular MG may not enroll.*
6. Receiving standard of care MG treatment at a stable dose consisting of any one of the following for the time intervals delineated below (*time intervals apply to medications and maintenance of stable dose level*):
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and no immunosuppressants
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or *only one of the following*:
        - Prednisone (up to 60 mg/day or equivalent) for at least two months prior to Screening, or
        - Azathioprine for at least 6 months prior to Screening, or
        - Mycophenolate mofetil for at least 6 months prior to Screening, or
        - Methotrexate for at least 6 months prior to Screening, or
        - Cyclosporine or tacrolimus for at least 3 months prior to Screening
    - Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or prednisone (up to 60 mg/day or equivalent) for at least one month prior to Screening and *only one of the following*:
        - Azathioprine for at least 6 months prior to Screening, or
        - Mycophenolate mofetil for at least 6 months prior to Screening, or
        - Methotrexate for at least 6 months prior to Screening, or
        - Cyclosporine or tacrolimus for at least 3 months prior to Screening
7. Subjects must be willing and able to provide written informed consent.
8. Subjects must be willing to comply with all aspects of the clinical trial protocol.

3.2.2 Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study:

1. Have received cyclophosphamide or any other immunosuppressive agent apart from the ones allowed per inclusion criteria within the past 6 months
2. Any change in MG treatment regimen between Screening (Week -3, Visit 0) and Baseline (Week 0, Visit 1)
3. *Greater than* two (>2) point change in QMG score, increased or decreased, between Screening (Week -3, Visit 0) and Baseline (Week 0, Visit 1)
4. Any episode of myasthenic crisis in the one month prior to Screening
5. Evidence of malignancy within the past 5 years (non-melanoma skin cancer, carcinoma in situ of cervix is allowed) or thymoma potentially requiring surgical intervention during the course of the trial (intent to perform thymectomy)
6. Thymectomy within the preceding six months
7. Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months
8. Have received immune globulin (Ig) treatment given by IV, subcutaneous, or intramuscular route within the last 3 months
9. Current known hyperviscosity or hypercoagulable state
10. Currently receiving anti-coagulation therapy (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate, rivaroxaban, edoxaban, and apixaban], parenteral anticoagulants [e.g., fondaparinux]). Note that oral anti-platelet agents are allowed (e.g., aspirin, clopidogrel, ticlodipine)
11. Plasma exchange (PLEX) performed within the last 3 months
12. History of non-response to IVIg when used in maintenance therapy of the subject's MG, as judged by the Investigator
13. Any comorbid condition that in the opinion of the Investigator would put the subject at undue safety risk or compromise the ability of the subject to participate in the trial or the scientific integrity of the study
14. Inadequate venous access to support repeated intravenous infusions
15. History of anaphylactic reactions or severe reactions to any blood-derived product
16. History of intolerance to any component of the IP
17. Documented diagnosis of thrombotic complications to polyclonal IVIg therapy in the past
18. History of recent (within the last year) myocardial infarction or stroke
19. Uncontrolled congestive heart failure; embolism; or historically documented (within the last year) electrocardiogram (ECG) changes indicative of myocardial ischemia or atrial fibrillation
20. History of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the Screening/Week -3 (Visit 0)
21. Active psychiatric illness that interferes with compliance or communication with health care personnel
22. Females of child-bearing potential who are pregnant or have a positive serum pregnancy test (beta-human chorionic gonadotropin [β-HCG]-based assay)
23. Females who are breastfeeding

24. Females of child-bearing potential who are unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence*) throughout the study.

    * True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
25. Currently receiving, or having received within 1 month prior to the Screening/Week -3 (Visit 0), any investigational medicinal product or device. In the case of an investigational medicinal product trial, at least five half-lives (if known) must have elapsed prior to Screening.
26. Known Immunoglobulin A (IgA) deficiency and anti-IgA serum antibodies
27. Renal impairment (i.e., serum creatinine exceeds more than 1.5 times the upper limit of normal [ULN] for the expected normal range for the testing laboratory)
28. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory.
29. Hemoglobin (Hb) levels <9 g/dL
30. Any medical condition which makes the clinical trial participation unadvisable or which is likely to interfere with the evaluation of the study treatment and/or the satisfactory conduct of the clinical trial according to the Investigator's judgment. Any factor that in the opinion of the Investigator would compromise the ability of the subject to complete the trial.

3.3 Study Time Periods and Definitions

3.3.1 Investigational Product Treatment Period

Subjects will receive a total of 8 doses of IP, which includes one initial loading dose at the Baseline (Week 0) Visit (after Baseline assessments are complete) and 7 maintenance doses at Weeks 3 through 21 (Visits 2 through 8), inclusive.

3.3.2 Worsening of MG Symptoms

All subjects will remain in the study until at least Week 9 (Visit 4) is completed. No premature discontinuation of IP administration is to be made for reasons of Treatment Failure (defined in Section 3.3.3) until the subject receives at least a total of 3 complete doses of the IP, which includes the initial loading dose and the first two maintenance doses irrespective of the QMG scores measured at Week 3 and Week 6 (Visit 2 and Visit 3).

At Week 9 (Visit 4) through Week 21 (Visit 8), if the subject suffers a worsening of his/her MG symptoms defined as a QMG increase ≥ 4 points relative to Baseline (Week 0), *and this worsening (increase in QMG of 4 points or more) is confirmed at the next scheduled consecutive visit* the subject will discontinue from the study. The earliest withdrawal for Treatment Failure will be at Week 9 and would occur only if QMG score is increased by 4 points or more (relative to Baseline) at both Week 6 (Visit 3) and Week 9 (Visit 4).

3.3.3 Definition of Treatment Failure Due to MG Worsening

During the study, MG worsening will be defined as:

- QMG increase by ≥4 points relative to Baseline/Week 0

If a subject experiences worsening in QMG score fulfilling the criterion above at or after Week 9, *and this worsening (increase in QMG of 4 points or more) is confirmed at the next scheduled consecutive visit*, the subject will be considered a Treatment Failure and will be discontinued from the study (at completion of the visit where confirmation of worsening is demonstrated).

If a subject experiences worsening in QMG score fulfilling the criterion above at Week 3 (Visit 2) or Week 6 (Visit 3) and the QMG increase by ≥ 4 points relative to Baseline is confirmed at the next scheduled visit (i.e., confirmation at Week 6 [Visit 3] or Week 9 [Visit 4], respectively), *and this ≥ 4-point QMG worsening is maintained through Week 9 (Visit 4)* the subject will be considered a Treatment Failure.

A subject will not be discontinued from the study for reasons of Treatment Failure until the Week 9 Visit or later as described in Section 3.3.2.

3.3.4 Myasthenic Crisis

Myasthenic (or MG) crisis will be defined as an episode of worsening (as defined in Section 3.3.2) which requires hospitalization. Hospitalizations solely for socioeconomic reasons would not fulfill criteria for MG crisis. Also see Early Termination Visit and Section 3.11.

3.4 Treatments

3.4.1 Treatments to Be Administered

3.4.1.1 Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C)

Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified (IGIV-C) is the active IP for this study, which is a marketed product. IGIV-C glass vials may be supplied in the vial sizes of 10 mL, 25 mL, 50 mL, 100 mL, and 200 mL. Detailed information regarding IGIV-C can be found in the IGIV-C Investigator Brochure.

Administration of IP will be via the IV route, and will be administered in a double-blinded fashion. The unblinded pharmacist or designee will prepare the IP to maintain the blind for all parties during infusions and study assessments. Reference the Pharmacy Manual for additional details.

3.4.1.2 Placebo

Sterile 0.9% sodium chloride injection, USP (0.9% NaCl, USP) or equivalent will be used as placebo to maintain the blind.

3.4.1.3 Labeling of Investigational Products

Labeling will be according to the requirements of local law and legislation. Label text will be approved according to Grifols Therapeutics Inc. procedures, and a copy of the labels will be made available to the study site upon request.

3.4.1.4 Storage of Investigational Products

IP must be stored in a secure area accessible to the unblinded pharmacist or designee responsible for the preparation and dispensing of IP.

Active IP (IGIV-C) must be stored at temperatures of 2°C to 8°C (36°F to 46°F). Do not freeze. The unblinded pharmacist or designee is responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the unblinded study monitor. Reference the Pharmacy Manual for additional details.

3.4.1.5 Preparation of Investigational Products

The volume (i.e., total infusion dose administered) of IP to be prepared for each IV infusion will be individualized for each subject based on body weight, and the protocol specified loading dose of 2 g/kg divided on 2 consecutive days starting after the randomization at Baseline (Week 0), followed by maintenance doses of 1 g/kg administered over 1 day every three weeks until Week 21 (Visit 8). Infusion solution will be visually masked to maintain the blind.

Note that the loading dosage is divided over 2 days as standard infusion time; however, extensions up to 4 days are allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight). Similarly, the maintenance dosage is infused in 1 day as standard; however, extension is allowed for divided dosage over 2 days for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight).

Subjects randomized to receive placebo will receive 0.9% sodium chloride injection, USP or equivalent, visually masked and at a volume approximate to that required for the appropriate weight-based dose of IGIV-C in order to maintain blinding of the subject, caregivers, Investigator, and assessors. The IP will be prepared by the unblinded study site pharmacist or designee.

The unblinded pharmacist must inspect IGIV-C visually before preparing for administration to subjects. The solution must not be used if turbid or if it contains visible particles. Solution which has been frozen should not be used.

Reference the Pharmacy Manual for detailed IP preparation and administration instructions.

3.4.1.6 Accountability for Investigational Products

IP is to be used only for the study in accordance with the directions given in this protocol. The study pharmacist or designee is responsible for the distribution of the IP in accordance with directions given in the protocol and Pharmacy Manual.

The unblinded study pharmacist or designee is responsible for maintaining accurate records of the IP for his/her site. IP inventory/dispensing documentation verifying the receipt, dispensing, destruction or return must be maintained and kept current by the pharmacist. The inventory must be made available for inspection during the study by the unblinded monitor. IP supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IP destruction. Written documentation from Grifols or designee of any used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols Therapeutics Inc.

3.4.2 Rationale for Selection of Doses/Timing of Investigational Product in the Study

3.4.2.1 Selection of IGIV-C Dose and Dosing Interval in the Study

The optimal dose of IVIg for MG maintenance dosing is still unclear; however, recent studies have supported a loading dose of 2 g/kg administered in as little as two consecutive daily doses of 1 g/kg each with no increase in side effects as compared to the longer dosing period of 3 to 5 days (7, 9, 11, 32, 35). Maintenance dosage of IGIV-C in CIDP has been well tolerated at 1 g/kg administered over 1 to 2 days every three weeks and has regulatory approval for this indication/dosage in both North America and Europe.

Based on the above, subjects will receive a loading IGIV-C dose of 2 g/kg of body weight followed by maintenance dosages at 3-week intervals at a dose of 1 g/kg of body weight.

3.4.3 Method of Assigning Subjects to Treatment Groups

This is a randomized, double-blind, placebo-controlled study. Subjects will be randomized in a 1:1 ratio via Interactive Web Response System (IWRS) into IGIV-C treatment group and Placebo treatment group to receive either IGIV-C or matching placebo every three weeks in a double-blind fashion via IV administration. Each subject's IGIV-C dose will be individualized based on the subject's body weight and the protocol specified loading dose of 2 g/kg over 2 consecutive days and maintenance dosage of 1 g/kg over 1 day every three weeks through Week 21 (Visit 8). Therefore, each subject's infusion volume and duration of the infusion will vary from subject to subject, and must be carefully prepared by the unblinded pharmacist who will prepare IP consisting of either IGIV-C or an equivalent volume of 0.9% sodium chloride injection. Note that for the loading dosage, 2 days is standard (2-4 days is allowed as an extension for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]). Similarly, the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).

3.4.3.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor) followed consecutively with a unique number for each subject (4 digits, including leading zeros). For example, if the Investigator's center number is 301, subject number will be 3010001, 3010002, 3010003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

3.4.3.2 Blinding

This is a double-blind, placebo-controlled study. Placebo infusion will be visually indistinguishable from IGIV-C to maintain blinding. The unblinded pharmacist or designee will prepare all IP infusion bags with no visual differences between IGIV-C and placebo and cover with a non-transparent blinding bag cover.

Additionally, results of the central laboratory analysis of immunoglobulin G (IgG) levels will not be shared with the Investigator, blinded study staff, clinical research organization (CRO) or blinded Sponsor personnel involved with study conduct.

3.4.3.3 Administration and Timing of Investigational Products for Each Subject

IGIV-C (or placebo) will be administered as a loading dose of 2 g/kg divided over 2 consecutive days starting after randomization at Week 0 (Visit 1), followed by maintenance doses of 1 g/kg over 1 day every three weeks through Week 21 (Visit 8). Note that for the loading dosage, 2 days are standard (2-4 days are allowed as an extension for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]). Similarly, the maintenance dosage is administered over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]). Infusion administration, including infusion rate, is provided in the Pharmacy Manual.

In the event that the subject is not able to tolerate the set infusion rate, the rate may be decreased for better tolerability. The initial and final infusion rates will be recorded.

3.4.3.4 Preparation and Handling of Investigational Products

Blinded IP (IGIV-C or placebo) should be infused using a separate line by itself, without mixing with other IV fluids or medications that the subject might be receiving. The IP infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride injection. **Do not flush with heparin**.

3.4.3.5 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the IP dose as prepared by the pharmacist or designee must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

All IV infusions will be administered at the study site under the supervision of the treating Investigator or designee.

3.5 Prior and Concomitant Therapy

Concomitant medications must be recorded in the eCRF, including the trade or generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency).

Diphenhydramine, acetaminophen/ibuprofen, and non-steroidal anti-inflammatory drugs are allowed during the trial as pre-medications for study drug infusions. These and any other concomitant medication taken during the study period must be documented in the subject's medical records and the eCRF.

3.5.1 Prohibited Medications Prior to Study Participation

The following medications are prohibited for the specified timeframe prior to study participation.

- Immune globulin treatment given by IV, subcutaneous or intramuscular route within the last 3 months
- Rituximab, belimumab, eculizumab, or use of any monoclonal antibody for immunomodulation within the past 12 months
- Cyclophosphamide or immunosuppressive agents other than those allowed per inclusion criteria within the past 6 months
- PLEX performed within the last 2 months
- Anti-coagulation therapy at the time of Screening (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate, rivaroxaban, edoxaban, and apixaban], parenteral anticoagulants [e.g., fondaparinux]). Note that oral anti-platelet agents are allowed (e.g., aspirin, clopidogrel, ticlodipine)
- Any investigational drugs within 30 days of Screening (or five half-lives if known)

3.5.2 Prohibited Concomitant Medications during the Study

Use of the following medications is prohibited during the study or during the specified timeframe:

- Any IgG therapy other than IGIV-C provided for this study
- Any investigational drugs which are not part of this study
- Introduction of new immunosuppressant(s) or other drugs for treatment of MG that the subject was not already taking at Screening

- Rituximab, belimumab, eculizumab, use of any monoclonal antibody for immunomodulation or any other investigational agent for treatment of MG
- Live viral vaccines (e.g., measles, mumps, rubella)
- PLEX

3.5.3 Restricted Concomitant Medications during the Study

This section describes medications that are restricted but not prohibited during the study participation:

- Any dose change in concomitant immunosuppressant therapy, corticosteroids, or standard of care MG treatment medications during the study is not allowed unless there is a real medical necessity for safety reasons in the Investigator's opinion.
- Any change in acetylcholinesterase inhibitor (e.g., Mestinon® [pyridostigmine]) dose during the study is not allowed unless there is a real medical necessity for safety reasons in the Investigator's opinion.

In case of a compelling, emergent medical need to make MG medication adjustments during study, the Medical Monitor must be contacted.

Use of medications known to potentially worsen MG is discouraged (unless medically required) including telithromycin, fluoroquinolones (e.g., Ciprofloxacin and Levofloxacin), azithromycin, aminoglycoside antibiotics, botulinum toxin, quinine, quinidine, procainamide, D-penicillamine, and β-blockers. For patients entering study already on β-blockers, continued use of β-blockers is allowed if medically needed; *de novo* use (initiation of β-blocker treatment for the first time) while on study is discouraged.

3.6 Efficacy Study Variables

3.6.1 Primary Variable

The primary endpoint is improvement in MG symptoms as measured by the mean change in QMG score from Baseline (Week 0) to Week 24 as compared to placebo.

3.6.2 Secondary Variables

Secondary efficacy variables assessed in this study are:

- Percentage of subjects who experience a clinical improvement assessed by QMG score from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in QMG score
- Percentage of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in the MG Composite
- Percentage of subjects who experience a clinical improvement assessed by MG-ADL from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 2-point decrease in MG-ADL

3.6.3 Exploratory Variables

The exploratory objectives for this study are to evaluate the effect of IGIV-C on:

- Percentage of subjects who experience a clinical improvement in QMG score (defined above) at Weeks 6, 9, 12, 15, 18, and 21
- Time to first clinical improvement in QMG score (at least a 3-point decrease)
- Time to Treatment Failure based on QMG definition (Section 3.3.3)
- Change from Baseline (Week 0) in QMG score to Weeks 6, 9, 12, 15, 18, and 21
- Percentage of subjects who experience a clinical improvement in the MG Composite (defined above) to Weeks 6, 9, 12, 15, 18, and 21
- Change from Baseline (Week 0) in MG Composite to Weeks 6, 9, 12, 15, 18, 21, and 24
- Percentage of subjects who experience a clinical improvement in MG-ADL (defined above) to Weeks 9 and 15
- Change from Baseline (Week 0) in MG-ADL to Weeks 9, 15, and 24
- Change from Baseline in the MG-QOL 15 to Weeks 9, 15, and 24
- MGFA postinterventional change in status at Week 24 relative to Baseline

3.6.4 Quantitative Myasthenia Gravis Score (QMG)

The MGFA, Inc. Task Force on Clinical Research Standards recognizes the utility of the QMG score in prospective clinical trials in MG (34) complemented by additional tools such as the MG Composite. The QMG is easy to administer by clinical evaluators and/or physicians in approximately 30 minutes with minimal equipment to measure spirometry and muscle strength testing. An average 3-point improvement in QMG score indicates clinically meaningful improvement in terms of minimal clinically important difference and precedent set by endpoints in other MG studies (37, 38). Subjects receiving cholinesterase inhibitors will be instructed not to take medication 12 hours prior to QMG.

QMG Test Items are listed in Appendix 3.

3.6.5 MG Composite Scale

The MG Composite scale takes less than five minutes to complete, and is made up of three ocular, three bulbar, one respiratory, one neck, and two limb items (39, 40).

The task force on MG study design of the medical scientific advisory board of the MGFA recommends using the MG Composite as the quantitative measure for determining improvement and worsening for subjects with generalized MG disease. A 3-point improvement in MG Composite score reliably indicates clinical improvement. A 3-point improvement in the MG Composite score also appears to be meaningful to the patient (41).

The MG Composite items are listed in Appendix 4.

3.6.6 MG-ADL

The MG-ADL is an 8-item, patient reported (or Investigator administered) questionnaire that is completed to assess the symptoms and activities in MG (42-44). A 2-point improvement in the MG-ADL indicates clinical improvement (42).

The questionnaire and scoring is provided in Appendix 5.

3.6.7 15-item MG Quality-of-Life Instrument (MG-QOL 15)

MG symptoms significantly impact quality of life (QOL) particularly in aspects of physical functioning. The 15 items on the MG-QOL 15 are derived from mobility, symptoms, general contentment, and emotional well-being categories assessed by the patient over the past few weeks. All individual items related to degree of disease-related impairment are rated on a Likert scale ranging from "not at all" (score 0 points) to "very much" (score 4 points) with higher scores indicating greater negative impact (worse disease) (45-47).

The MG-QOL 15 and scoring are provided in Appendix 6.

3.6.8 MGFA Postinterventional Change in Status

An MGFA postinterventional change in status relative to Baseline will be evaluated at Week 24 (Visit 9) wherein the Investigator will classify the patient as: (I) Improved, defined as a substantial decrease in pretreatment clinical manifestations of MG, QMG decrease ≥ 3 points; (U) Unchanged, defined as no substantial change in pretreatment clinical manifestations of MG; (W) Worse, defined as a substantial increase in pretreatment clinical manifestations of MG, QMG increase ≥ 3 points.

3.7 Safety Study Variables

The following safety variables will be assessed in this study:

- Adverse events (AEs), suspected adverse drug reactions (Suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs (including myasthenic crisis)
- Vital Signs (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]); during infusions vital signs will be carefully monitored.
- Physical examinations: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Blood chemistry and Hematology
- Thromboembolic events (TEs) and hemolysis events

3.7.1 Thromboembolic Events Risk

During the clinical trial, TE risk will be determined by the Investigator or study staff using the measurement of D-dimer blood levels, the Wells clinical prediction rule for both deep

venous thrombosis (DVT) and for pulmonary embolism (PE), and evaluation of clinical signs and symptoms of TEs (such as pain, dyspnea, discoloration [paleness or redness] in lower extremities). Monitoring will be performed at Screening, Baseline/Week 0 (Visit 1) prior to infusion, Visit 1 after the first loading infusion, at the time when the last loading infusion is complete, and at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6), after the completion of each maintenance dosage.

Procedures for the monitoring of TE risk are provided in Appendix 7.

3.7.2 Hemolysis

Blood assessments including whole blood Hb, serum free Hb, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), red blood count (RBC), hematocrit, total (TBL) and indirect bilirubin, and blood smear, and urinalysis including urinary sediment and hemoglobinuria will be conducted for hemolysis detection at Baseline (Week 0 [Visit1], prior to infusion), Week 0/Visit 1 (after the first loading infusion), at the time when the last loading dose infusion is complete, and at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6), after the completion of each maintenance dosage. In addition, clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) will be assessed at Baseline/Week 0 (Visit 1) and the time points specified above. Hemolysis laboratory assessments will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post maintenance infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).

Procedures for hemolysis detection are provided in Appendix 8.

3.8 Assessments

3.8.1 Assessment Periods

The study consists of a three-week Screening period during which assessments are performed to determine eligibility. Eligible subjects will have Baseline assessments performed, and be randomized at Week 0 (Visit 1). At this time, an initial loading dose of blinded IP will be administered at a dose of 2 g/kg divided on 2 consecutive days starting after randomization. Maintenance infusions of blinded IP will be given at doses of 1g/kg over 1 day every three weeks through Week 21 (Visit 8). Note that the loading dosage is divided over 2 days as standard infusion time; however, extensions to 4 days are allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight). Similarly the maintenance dosage is infused in 1 day as standard; however, extensions for divided dosage over 2 days are allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day (corresponding to 80 kg body weight).

3.8.2 Observations and Measurements

During the course of the study, subjects will receive scheduled general physical examinations, neurological assessments of strength and endurance, symptom questionnaires, quality of life assessments, and laboratory evaluations.

The following is a description of the procedures/assessments to take place at each study visit. Each MG assessment should be performed by the same clinical staff member whenever possible. See the Schedule of Study Procedures in Appendix 1 for a summary of study visits and the procedures conducted at each visit.

3.8.2.1 Overview of Screening, Treatment and Post infusion Follow-up Phases

All subjects will start their participation in the study upon the signing of the informed consent form (ICF). If applicable, a legally authorized representative may provide informed consent on behalf of the subject (see Section 7.4).

Subjects deemed eligible based on screening evaluations will complete the Baseline assessments, thereafter initiating treatment. Subjects will continue with assessments for 24 weeks, with scheduled assessments at Week 0 (Visit 1) (Baseline, post-Baseline loading infusion over 2 days), followed by assessments and maintenance dosages every 3 weeks through Week 24 (Visit 9). *Visits/procedures and assessments should be scheduled at the protocol specified study day ± 3 days*.

3.8.2.2 Screening: Week -3 (Visit 0)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Screening/Week -3 (Visit 0) to assure accurate assessment of the QMG. The following procedures and assessments will be conducted during the Screening/Week -3 (Visit 0) (Note: *Screening is considered Visit 0; assessments are to be conducted within 3 weeks of Baseline/Week 0 [Visit 1]*):

- Informed consent prior to the initiation of Screening procedures
- Inclusion/exclusion criteria review
- Medical history including demographics and prior/concomitant diseases
- Full physical exam (excluding breast and genitourinary areas)
- Height
- Weight (Screening will be used to calculate IP infusion dose for Visits 1-3)
- Vital signs including temperature (T), respiration rate (RR), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)
- Laboratory assessments (see Section 3.8.3)
  - Blood
    - Serum Pregnancy Test (β-HCG) (women of child-bearing potential only; results must be negative for the subject to continue in the study)
    - Chemistry
    - Hematology
    - D-dimer
    - AChR antibodies (See Section 3.8.3.4)
- QMG score
- MG Composite Score
- MGFA Clinical Classification
- Thromboembolic events risk monitoring assessment
- AEs with onset after informed consent is signed

- Prior and concomitant medications

3.8.2.3 Baseline, Randomization, and Loading Dose Infusion: Week 0 (Visit 1)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Baseline/Week 0 (Visit 1) to assure accurate assessment of the QMG.
All Screening laboratory results and assessments must be available and all inclusion and exclusion criteria must have been satisfied prior to initiating treatment. For eligible subjects, following completion of all Baseline assessments, IGIV-C (or placebo) will be administered as a loading dose of 2 g/kg given in divided doses on two consecutive days.

The listed procedures and assessments will be conducted at Baseline/Week 0 (Visit 1). Baseline assessments will be immediately followed by randomization and initiation of IP loading infusions.

Baseline, Prior to Randomization

- Inclusion/Exclusion criteria review
- Physical examination (excluding breast and genitourinary areas)
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.8.3):
  - Urine
    - Urine sediment and measuring of hemoglobinuria/hematuria
    - Urine pregnancy test for women of childbearing potential only (to be eligible urine pregnancy test must be negative)
  - Blood
    - D-dimer
    - Chemistry
    - Hematology
    - Whole blood Hb, RBC, hematocrit (from hematology specimen, see Section 3.8.3), ARC, blood smear for erythrocyte morphology, serum free Hb, haptoglobin, LDH, DAT, TBL (TBL from chemistry specimen, see Section 3.8.3) and indirect bilirubin (Hemolysis assessment Appendix 8)
    - IgG levels
    - Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies
    - Retain samples for virus safety testing as detailed in Section 3.8.3.3 and Table 3-1 (These retention samples will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete.)
- QMG score (to be eligible QMG score must be within ≤ 2 points of Screening value [a 3-point change is exclusionary])
- MG Composite
- MG-QOL 15
- MG-ADL

- MGFA Clinical Classification
- Thromboembolic events risk monitoring assessment (Appendix 7) (**prior to IP infusion**)
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Prior and concomitant medications

RANDOMIZATION

- Randomization will occur via IWRS once all Baseline assessments are performed and eligibility is confirmed. A randomization number will be assigned to each subject based on a 1:1 randomization schedule.

POST-BASELINE/POST-RANDOMIZATION LOADING DOSE INFUSION

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and the Pharmacy Manual
- Administer the loading infusion dosage (blinded active or placebo) of 2 g/kg divided over 2 days (per Pharmacy Manual). Note that for the loading dosage 2 days is standard (2-4 days is allowed as an extension for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).
- During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.
- Hemolysis evaluation (laboratory parameters: Hb, hematocrit, RBC, blood smear, serum free-Hb, haptoglobin, LDH, DAT, ARC, total and direct/indirect bilirubin; urine for urinary sediment and hemoglobinuria/hematuria), and Thromboembolism evaluation (Wells score and D-dimer) will be performed at the end of the first infusion of the loading dose, and at the time when last loading infusion is complete. Appendix 7 and Appendix 8 provide details.
- For each infusion, documentation of total infusion volume prepared (as received from pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medications
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post loading dose infusion

3.8.2.4 Investigational Product Maintenance Phase: Weeks 3 and 6 (Visits 2 and 3)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Weeks 3 and 6 (Visits 2 and 3) to assure accurate assessment of the QMG.
At Weeks 3 and 6 (Visits 2 and 3), the following will be performed:

- QMG score to be assessed pre-infusion

- MG Composite to be assessed pre-infusion
- Vital signs including T, RR, HR, SBP, and DBP (pre-infusion)
- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual
  - Note: Screening subject weight is used for IP dose calculations for Visits 1 to 3.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note that the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).
- During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.
- Hemolysis evaluation (laboratory parameters: Hb, hematocrit, RBC, blood smear, serum free-Hb, haptoglobin, LDH, DAT, ARC, total and direct/indirect bilirubin; urine for urinary sediment and hemoglobinuria/hematuria), and Thromboembolism evaluation (Wells score and D-dimer) will be performed after each maintenance infusion dosage is entirely completed. Appendix 7 and Appendix 8 provide details.
- For each infusion, documentation of total infusion volume prepared (as received from pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medication
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion

3.8.2.5 Investigational Product Maintenance Phase: Week 9 (Visit 4)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 9 (Visit 4) to assure accurate assessment of the QMG. At Week 9 (Visit 4), the following will be performed:

Assessments to be performed pre-infusion:

- Full physical examination (excluding breast and genitourinary areas)
- Weight (to be used to calculate IP infusion dosage for the scheduled visit and subsequent IP infusions until the next scheduled weight measurement)
  - Note: Subject weight collected at Visit 4 is used for IP dose calculations for Visit 4 and Visit 5.
- Vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments drawn pre-infusion (see Section 3.8.3)
  - Hematology
  - Chemistry

  - Blood for IgG (trough) (data will be assessed centrally and not provided to centers/Sponsor until the end of the study due to the potential for unblinding)
  - Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies
- QMG score to be assessed pre-infusion
- MG Composite to be assessed pre-infusion
- MG-QOL 15 to be assessed pre-infusion
- MG-ADL to be assessed pre-infusion

IP Infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual
  - Note: Subject weight this visit is used for IP dose calculation.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note that the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).
- During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.
- For each infusion, documentation of total infusion volume prepared (as received from pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medications

3.8.2.6 Investigational Product Maintenance Phase: Weeks 12, 18, and 21 (Visits 5, 7, and 8)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 12, 18, and 21 (Visits 5, 7, and 8) to assure accurate assessment of the QMG. At Weeks 12, 18, and 21 (Visits 5, 7, and 8), the following will be performed:

- QMG score to be assessed pre-infusion
- MG Composite to be assessed pre-infusion
- Vital signs including T, RR, HR, SBP, and DBP (pre-infusion)
- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual
  - Note: The subject weight measured at Visit 4 is used for IP dose calculations for Visit 5, and the weight measured at Visit 6 is used for IP dose calculations for Visits 6-8.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note that the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher

weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).
- During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.
- For each infusion, documentation of total infusion volume prepared (as received from pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medications

3.8.2.7 Investigational Product Maintenance Phase: Week 15 (Visit 6)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 15 (Visit 6) to assure accurate assessment of the QMG. At Week 15 (Visit 6), the following will be performed:

Assessments to be performed pre-infusion (except as specified):

- Full physical examination (excluding breast and genitourinary areas)
- Weight (to be used to calculate IP infusion dosage for the scheduled visit and subsequent IP infusions)
  - Note: Subject weight collected at Visit 6 is used for IP dose calculations for Visit 7 and Visit 8.
- Full vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments drawn pre-infusion (see Section 3.8.3)
  - Hematology
  - Chemistry
  - Blood for IgG (trough) (data will be assessed centrally and not provided to centers/Sponsor until the end of the study due to the potential for unblinding)
- Hemolysis evaluation (laboratory parameters: Hb, hematocrit, RBC, blood smear, serum free-Hb, haptoglobin, LDH, DAT, ARC, total and direct/indirect bilirubin; urine for urinary sediment and hemoglobinuria/hematuria), and Thromboembolism evaluation (Wells score and D-dimer) will be performed when last maintenance infusion is complete. Appendix 7 and Appendix 8 provide details.
- QMG score to be assessed pre-infusion
- MG Composite to be assessed pre-infusion
- MG-QOL 15 to be assessed pre-infusion
- MG-ADL to be assessed pre-infusion

IP Infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual

  - Note: The subject weight measured at Visit 6 is used for IP dose calculations for Visit 6, Visit 7, and Visit 8.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note that the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]).
- During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.
- For each infusion, documentation of total infusion volume prepared (as received from pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medications
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion

3.8.2.8 End of Study: Week 24 (Visit 9)

Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 24 (Visit 9) to assure accurate assessment of the QMG. At Week 24 (Visit 9), the following will be performed:

- Full physical examination (excluding breast and genitourinary areas)
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.8.3):
  - Chemistry
  - Hematology
  - Blood for IgG (trough) (data will be assessed centrally and not provided to centers/Sponsor until the end of the study due to the potential for unblinding)
  - Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies
  - Serum Pregnancy Test (qualitative β-HCG) (women of child-bearing potential only)
- QMG score
- MG Composite
- MG-QOL 15
- MG-ADL
- MGFA postinterventional change in status relative to Baseline at Week 24 (Investigator classification of subject status as improved, unchanged, or worse)
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia etc])
- Concomitant medications

3.8.2.9 Early Termination Visit

The Early Termination visit will consist of the same assessments as Week 24 (Visit 9) except for quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies which are not required.

If a subject discontinues at any point during the study after receiving IP, the subject will be requested to return to the clinic to have the procedures and assessments outlined in Appendix 1 conducted as soon as practical following the decision to withdraw (at least within 14 days after the termination date) if the subject is willing. *Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Early Termination Visit to assure accurate assessment of the QMG.*

3.8.3 Description of Laboratory Tests and Procedures

Table 3-1 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Hematology [a]	Hb, hematocrit, platelets, RBC count, including RBC morphology, white blood cell count with differential	Central
Chemistry [a]	Creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBL)	Central
Hemolysis	Whole blood Hb, RBC, hematocrit, serum free Hb, haptoglobin, LDH, DAT, ARC, TBL, and indirect bilirubin, and blood smear	Central
	Urine sediment and measuring of hemoglobinuria	
Thromboembolic events risk	D-dimer	Central
AChR [a]	Acetylcholine Receptor Antibody at Screening (diagnostic - defining MG); Baseline, Week 9, and Week 24 quantitative/semi-quantitative measurement of binding, blocking, modulating AChR antibody (Please see Section 3.8.3.4 for details)	Central
IgG levels	Immunoglobulin G levels	Central
Serum pregnancy [a]	Qualitative serum β human chorionic gonadotropin (β-HCG) for females of child-bearing potential. Results must be negative to continue in the study.	Central
Viral Nucleic Acid Amplification Technology (NAT) Testing	Retains [b]: Hepatitis A virus (HAV) ribonucleic acid (RNA), Hepatitis B virus (HBV) DNA, Hepatitis C virus (HCV) RNA, Human immunodeficiency virus (HIV) RNA, parvovirus B19 (B19V) deoxyribonucleic acid (DNA)	Central
Viral Serology Testing	Retains [b]: HAV antibody differential (Immunoglobulin M [IgM]/IgG), HBV core antibody differential (IgM/IgG), HCV antibody, HIV-1/-2 + Group O antibody, B19V antibody differential (IgM/IgG)	Central

[a] Samples collected for laboratory analyses that are non-analyzable due to any factor (*i.e.*, lost, quantity not sufficient, laboratory error) need to be recollected by contacting the subject and arranging for re-sampling.

[b] Blood samples for viral NAT and viral serology testing will be collected at Baseline/Week 0 (Visit 1) prior to randomization but will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. Additional blood samples for viral NAT and viral serology may be collected and tested during the study *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV or parvovirus B19 infection while participating in the study.

3.8.3.1 Thromboembolic Events Risk Testing

Measurement of D-dimer blood levels and thromboembolic events risk testing will be performed at Screening, Baseline (Week 0 prior to randomization), at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of maintenance infusion dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6). Appendix 7 provides details.

3.8.3.2 Hemolysis Testing

Laboratory assessments (urine, whole blood Hb, serum free Hb, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL and indirect bilirubin, and blood smear) and urine assessments (for urinary sediment and hemoglobinuria, hematuria) will be conducted at Baseline (Week 0 prior to randomization), at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of maintenance infusion dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6). Hemolysis laboratory assessments will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post maintenance infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6). Appendix 8 provides details.

3.8.3.3 Virus Safety Testing

Blood samples for virus safety (viral NAT and viral serology) testing will be collected at Baseline/Week 0 (Visit 1) prior to randomization, but will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. Additional blood samples for viral NAT and viral serology may be collected and tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study.

3.8.3.4 AChR Antibody Testing

AChR antibody levels will be measured in all subjects at Screening and must be present for the subject to be eligible to participate in the study. Additionally, quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies will be measured at Baseline, Week 9 (Visit 4), and at the End of Study Visit.

Baseline and Week 9 (Visit 4) and End of Study Visit (Week 24) results will not be shared during study conduct with the investigator, blinded study staff, CRO, or blinded Sponsor personnel involved with study conduct. All measurements will be conducted using qualified

assays. Specific details regarding all aspects of sample collection and processing can be found in the central laboratory Study Reference Manual.

3.8.3.5 IgG Concentration Measurements

Serum total IgG concentrations will be measured in all subjects at specified visits. Results of the central laboratory analysis of IgG levels will not be shared with the Investigator, blinded study staff, CRO or blinded Sponsor personnel involved with study conduct. All measurements will be conducted using qualified assays. Specific details regarding all aspects of sample collection and processing can be found in the Study Reference Manual at each site.

3.9 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment at the Baseline Visit. Subjects who fail to meet eligibility criteria during Screening evaluations will be considered screen failures. Subjects may re-screen for the study if the reason for screen failure is no longer relevant; a new informed consent form must be signed for re-screening.

3.10 Removal of Subjects

Removal from Study: Subjects who discontinue the study prematurely will receive an Early Termination Visit with same assessments as Week 24 (Visit 9) in Appendix 1 with the exception of quantitative/semi-quantitative binding, blocking, and modulating acetylcholine receptor antibodies which are not required.

Subjects may withdraw or be withdrawn from the study for the following reasons:

1. At their own request or at the request of their legally acceptable representative.
2. If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
3. At the specific request of the Sponsor.

Also, subjects must be withdrawn for the following reasons:

- Subjects not meeting the inclusion and exclusion criteria prior to the Baseline (Week 0) Visit based on laboratory results
- Subjects with an occurrence of a concomitant disease or any medical condition which, either because of its severity or duration or necessary change in treatment, contravenes the condition of the study or puts the patient at unnecessary risk or harm
- Subjects with an occurrence of an AE which in the opinion of the Investigator and/or subject requires termination of treatment
- QMG increase by ≥ 4 points relative to Baseline (Week 0) occurring at or after Week 9 (Visit 4) *with worsening (increase in QMG of 4 points or more) confirmed at the next scheduled consecutive visit* indicating worsening MG (Section 3.3.3)
- MG crisis (defined in Section 3.3.4)
- Subjects who are noncompliant with the protocol per the Investigator’s discretion

- Pregnancy

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's records.

3.11 Follow-up of Subjects Withdrawn from Study

Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Early Termination Visit procedures (see Section 3.8.2.9) as soon as practical following decision to withdraw (at least within 14 days after the termination date) if the subject is willing.

3.12 Premature Termination of Study/Closure of Center

The Sponsor, Institutional Review Board/Ethics Committee (IRB/EC), and/or regulatory authorities have the right to close this study or a study center, and the Investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator will retain all other documents until notification given by the Sponsor for destruction.

A study center can be closed for the following reasons:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP)

4 ADVERSE EVENTS

4.1 Warnings/Precautions

For complete IGIV-C safety information, refer to the current IGIV-C IB. It is possible that unknown, unforeseen adverse reactions may occur in subjects with MG exacerbations.

4.1.1 Interaction/Overdose

In an overdose situation, cardiovascular overload would be the primary concern and should be managed accordingly. Since up to 2 g/kg have been tolerated by many subjects, and the maximum g/kg dose allowed at any single infusion day in this study is 1 g/kg, no cardiovascular events are expected.

4.1.2 Live Viral Vaccines

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella. Inform subjects that blinded

IGIV-C/placebo can interfere with their immune response to live viral vaccines. Inform subjects to notify their healthcare professional/immunizing physician of recent participation in a clinical study including blinded study drug (IGIV-C or placebo). The Investigator must consider any potential interaction prior to receiving vaccinations so that appropriate measures may be taken.

4.2 Specification of Safety Parameters

Aspects of clinical safety will be evaluated in this clinical trial.

Safety endpoints will include:

- AEs, SAEs and suspected ADRs
- Vital signs
- Physical examinations
- Blood chemistry and hematology
- Thromboembolic events
- Hemolysis

4.3 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Safety will be assessed throughout the clinical trial for all individuals who have received at least one infusion of the IP.

4.3.1 Adverse Events

AEs (includes suspected ADRs) occurring at any time between signature of the subject's ICF and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's eCRF entry.

It is the Investigator's responsibility to ensure that all AEs are appropriately recorded.

AEs will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

4.3.2 Vital Signs

During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.

Clinically relevant changes in vital signs during infusions of IP will be reported as AEs temporally associated to the infusion. Clinical relevance will be based on the Investigator's criteria.

In addition, vital signs will be assessed at scheduled visits. Abnormal vital signs judged as clinically relevant by the Investigator in the context of the patient's medical history will be considered AEs.

4.3.3 Physical Examination

Physical exams will be registered as normal or abnormal, according to the physician's judgment or study staff's criteria and findings will be recorded. Abnormal physical findings judged as clinically relevant by the Investigator in the context of the patient's medical history will be considered AEs.

4.3.4 Blood Chemistry and Hematological Parameters

All clinical laboratory data for renal (creatinine, BUN), hepatic (ALT, AST, ALP and TBL) and hematological parameters (complete blood count [CBC] including differential leukocyte count) will be listed for each clinical trial subject (see Section 3.8.3). Clinical laboratory results and the change from Baseline values at Week 24 will be summarized by treatment group using summary statistics. Shift tables will be provided to summarize values that fall outside the normal ranges.

The Investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically relevant or not according to his/her criteria in the context of the patient's medical history.

Laboratory results out of the normal range judged by the Investigator as clinically relevant in the context of the patient's medical history/underlying comorbid conditions will be considered AEs.

4.3.5 Thromboembolic Event Risk

Procedures for the monitoring of TE risk are provided in Appendix 7. Pulmonary embolism and deep venous thrombosis will be considered AEs and/or SAEs if criteria for seriousness are met.

4.3.6 Hemolysis

Procedures for hemolysis detection are provided in Appendix 8. In the event that true hemolytic anemia develops, it will be considered an AE and/or an SAE depending on whether seriousness criteria are met. Hemolytic ARs are defined as temporally associated with the study drug within 7 days post infusion.

4.4 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Events and Intercurrent Illnesses

4.4.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily

have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any AE that occurs at any time between the signature of the ICF and last day of the subject's participation in the clinical trial must be reported and recorded on the AE eCRF entry.

4.4.2 Suspected Adverse Drug Reaction (ADR)/Adverse Reaction (AR)

All noxious and unintended responses to a medicinal product related to any dose should be considered suspected ADRs. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, that is, the relationship cannot be ruled out. In the framework of this study, a suspected ADR with a causal relationship of "definite" will be labeled as an AR; thus, ARs are a subset of suspected ADRs.

The Sponsor is responsible for assessing the suspected ADR expectedness during the clinical trial.

4.4.3 Causality of Adverse Event

The Investigator is required to provide a causality assessment for each AE reported to the Sponsor. The Sponsor will consider the Investigator's causality assessment. Assessment of the causal relationship to the study drug will be made according to the following classifications based on Karch FE, et al (48):

Definite: An event that follows a reasonable temporal sequence from administration of the treatment or in which the treatment level has been established in body fluids or tissues; that follows a known response pattern to the suspected treatment; and that is confirmed by improvement on stopping the treatment (dechallenge), and reappearance of the event on repeated exposure (rechallenge).

Probable: An event that follows a reasonable temporal sequence from administration of the treatment; that follows a known response pattern to the suspected treatment; that is confirmed by dechallenge; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

Possible: An event that follows a reasonable temporal sequence from administration of the treatment that follows a known response pattern to the suspected treatment but that could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Doubtful/Unlikely: An event that follows a reasonable temporal sequence from administration of the treatment; that does not follow a known response pattern to the suspected treatment; but that could not be reasonably explained by the known characteristics of the patient's clinical state.

Unrelated: Any event that does not meet the criteria above.

The operational tool to decide the AE causal relationship is based on algorithms by Karch and Lasagna and Naranjo et al (49, 50).

When an AE is classified, assessing causal relationship by the Investigator, as definitive, probable, possible or doubtful/unlikely, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an AR. When the causal relationship is labeled "Unrelated", then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.

In addition, when a causal relationship between the study treatment and the AE cannot be ruled out by the Investigator and/or Sponsor, it means that the AE cannot be labeled "unrelated".

For any subject, all AEs that occur at any time, between the beginning of the first infusion of IGIV-C and the final visit of the clinical trial, will be considered treatment emergent adverse events (TEAEs).

AEs occurring during the actual IP infusions (i.e., from the initiation of the IP infusion on the first day to the completion of the total dosage of IP on the last day) and within 72 hours following the completion of the infusion of the total dosage of IP on the last day, regardless of other factors that may impact a possible causal association with product administration, will be defined as infusional AEs (i.e., an AE temporally associated with an infusion of the IP) and labeled infusional TEAEs (a subset of TEAEs).

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE changes materially in intensity and/or resolves will be captured.

4.4.4 Intensity of Adverse Event or Suspected Adverse Drug Reaction

AEs and suspected ADRs will be classified depending on their intensity (severity) according to the following definitions:

1. Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.
2. Moderate: an AE that interferes with the subject's normal activities.
3. Severe: an AE that prevents the subject from performing their normal activities.

AE and suspected ADR intensity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate or severe but usually is not serious in all these cases.

The Investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account the criteria currently included in this section.

4.4.5 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness of a suspected ADR shall be determined by the Sponsor according to the reference document (IB or Summary of Product Characteristics [SPC] or product label).

Events not listed for the particular drug under investigation in the IB or SPC are considered "unexpected" and those listed are considered "expected." When new Serious ADRs (Serious potentially-related AEs) are received, it is the Sponsor's responsibility to determine whether the events are "unexpected" for expedited safety reporting purposes.

4.4.6 Seriousness of Adverse Event or Suspected Adverse Drug Reaction, Serious Adverse Event

An AE or suspected ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

1. Death
2. Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject 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 were more severe)
3. In-patient hospitalization or prolongation of existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. An important medical event (important medical event in the definition of "serious") refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above

This definition permits either the Sponsor or the Investigator to decide whether an event is "serious". If either the Sponsor or the Investigators believes that the event is serious, the event must be considered "serious" and evaluated by the Sponsor for expedited reporting.

A distinction should be drawn between serious and severe AEs. The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

According to the medical criteria, an AE or a suspected ADR can be classified as serious, although it does not fulfill the conditions fixed in this section, if it is considered important from a medical point of view.

4.4.6.1 Hospitalization or Prolongation of Hospitalization

An AE or suspected ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in hospitalization or prolongation of hospitalization UNLESS this hospitalization or prolongation of hospitalization is part of the clinical practice (according to the Investigator's criteria) for the treatment of the MG.

4.4.7 Adverse Events of Special Interest

4.4.7.1 Thromboembolic Events

Subjects will be monitored for signs and symptoms of arterial and venous thromboses. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible thromboses. Arterial and venous thromboses will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Such thrombotic events include, but are not limited to, DVT, PE, myocardial infarction, cerebrovascular accident, acute coronary syndrome, limb thrombosis, sagittal sinus thrombosis, and portal vein or mesenteric artery thrombosis. All thrombosis will be recorded as AEs, reported accordingly, and if serious, may require early discontinuation from study. See Appendix 7 for details.

4.4.7.2 Hemolysis

Subjects will be monitored for signs and symptoms of hemolysis. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible hemolysis. Hemolysis will be recorded as an AE, reported accordingly, and if resulting in serious hemolytic anemia, may require early discontinuation from study. See Appendix 8 for details.

4.4.7.3 MG Events That Are Not Considered AEs

Given that variations in symptoms are an inherent part of the natural history of MG, all recorded information regarding severity of MG manifestations will be considered efficacy data.

For the purpose of this study, variation in MG symptoms will not be considered an AE unless MC requires hospitalization. If a subject is hospitalized for MG, it will be reported as an SAE.

4.4.8 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Events and Suspected Adverse Drug Reactions

The occurrence and follow-up details of all AEs experienced by any of the subjects during the clinical trial, from signature of the *Clinical Trial Written Informed Consent Form* to the last follow-up visit, will be recorded on the AE eCRF entry and in the subject's hospital record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible. It is responsibility of the Investigator to ensure that AEs are appropriately recorded.

The following variables must be recorded on the AE eCRF entry:

1. the verbatim term (a diagnosis is preferred)
2. date/time of onset
3. date/time of resolution
4. severity (mild, moderate, severe)
5. causality (unrelated, doubtful/unlikely, possible, probable, definite)*
6. seriousness (yes, no)
7. action taken (with regard to IP)
8. other action (to treat the event)
9. outcome and sequel (follow-up on AE)

**AEs occurring before subject's exposure to IP will be always labeled as "unrelated".*

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE changes materially in intensity and/or resolves will be captured the eCRF entry.

In addition to the Investigator's own description of the AEs, each AE will be encoded by the Sponsor or CRO according to the Medical Dictionary for Regulatory Activities (MedDRA®).

For example, a laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

A pregnancy not verified before the Baseline Visit but occurring during the course of the study will be not considered an AE, unless a relation to the study drug is suspected. In any case, a *Pregnancy Report Form* must be completed and sent as soon as possible to the Sponsor, and the study treatment must be discontinued. A copy of the form should be filed at the study site for follow-up until the end of the pregnancy.

4.4.9 Timelines and Reporting of Serious Adverse Events

Any SAE (see Section 4.4.6) that occurs after signing the ICF through the last day of subject´s participation in the clinical trial must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully recorded in the subject's eCRF or SAE Report Form.

SAEs will be reported using the designated SAE Report form. When the Investigator becomes aware of an SAE, she/he must submit electronically through the Electronic Data Capture (EDC) system or when the EDC system is not available submit a completed, signed and dated SAE Report Form (in English) **within 24 hours** to the Sponsor by email/fax.

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow up, and for the outcome, must also be supplied to the Sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report Form. In addition, the Sponsor or CRO may request additional information and/or reports.

All SAE Report Forms must be reported to Grifols electronically through the EDC system or when the EDC system is not available, reported to:

Grifols Global Pharmacovigilance

FAX (back-up only): [redacted] (US/Canada)
and [redacted] (International)

When required, and according to local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities.

4.4.10 Type and Duration of the Follow-Up of Subjects after Adverse Event or Suspected ADR

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known or the event has been stabilized and no further change is expected and the Investigator decides that no further follow-up is necessary.

Any pregnancy must be followed by the Investigator until delivery or to the end of pregnancy.

5 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

5.1 Statistical and Analytical Plan

Unless otherwise specified, descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data. All statistical tests will be two-sided at alpha = 0.05.

Detailed data handling and evaluation procedures will be described in the Statistical Analysis Plan.

5.1.1 Subject Populations for Analysis

INTENT-TO-TREAT (ITT) POPULATION

The ITT population consists of all subjects who are randomized.

SAFETY POPULATION

The Safety population consists of all subjects who received any amount of IP.

PER PROTOCOL (PP) POPULATION

The PP population consists of all subjects in the ITT population without any major protocol deviation which has an impact on the primary efficacy data. Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in the PP population will be assessed at a review meeting that will take place before finalizing the database. The review meeting will review the protocol deviation list, as well as data listings. If protocol deviations are identified which justify removing a subject from the per-protocol population, then these decisions will be documented.

5.1.2 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics.

5.1.3 Efficacy Analyses

5.1.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change in QMG score from Baseline (Week 0) to Week 24. The treatment comparison will be performed using analysis of covariance (ANCOVA) with change in QMG score as dependent variable, treatment and *Baseline* standard of care treatment regimen as fixed factors and Baseline QMG score as a covariate. The null hypothesis (H_0) and the alternative hypothesis (H_a) are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2$$

Where μ_1 and μ_2 represent the population mean in the IGIV-C and Placebo groups, respectively.

For subjects who discontinued the study early, the last observation carried forward (LOCF) method will be used to impute the change in QMG from Baseline to Week 24. A sensitivity analysis of completers with non-missing QMG score at Week 24 will be performed. For subjects who experience Treatment Failure (defined in Section 3.3.3) or MG crisis (defined in Section 3.3.4) the value at time of failure will be employed.

For the longitudinal measurements of QMG score at various time points, the treatment effects will be explored by using the mixed-effect model repeated measures (MMRM) with change from Baseline as dependent variable; treatment, *Baseline* standard of care treatment regimen, protocol-specified visits, treatment-by-visit interaction as fixed effects; Baseline QMG value as covariate; and measures within-subject at each visit as a repeated measure.

Primary Efficacy analyses will be based on the ITT population. For sensitivity analysis, the same analysis will be repeated using the PP population.

5.1.3.2 Secondary Efficacy Analyses

Secondary endpoints include the percentage of subjects achieving clinical response as measured by QMG, MG Composite, and MG-ADL at Week 24.

The following secondary efficacy variables will be analyzed using the ITT population:

- Percentage of subjects who experience a clinical improvement assessed by QMG score from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in QMG
- Percentage of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 3-point decrease in the MG Composite
- Percentage of subjects who experience a clinical improvement as assessed by MG-ADL from Baseline (Week 0) to Week 24 where clinical improvement is defined as at least a 2-point decrease in MG-ADL

Treatment comparison will be performed by Cochran-Mantel-Haenszel (CMH) test adjusted for *Baseline* standard of care treatment regimen. Subjects who discontinued from the study early will be considered as not showing clinical improvement.

5.1.3.3 Exploratory Efficacy Analyses

Exploratory efficacy analyses will be based on the ITT population. The following exploratory efficacy variables will be analyzed:

- Percentage of subjects who experience a clinical improvement in QMG score (defined above) at Weeks 6, 9, 12, 15, 18, and 21
- Time to first clinical improvement in QMG score (at least a 3-point decrease)
- Time to Treatment Failure based on QMG score definition (Section 3.3.3)
- Change from Baseline (Week 0) in QMG score to Weeks 6, 9, 12, 15, 18, and 21
- Percentage of subjects who experience a clinical improvement in the MG Composite (defined above) to Weeks 6, 9, 12, 15, 18, and 21
- Change from Baseline (Week 0) in MG Composite to Weeks 6, 9, 12, 15, 18, 21, and 24
- Percentage of subjects who experience a clinical improvement in MG-ADL (defined above) to Weeks 9 and 15
- Change from Baseline (Week 0) in MG-ADL to Weeks 9, 15, and 24
- Change from Baseline in the 15-item MG-QOL 15 to Weeks 9, 15, and 24

- MGFA postinterventional change in status at Week 24 relative to Baseline

For the time to event variables, Kaplan-Meier estimates will be provided and the treatment comparison will be performed using a log-rank test. For change from Baseline variables, ANCOVA and/or MMRM methods similar to the primary efficacy endpoint will be used. For percentage variables, the CMH test adjusted for Baseline standard of care treatment regimen will be used.

MGFA postinterventional change in status at Week 24 relative to Baseline will be summarized by treatment group.

5.1.4 Safety Analyses

The safety analysis will be based on safety population.

The safety analyses will be addressed by listing and tabulation of AEs (including suspected ADRs), vital signs, physical examinations and clinical laboratory tests. Data will be described using descriptive analyses.

Adverse events:

Safety analysis will be primarily focused on a descriptive analysis of suspected ADRs. Safety assessment will be based on the prevalence of suspected ADRs that occurred during the clinical trial.

Adverse events will be coded and classified using MedDRA® terms (system organ class and preferred terms).

Adverse events will be classified as TEAEs or non-TEAEs. A TEAE will be defined as an AE which occurs between the beginning of the first infusion of IGIV-C and the final visit of the clinical trial. A non-TEAE will be defined as an AE which occurs prior to the first dose of IP. Non-TEAEs and TEAEs will be summarized separately.

All AEs will be summarized by presenting subject incidences and percentages, and they will also be listed by body systems with subject identification codes.

In addition, TEAEs, including suspected ADRs, will be summarized by system organ class, preferred term, causal-relationship, intensity (severity) and seriousness (serious vs. non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe or causal relationship AE.

AEs temporally associated with the infusion of the IP (i.e., infusional AEs, including infusional suspected ADRs), will be summarized by presenting infusion/subject incidences and percentage and listed. In addition, the infusion rate in effect at the time of onset of the AE, the time the AE is first reported and the time the AE changes materially in intensity and/or resolves will be also reported and listed.

Subjects with deaths, SAEs, suspected ADRs and AEs leading to premature discontinuation from the study will be listed and presented in a narrative form.

Any AEs for which the Investigator causality assessment is missing or undetermined will be individually listed.

Vital signs:

Vital signs (T, RR, HR, SBP and DBP) will be listed for each clinical trial subject and summarized by treatment group. In case a subject presents a clinically relevant abnormality of vital signs during an infusion, the event will be flagged and reported as an AE temporally associated to the infusion. For each subject and for each infusion, every vital sign will be considered. Clinical relevance will be based on the Investigator's criteria. Abnormal vital signs judged as clinically relevant by the Investigator in the context of the patient's medical history will be considered AEs.

Physical examination:

Physical examination findings (normal and abnormal) will be listed for each clinical trial subject with the specific findings observed. Abnormal findings judged as clinically relevant by the Investigator in the context of the patient's medical history will be considered AEs.

Blood chemistry and hematology:

All clinical laboratory data for renal (creatinine, BUN), hepatic (ALT, AST, ALP, and TBL) and hematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subject and summarized by treatment group. Laboratory results out of the normal range judged as clinically relevant by the Investigator in the context of the patient's medical history will be considered AEs.

Lab tests for TEs and hemolysis:

The D-dimer for TE assessment and the laboratory tests for detecting hemolysis (including whole blood Hb, serum free Hb, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL and indirect bilirubin, and blood smear) will be listed and out of normal range results will be flagged.

5.2 Determination of Sample Size

According to a study by Tackenberg and colleagues in 16 MG subjects with IGIV as maintenance therapy, the change from Baseline to endpoint in QMG score averaged 9.81 with a standard deviation of 4.21 (52). Assuming that the IGIV treatment group is 50% better than the Placebo group, with alpha=0.05 and two-sided test, 28 subjects are needed for each treatment group (total 56 subjects) to have at least 80% power to detect the treatment difference. Assuming a 10% drop out rate, 62 subjects are planned to be randomized.

6 ADMINISTRATIVE

6.1 Investigators, Other Study Personnel and External Committees

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating Investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the Sponsor and at the Investigator sites within the Study Reference Manual/file.

Investigators and staff will receive training via an Investigators meeting, site initiation visit or other appropriate individual site training session(s).

6.1.1 Independent Safety Review Committee

This study will utilize an Independent Safety Review Committee (ISRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. The clinical trial team will remain blinded to subject treatment assignment. The ISRC will review relevant safety information from the study as outlined in the ISRC Charter. At a minimum, after the first 20 subjects are enrolled and have completed half of the treatment period, the ISRC will conduct a safety review of the following data at a minimum:

- AEs, SAEs, and discontinuations due to AEs and SAEs
- Vital signs
- Blood chemistry and hematology
- Assessing for TEs
- Assessing for hemolysis

During the study, the Medical Monitor will review all relevant safety information from the study in order to protect subject welfare and preserve study integrity. Data to be reviewed include but are not limited to the following: eCRFs, listings from the clinical and safety databases, AEs/SAE reports, concomitant medications, laboratory data, vital signs, and physical examinations data.

6.2 Data Quality

Monitoring and auditing procedures defined/agreed by the Sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, ICH GCP and legal aspects. The on-site verification of the eCRF for completeness and clarity will include cross checking with source documents and clarification of administrative matters. Query verification of data will be described in the Data Management Plan.

6.3 Documentation

The study data will be recorded and kept current in the eCRF by the site study personnel directly responsible for the information. Entries made in the eCRF must be verifiable against

source documents or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered the source data.

The data in the eCRF will be monitored at the site by Grifols Therapeutics Inc. representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of source documents include individual subject medical records, which are separate from the eCRFs.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE form. The SAE form must be kept in site records with a copy provided to the designated person as detailed in Section 4.4.9.

6.3.1 Record Retention

At study completion, all study data will be transferred to Grifols Therapeutics Inc. according to ICH GCP guidelines, local laws, regulations and Grifols Therapeutics Inc. requirements. The study file and all source data should be retained until notification is given by the Sponsor for destruction.

An Investigator is required by ICH GCP guidelines to retain the study files. If an Investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g., other Investigator). Grifols Therapeutics Inc. must be notified in writing of the person responsible for record retention and the notification will be retained in the Sponsor study file and the Investigator site file.

6.3.2 Access to Information for Monitoring

The data will be recorded and kept current in eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols Therapeutics Inc. personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency and to verify adherence to the protocol and the completeness, consistency and accuracy of data entered. "Source documentation" includes individual subject files, separate from the eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, IP dispensing logs and other notes as appropriate. The Investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

6.3.3 Access to Information for Audits or Inspections

Representatives of regulatory authorities or of Grifols Therapeutics Inc. may conduct audits or inspections of the Investigator study site. If the Investigator is notified of an audit or inspection by a regulatory authority, the Investigator agrees to notify the Grifols Therapeutics Inc. Medical Monitor immediately. The Investigator agrees to provide to representatives of a Regulatory Agency or Grifols Therapeutics Inc. access to records, facilities and personnel for the effective conduct of an audit or inspection.

7 ETHICAL AND LEGAL ASPECTS

7.1 Institutional Review Board/Ethics Committee

Documented approval from appropriate IRBs/ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRBs/ECs approval must be obtained and also forwarded to the Sponsor. The IRBs/ECs must supply to the Sponsor, upon request, a list of the IRBs/ECs members involved in the vote and a statement to confirm that the IRB/EC is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

7.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the Sponsor representatives and/or an inspection by Regulatory Authority representatives at any time. The Investigator must agree to the audit or inspection of study-related records by the Sponsor representatives and/or Regulatory Authority representatives and must allow direct access to source documents to the Sponsor and/or Regulatory Authority representatives.

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/EC/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/EC/Sponsor. Any deviations from the protocol must be fully explained and documented by the Investigator.

7.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for Investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

7.4 Subject Information and Informed Consent Form

Subject information and ICF will be provided to Investigator sites. Prior to the beginning of the study, the Investigator must have the IRB/EC written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the IRB/EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to the Sponsor by the Investigator site.

Written ICF must be obtained before any study specific procedure takes place. If applicable, a legally authorized representative may provide informed consent on behalf of the subject. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

7.5 Insurance

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss or liability caused or incurred by Sponsor, or as otherwise required by applicable laws and/or regulations.

7.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the eCRF, and if the subject's name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the Sponsor, IRB/EC or Regulatory Authorities may inspect their medical records to verify the information collected and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects' records to be identified.

8 USE OF DATA AND PUBLICATION

Institution and the Investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriates sites. If such a multi-center publication is not submitted within twelve (12) months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or Investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or Investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
- Within said thirty (30) day period, Grifols shall:
  - Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and other applicable privacy laws;

  - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
  - By written notice to the Investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
  - By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
- Institution and/or Investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentations.

9 REFERENCES

1. Jani-Acsadi A and Lisak RP. Myasthenic Crisis: Guidelines for prevention and treatment. Journal of the Neurological Sciences 2007; 261(1-2): 127-133.

2. Vincent A. Unraveling the pathogenesis of myasthenia gravis. Nature Reviews: Immunology 2002; 2: 797-804.

3. Ropper AH, Samuels MA, Klein JP (2014). *Adams and Victor's Principles of Neurology*. 10th ed. New York: McGraw Hill Medical. Chapter 49 Myasthenia Gravis and Related Disorders of the Neuromuscular Junction: 1472-1489.

4. Meriggioli MN and Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009; 8:475-490.

5. Zinman L and Bril V. IVIG treatment of myasthenia gravis – effectiveness, limitations, and novel therapeutic strategies. Ann NY Acad Sci 2008; 1132: 264-270.

6. Seib JP. Myasthenia gravis: an update for the clinician. Clinical & Experimental Immunology 2013; 175: 408-418.

7. Barth D, Nabavi M, Nouri, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 2011; 76: 2017–2023.

8. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol 1997; 41(6): 789-796.

9. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. Archives of Neurology 2005; 62(11): 1689–1693.

10. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database of Systematic Reviews 2012, Issue 12.

11. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis. A randomized controlled trial. Neurology 2007; 68 (11):837–841.

12. Ronager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artificial Organs 2001; 25(12):967–973. [PUBMED: 11843764].

13. Wolfe GI, Barohn RJ, Foster BM, Jackson CE, Kissel JT, Day JW, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle and Nerve 2002;26(4):549–552. [PUBMED: 12362423].

14. The Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 2008; 71: 394-399.

15. Ericson-Neilsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. The Ochsner Journal 2014; 14:203-207.

16. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW. Guidelines for treatment of autoimmune neuromuscular transmission disorders. European Journal of Neurology 2010; doi: 10.1111/j. 1468-1331.2010.03019.x.

17. Palace J, Newsom-Davis J, Lecky B and the Myasthenia Gravis Study Group. Neurology 1998;50:1778-83.

18. Tindall RSA, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. New Engl J Med 1987;316:719–24.

19. Tindall RSA, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann NY Acad Sci 1993;681:539–55.

20. Nagane Y, Utsugisawa K, Obara D, Kondoh R, Terayama Y. Efficacy of low-dose FK506 in the treatment of myasthenia gravis—a randomized pilot study. Eur Neurol 2005;53:146–50.

21. De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve 2002;26:31-6.

22. Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. Autoimmunity 2010;43(5–6):428–35.

23. Fardet L, Kassar A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. Drug Saf. 2007;30(10):861-81.

24. Fardet L, Flahault A, Kettaneh A, Tiev KP, Genereau T, Toledano C, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. Br J Dermatol 2007;157(1):142-8.

25. Thymectomy trial in non-thymomatous myasthenia gravis patients receiving prednisone therapy, [Internet], (2015) [updated 2015 Jun 17]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00294658?term=thymectomy+myasthenia+gravis&rank=1.

26. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011;76**:**294–300.

27. Ephrem A, Chamat S, Miquel C, Fisson S, Mouthon L, Caligiuri G, et al. Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis. Blood 2008; 111:715–22.

28. Soueidan SA, Dalakas MC. Treatment of autoimmune neuromuscular diseases with high-dose intravenous immune globulin. Pediatr. Res 1993; 33**:**S95–S100.

29. Anthony RM, Wermeling F, Karlsson MCI, Ravetch JV. Identification of a receptor required for the anti-inflammatory activity of IVIG. Proc Natl Acad Sci. *USA*. 2008; 105:19571–8.

30. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. J Allergy Clin Immunol 2011; 127 (2): 315-323.

31. Maddur MS, Othy S, Hegde P, et al. Immunomodulation by intravenous immunoglobulin: role of regulatory T cells. J Clin Immunol 2010; 30 (Suppl 1):S4-8.

32. Ahmed S, Kirmani JF, Janjua N, et al. An update on myasthenic crisis. Current Treatment Options in Neurology 2005; 7: 129-141.

33. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the Am Acad Neur 2012; 78(13): 1009-1015.

34. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: Recommendations for clinical research standards. Neurology 2000; 55: 16-23.

35. Hohfeld R, Melms A, Schneider C, et al. Therapy of myasthenia gravis and myasthenic syndromes; in Neurological Disorders Course and Treatment, Second Edition, Elsevier Science (USA), Copyright 2003, pp 1341-1362.

36. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database of Systematic Reviews 2012;7. Art. No.: CD002063. DOI: 10.1002/14651858.CD002063.pub5.

37. The evaluation of belimumab in myasthenia gravis (MG), [Internet], (2015) [updated 2015 Jun 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT01480596?term=NCT01480596&rank=1

38. Katzberg HD, Barnett C, Merkies ISJ, Bril V. Minimal clinically important difference in myasthenia gravis: Outcomes from a randomized trial. Muscle & Nerve 2014; 49: 661-665.

39. Burns TM, Conaway M, Sanders DB, et al. The MG composite: A valid and reliable outcome measure for myasthenia gravis. Neurology 2010; 74: 1434-1440.

40. Burns TM. The MG composite: an outcome measure for myasthenia gravis for use in clinical trials and everyday practice. Ann. N.Y. Acad. Sci. 2012; 1274: 99-106.

41. Benatar M, Sanders DB, Burns T, et al. Recommendations for myasthenia gravis clinical trials. Muscle Nerve 2012;45: 909-917.

42. Muppidi S. The myasthenia gravis-specific activities of daily living profile. Ann. N.Y. Acad. Sci. 2012; 1274: 114-119.

43. Muppidi S, Wolfe GI, Conaway M, Burns TM and the MG Composite and MG-QOL 15 Study Group. MG-ADL: Still a relevant outcome measure. Muscle Nerve 2011; 44: 727-731.

44. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology 1999; 52: 1487-1489.

45. Burns TM, Conaway MR, Cutter GR, Sanders DB, and the Muscle Study Group. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. Muscle Nerve 2008; 38: 957-963.

46. Burns TM, Grouse CK, Conaway MR, Sanders DB, and the MG Composite and MG-QOL 15 Study Group. Construct and concurrent validation of the MG-QOL 15 in the practice setting. Muscle Nerve 2010; 41: 219-226.

47. Burns TM, Grouse CK, Wolfe GI, Conaway MR, Sanders DB, and the MG Composite and MG-QOL 15 Study Group. The MG-QOL 15 for following the health-related quality of life of patients with myasthenia gravis. Muscle Nerve 2011; 43: 14-18.

48. Karch FE, Lasagna L. Adverse drug Reactions. A critical review. JAMA 1975; 234: 1236-1241.

49. Karch FE, Lasagna L. Towards the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977; 21: 247-254.

50. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

51. World Health Organization Internal Classification of Diseases (ICD), [Internet], (2015) [updated 2015]. Available from: http://www.who.int/classifications/icd/en/

52. Eienbroker C, Seitz F, Spengler A, et al. IVIg maintenance in myasthenia gravis – a RCT sample size simulation. Muscle and Nerve. http://onlinelibrary.wiley.com/doi/10.1002/mus.24259/abstract. accessed 08/27/2014.

53. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost 2007; 5 Suppl 1: 41-50.

54. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood 2009; 113(13): 2878-2887.

55. Health Canada. Canadian Adverse Reaction Newsletter. Intravenous immune globulin (IVIg): hemolytic reactions. 2009; 19(4).

56. Thavendiranathan P, Bagai A, Ebidia A, et al. Do Blood Tests Cause Anemia in Hospitalized Patients? The Effect of Diagnostic Phlebotomy on Hemoglobin and Hematocrit Levels. J Gen Intern Med 2005; 20: 520–524.

57. Tuncer Elmaci N, Ratip S, Ince-Günal D, et al. Myasthenia gravis with thymoma and autoimmune haemolytic anaemia. A case report. Neurol Sci. 2003; 24(1): 34-36.

58. Chant C, Wilson G, Friedrich J. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. Critical Care 2006, 10:R140 (doi:10.1186/cc5054).

59. Kameoka J, Endo K, Sugawara T, et al. Autoimmune hemolytic anemia and myasthenia gravis. Jpn J Med. 1991; 30(4): 330-332.

10 APPENDICES

Appendix 1 Schedule of Study Procedures

	Screening	Baseline & 1st IP Dose	Completion of Loading IP Dose		Maintenance Infusion Treatment Period										End of Study/ Early Termination [n]
Visit	**0**	**1** (Day 1)	**1** (Day 2)		**2**		**3**		**4**	**5**	**6**		**7**	**8**	**9**
Study Week (or days post study drug infusion)	**-3**	**0**	**0**	**+7 days post**	**3**	**+7 days post**	**6**	**+7 days post**	**9**	**12**	**15**	**+7 days post**	**18**	**21**	**24**
Informed consent	X														
Inclusion/Exclusion Criteria[a]	X	X													
Randomization [b]		X													
Serum Pregnancy Test [c]	X														X
Urine Pregnancy Test [c]		X [e]													
Demographics	X														
Medical History	X														
Physical Exam [d]	X	X [e]							X [e]		X [e]				X
Height	X														
Weight [f]	X								X [e]		X [e]				
Vital signs [g]	X	X	X		X		X		X	X	X		X	X	X
Collection of Virus Safety Retain Samples [h]		X [e]													
Clinical laboratory Assessments (Hematology, Chemistry)	X	X [e]							X [e]		X [e]				X
QMG score [i]	X	X [e]			X [e]		X [e]		X [e]	X [e]	X [e]		X [e]	X [e]	X
MG Composite	X	X [e]			X [e]		X [e]		X [e]	X [e]	X [e]		X [e]	X [e]	X
MG-QOL 15		X [e]							X [e]		X [e]				X

	Screening	Baseline & 1st IP Dose	Completion of Loading IP Dose		Maintenance Infusion Treatment Period									End of Study/ Early Termination [n]
Visit	**0**	**1** (Day 1)	**1** (Day 2)		**2**		**3**		**4**	**5**	**6**		**7**	**8**	**9**
Study Week (or days post study drug infusion)	**-3**	**0**	**0**	**+7 days post**	**3**	**+7 days post**	**6**	**+7 days post**	**9**	**12**	**15**	**+7 days post**	**18**	**21**	**24**
MG-ADL		X [e]							X [e]		X [e]				X
MGFA Clinical Classification	X	X													
MGFA Postinterventional change in status[j]															X
Blood for IgG (trough)		X [e]							X [e]		X [e]				X
Blood for Anti-AChR Antibodies	X														
Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies		X [e]							X [e]						X
Hemolysis evaluation		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]			X[k]	X[k]			
Thromboembolism evaluation (Wells Score and D-Dimers)	X	X[k]	X[k]		X[k]		X[k]				X[k]				
AE Assessment (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])	X	X		X	X		X		X	X	X		X	X	X
Concomitant Medications	X	X	X		X		X		X	X	X		X	X	X
Administration of IP		X [l]	X [l]		X [m]		X [m]		X [m]	X [m]	X [m]		X [m]	X [m]	

AChR = acetylcholine receptor, AE = adverse event, IgG = immunoglobulin G, IP = investigational product, MG = myasthenia gravis, MG-ADL = myasthenia Gravis-Activities of Daily Living, MGFA = Myasthenia Gravis Foundation of America, MG-QOL = Myasthenia Gravis-Quality of Life, QMG = quantitative myasthenia gravis.

[a] Inclusion/exclusion criteria must be satisfied before the subject is randomized and receives the first IP infusion.

[b] A randomization number will be assigned to each subject based on a 1:1 randomization schedule.

[c] Potential child-bearing females only; results must be negative at Screening and Baseline for subject to continue in the study.

[d] Excludes breast and genitourinary exam.

[e] Assessments to be performed prior to IP infusion.

[f] Each recorded weight will be used to calculate the IP infusion dose for the scheduled visit and subsequent IP infusions until the next scheduled weight is measured.

[g] Full vital signs including temperature, respiratory rate, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) will be recorded at each visit. During the infusions, abbreviated vital signs (HR, SBP, and DBP) will be recorded just before the start of each infusion (within 15 ± 5 minutes before the beginning of each infusion), 30 ± 10 minutes after starting infusion, and immediately after infusion completes.

[h] Collect blood samples at Baseline/Week 0 (Visit 1) prior to randomization but test *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or parvovirus B19 infection while participating in the study. See Section 3.8.3.3 and Table 3-1 for details.

[i] Subjects must withhold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the visit to assure accurate assessment of the QMG.

[j] Modified Myasthenia Gravis Foundation of America (MGFA) postinterventional change in status relative to Baseline will be evaluated at Week 24 (Visit 9) wherein the Investigator will classify the patient as: (I) Improved, defined as a substantial decrease in pretreatment clinical manifestations of MG, QMG decrease ≥ 3 points; (U) Unchanged, defined as no substantial change in pretreatment clinical manifestations of MG; (W) Worse, defined as a substantial increase in pretreatment clinical manifestations of MG, QMG increase ≥ 3 points.

[k] Hemolysis evaluation (laboratory parameters) and thromboembolism evaluation will be performed at Baseline prior to start of first IP loading infusion, at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of each designated maintenance dosage at Week 3 and Week 6 (Visit 2 and 3) and at Week 15 (Visit 6). Hemolysis evaluation includes hemoglobin (Hb), hematocrit, red blood cell count (RBC), blood smear, serum free-Hb, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), total and direct/indirect bilirubin, urine for urinary sediment and hemoglobinuria, and hematuria. Hemolysis evaluation (laboratory parameters) will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post study drug infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).

[l] Initiation of induction (loading) dose of IVIG 2 g/kg of body weight begins after all Baseline assessments are complete and patient is randomized. Loading dose is infused over 2 days. Note that for the loading dosage 2 days is standard (2 to 4 days is allowed as an extension for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80g/day [corresponding to 80 kg body weight]).

[m] Maintenance doses of 1 g/kg of body weight are administered over 1 day every three weeks through Week 21 (Visit 8). Note that the maintenance dosage is given over 1 day as the standard time interval (divided dosage over 2 days is allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80g/day [corresponding to 80 kg body weight]).

[n] The Early Termination visit will consist of the same assessments as Week 24 (Visit 9) except for quantitative/semi-quantitative binding, blocking, and modulating acetylcholine receptor (AChR) antibodies which are not required.

Appendix 2 MGFA Clinical Classification

Classification	Description
Class I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal
Class II	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

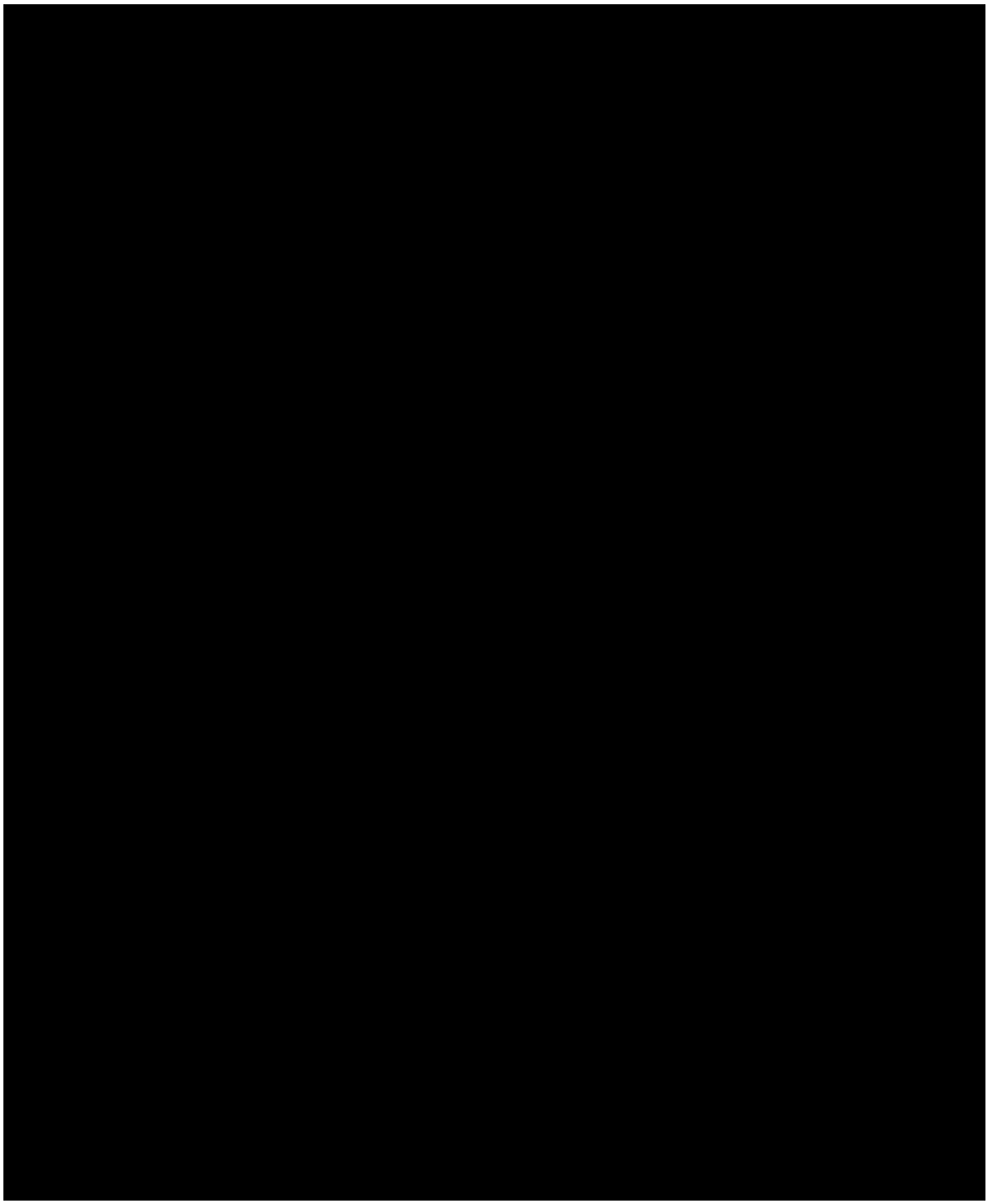
Appendix 3 QMG Test Items

[redacted]

Appendix 4 MG Composite Scale

Appendix 5 MG Activities of Daily Living (MG-ADL) Profile

Appendix 6 MG-Quality of Life (QOL) 15



Appendix 7 Monitoring of Thromboembolic Events Risk

Subjects will be monitored for signs and symptoms of arterial and venous thromboembolic (TE) events. Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases (ICD) [51]. Such events include, but are not limited to, deep vein thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction, cerebral infarction, acute ischemic heart disease, embolism or thrombosis of arteries of lower extremities, sagittal sinus thrombosis, portal vein thrombosis and injury of mesenteric artery.

All TE events will be recorded as adverse events (AEs) and reported accordingly. Any TE event fulfilling any of the criteria for "serious" will be reported as a serious adverse event (SAE).

The Sponsor's Medical Monitor (or designee) will routinely review reported AEs for possible TE events.

Thromboembolic events risk will be determined by the Investigator or appropriate study staff as indicated by the following schedule (Table 1):

Table 1. Schedule of Monitoring of Thromboembolic Events Risk

Study visit	Wells score	D-dimer	Signs & symptoms of DVT and PE*
Screening	X	X	X
Baseline (Week 0/prior to randomization)	X	X	X
End of first IP loading dose	X	X	X
At the time when last loading infusion is complete	X	X	X
Weeks 3, 6, and 15 following completion of each maintenance infusion dosage	X	X	X

* Evaluation of clinical signs and symptoms of arterial and venous TE as part of AEs assessment.

And using the following assessments:

The Wells Score [53] will be utilized to assess the clinical characteristics indicative of possible DVT or PE (Table 2);

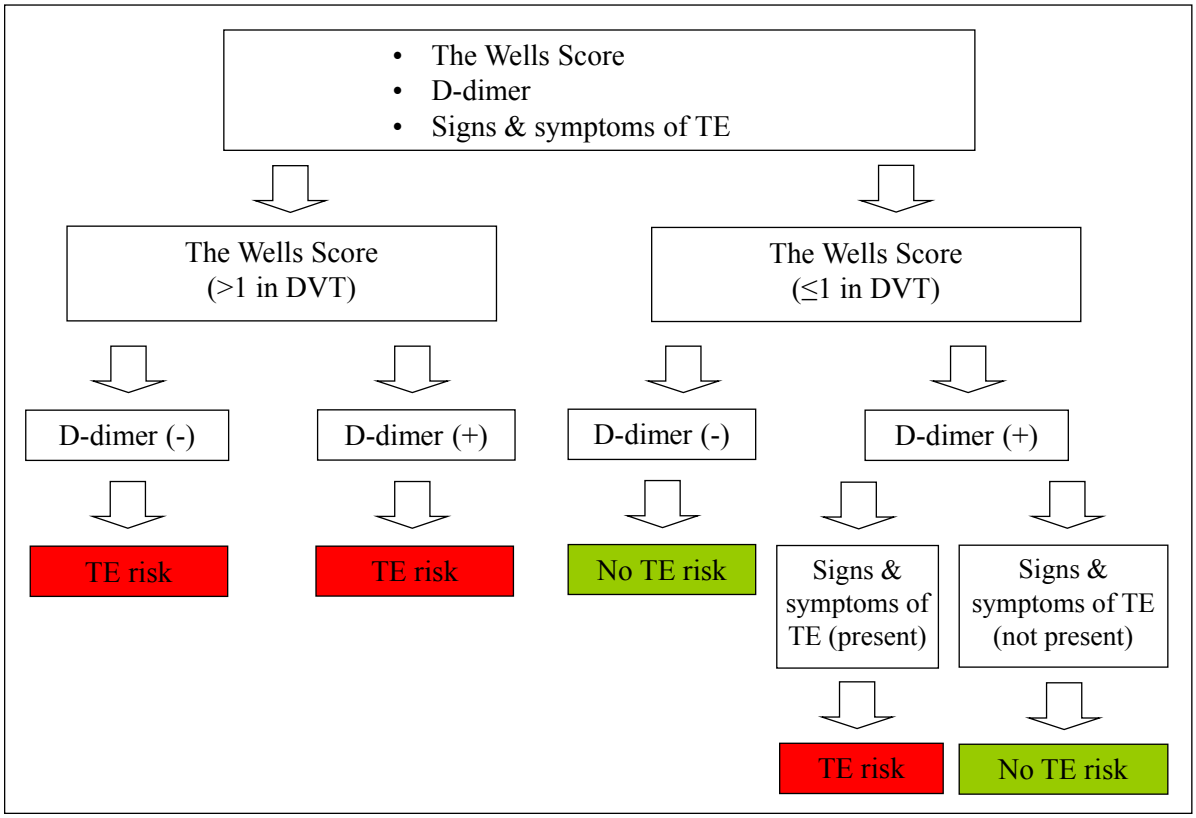
Measurement of D-dimer blood levels [54]; Evaluation of clinical signs and symptoms of arterial and venous TE as part of AEs assessment.

Table 2. Schedule of Monitoring of Thromboembolic Events Risk

DEEP VEIN THROMBOSIS	
Clinical Characteristic	**Score**
Active cancer (treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within previous 12 weeks requiring general or regional anesthesia	1
Previously documented DVT	1
Localized tenderness along distribution of deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis at least as likely as DVT	-2
Total Score:	
PULMONARY EMBOLISM	
Clinical Characteristic	**Score**
Previous DVT or PE	1.5
Surgery or bedridden for 3 days during past 4 weeks	1.5
Active cancer (treatment within 6 months or palliative)	1
Hemoptysis	1
Heart rate >100 beats/min	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Total Score:	

Thromboembolic events risk will be assessed according to the following algorithm adapted from Wells [53] (Figure 1 and Figure 2):

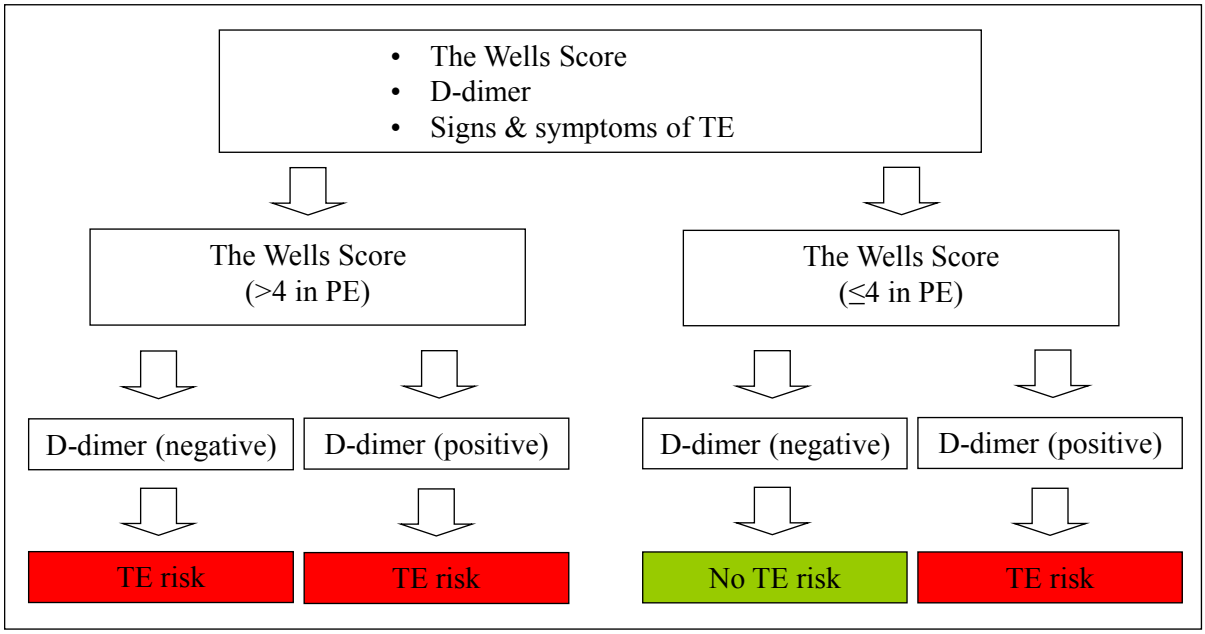
Figure 1. Algorithm to Assess Thromboembolic Events Risk for DVT



Any subject with a total Wells prediction score >1 for DVT assessment should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE (Figure 1).

Any subject with a total Wells prediction score ≤1 for DVT assessment and a positive D-dimer value (i.e., above Baseline, out of normal range of the reporting laboratory) in combination with clinical signs or symptoms of a TE (as per AEs assessment and such as pain, dyspnea, discoloration -paleness or redness- in lower extremities) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE (Figure 1).

Figure 2. Algorithm to Assess Thromboembolic Events Risk for PE



Any subject with a total Wells prediction score >4 for PE assessment should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE (Figure 2).

Any subject with a total Wells prediction score ≤4 for PE assessment and a positive D-dimer value (i.e., above Baseline, out of normal range of the reporting laboratory) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE (Figure 2).

Appendix 8 Hemolysis Detection

Schedule of the Procedures:

Study visit	Blood testing	Urine testing	Clinical parameters
Baseline (Week 0/prior to randomization)	X	X	X
End of first IP loading dose	X	X	X
At the time when last loading infusion is complete [a]	X	X	X
Weeks 3, 6, and 15 following completion of each maintenance infusion dosage [a]	X	X	X

[a] Hemolysis evaluation (laboratory parameters) will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post study drug infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).

Description of the procedures:

For the detection of hemolysis, the following procedure will be carried out to all the study population:

1. Blood testing: whole blood Hb, serum free Hb, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL and indirect bilirubin, and blood smear.
2. Urine testing: urinary sediment and hemoglobinuria.
3. Clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia).

Definition of hemolysis associated with the use of IGIV-C:

In this clinical trial, an IVIg-associated hemolytic reaction is one in which there is evidence of a new hemolytic process [55]. Consideration of possible hemolysis as defined below should only be triggered if other explanatory factors/conditions can be excluded. Subjects from this study may be severely ill and may have anemia for a number of reasons. Therefore, it is important to exclude the underlying conditions and concomitant medications as a cause of anemia. The exclusions are:

- History or examination consistent with an alternative cause of anemia including blood loss (e.g., frequent phlebotomy is highly associated with changes in Hb and hematocrit levels for patients admitted to an internal medicine service [56, 57]), iron-deficiency anemia, other drug-induced hemolytic anemia, or anemia associated with an underlying disease (e.g., autoimmune hemolytic anemia [58, 59]).
- Negative DAT.

Absence of other inclusion criteria, in particular absence of evidence for hemolysis.

Potential events would require the following laboratory signs to be present (with the above caveats):

1. Drop in whole blood Hb of ≥10 g/L*

   AND

2. Positive DAT

   AND

3. At least 2 of:

- increased ARC*	- hemoglobinemia
- increased LDH level*	- hemoglobinuria
- significant spherocytosis	- low haptoglobin level*
- unconjugated hyperbilirubinemia	

* Abnormal values without other explanation (e.g., LDH elevation due to muscle damage or increased reticulocyte count in the setting of hemorrhage) which show a clinically relevant change from pre-treatment values.

Appendix 9 Summary of Changes for Amendment 1

(Note: Administrative changes including minor administrative corrections and the changes in the protocol synopsis are not included in Protocol Summary of Changes.)

Sections	Change From:	Change To:	Rationale:
Protocol Synopsis	Approximately 30 study centers	Approximately ~~30~~ **40** study centers	Number of study centers increased to enhance recruitment
Protocol Synopsis 3.2.1	Inclusion Criterion #6 2. Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or *only one of the following*: • Prednisone (up to 60 mg/day or equivalent) for at least one month prior to Screening, or • Azathioprine for at least 6 months prior to Screening, or • Mycophenolate mofetil for at least 6 months prior to Screening, or • Cyclosporine or tacrolimus for at least 3 months prior to Screening 3. Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or prednisone (up to 60 mg/day or equivalent) for at least one month prior to Screening and only one of the following: • Azathioprine for at least 6 months prior to Screening, or • Mycophenolate mofetil for at least 6 months prior to Screening, or • Cyclosporine or tacrolimus for at least 3 months prior to Screening	Inclusion Criterion #6 4. Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or *only one of the following*: • Prednisone (up to 60 mg/day or equivalent) for at least ~~one~~ **two** month**s** prior to Screening, or • Azathioprine for at least 6 months prior to Screening, or • Mycophenolate mofetil for at least 6 months prior to Screening, or • **Methotrexate for at least 6 months prior to Screening, or** • Cyclosporine or tacrolimus for at least 3 months prior to Screening 5. Cholinesterase inhibitor (pyridostigmine or equivalent) for at least 2 weeks prior to Screening and/or prednisone (up to 60 mg/day or equivalent) for at least one month prior to Screening and only one of the following: • Azathioprine for at least 6 months prior to Screening, or • Mycophenolate mofetil for at least 6 months prior to Screening, or • **Methotrexate for at least 6 months prior to Screening, or** • Cyclosporine or tacrolimus for at least 3 months prior to Screening	Prednisone requirement modified from "one month" to "two months" for the portion of the inclusion criterion describing monotherapies so that those subjects on prednisone monotherapy at study entry will establish 2 months stable dosing on monotherapy. Criterion modified to include methotrexate to accommodate current clinical practice patterns for myasthenia gravis (MG) management

Sections	Change From:	Change To:	Rationale:
Protocol Synopsis 3.2.1	Inclusion Criterion #7 Subjects must be willing and able to provide written informed consent (if applicable, a legally authorized representative may provide informed consent on behalf of the subject).	Inclusion Criterion #7 Subjects must be willing and able to provide written informed consent ~~(if applicable, a legally authorized representative may provide informed consent on behalf of the subject)~~.	Intended subjects participating in study are those who are competent and can provide their own informed consent.
Protocol Synopsis 3.2.2	Exclusion Criterion #5 Evidence of malignancy or bulky thymoma potentially requiring surgical intervention during the course of the trial	Exclusion Criterion #5 Evidence of malignancy **within the past 5 years (non-melanoma skin cancer, carcinoma in situ of cervix is allowed)** or ~~bulky~~ thymoma potentially requiring surgical intervention during the course of the trial **(intent to perform thymectomy)**	Clarification provided regarding malignancy exclusion (timeframe and exceptions)
Protocol Synopsis 3.2.2	Exclusion Criterion #6 Thymectomy within the preceding three months	Exclusion Criterion #6 Thymectomy within the preceding ~~three~~ **six** months	Longer timeframe post thymectomy allowed for MG symptom stabilization post intervention
Protocol Synopsis 3.2.2	Exclusion Criterion #11 Plasma exchange (PLEX) performed within the last 2 months	Exclusion Criterion #11 Plasma exchange (PLEX) performed within the last ~~2~~ **3** months	Timing updated to make eligibility consistent across MG maintenance program

Sections	Change From:	Change To:	Rationale:
Protocol Synopsis	New text added to Safety Analysis section	**This study will utilize an Independent Safety Review Committee (ISRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. The clinical trial team will remain blinded to subject treatment assignment. The ISRC will review relevant safety information from the study as outlined in the ISRC Charter. At a minimum, after the first 20 subjects are enrolled and have completed half of the treatment period, the ISRC will conduct a safety review of the following data at a minimum:** **6. AEs, SAEs, and discontinuations due to AEs and SAEs** **7. Vital signs** **8. Blood chemistry and hematology** **9. Assessing for TEs** **10. Assessing for hemolysis** **During the study, the Medical Monitor will review all relevant safety information from the study in order to protect subject welfare and preserve study integrity. Data to be reviewed include but are not limited to the following: eCRFs, listings from the clinical and safety databases, AEs/SAE reports, concomitant medications, laboratory data, vital signs, and physical examinations data.**	Addition of Independent Safety Review Committee to provide assurance of objective, regular and comprehensive safety data review at defined intervals; also included is further detail regarding medical monitoring activities.
3.1	Approximately 62 adult subjects will be randomized at approximately 30 global study centers.	Approximately 62 adult subjects will be randomized at approximately ~~30~~ **40** global study centers.	Number of study centers increased to enhance recruitment
3.5	New text added to Prior and Concomitant Therapy	**Diphenhydramine, acetaminophen/ibuprofen, and non-steroidal anti-inflammatory drugs are allowed during the trial as pre-medications for study drug infusions. These and any other concomitant medication taken during the study period must be documented in the subject's medical records and the eCRF**.	Clarification that discretionary pre-medication for study drug infusion is allowed at the investigator's discretion.

Sections	Change From:	Change To:	Rationale:
3.6.4	…An average 3-point improvement in QMG score indicates clinically meaningful improvement (37, 38).	…An average 3-point improvement in QMG score indicates clinically meaningful improvement **in terms of minimal clinically important difference and precedent set by endpoints in other MG studies** (37, 38).	Additional details provided and new reference added pertaining to QMG categorical efficacy endpoint
3.7.2	….will be assessed at Baseline/Week 0 (Visit 1) and the time points specified above.	….will be assessed at Baseline/Week 0 (Visit 1) and the time points specified above. **Hemolysis laboratory assessments will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post maintenance infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance
3.8.2	The following is a description of the procedures/assessments to take place at each study visit. See the Schedule of Study Procedures in Appendix 1 for a summary of study visits and the procedures conducted at each visit.	The following is a description of the procedures/assessments to take place at each study visit. **Each MG assessment should be performed by the same clinical staff member whenever possible.** See the Schedule of Study Procedures in Appendix 1 for a summary of study visits and the procedures conducted at each visit.	Clarification provided to emphasize consistency in evaluator where feasible
3.8.2.3	Post-Baseline/Post-Randomization Loading Dose Infusion – new assessment added	Post-Baseline/Post-Randomization Loading Dose Infusion **11. Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post loading dose infusion**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance
3.8.2.4	New assessment added	12. **Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance
3.8.2.7	Assessments to be performed pre-infusion New Assessment added	Assessments to be performed pre-infusion **(except as specified)**: 13. **Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance

Sections	Change From:	Change To:	Rationale:
3.8.3 Table 3-1	b. At time points (Baseline and Week 15) where Chemistry and Hematology are coincidentally drawn, whole blood Hb, hematocrit, RBC will be obtained from hematology specimen; similarly TBL will be from the Chemistry sample.	~~b. At time points (Baseline and Week 15) where Chemistry and Hematology are coincidentally drawn, whole blood Hb, hematocrit, RBC will be obtained from hematology specimen; similarly TBL will be from the Chemistry sample.~~	Footnote removed since timing of these parameters is post infusion
3.8.3.2	Laboratory assessments (whole blood hemoglobin, serum free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL and indirect bilirubin, and blood smear) and urine assessments (for urinary sediment and hemoglobinuria, hematuria) will be conducted at Baseline (Week 0 prior to randomization), at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of maintenance infusion dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6). Appendix 8 provides details.	Laboratory assessments (whole blood ~~hemoglobin~~**Hb**, serum free ~~hemoglobin~~**Hb**, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL and indirect bilirubin, and blood smear) and urine assessments (for urinary sediment and hemoglobinuria, hematuria) will be conducted at Baseline (Week 0 prior to randomization), at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of maintenance infusion dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 15 (Visit 6). **Hemolysis laboratory assessments will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post maintenance infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).** Appendix 8 provides details.	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance
3.8.3.4	*[In reference to quantitative/semi-quantitative binding, blocking and modulating acetylcholine receptor antibodies]* All measurements will be conducted using qualified assays. Specific details regarding all aspects of sample collection and processing can be found in the central laboratory Study Reference Manual.	*[In reference to quantitative/semi-quantitative binding, blocking and modulating acetylcholine receptor antibodies]* **Baseline and Week 9 (Visit 4) and End of Study Visit (Week 24) results will not be shared during study conduct with the investigator, blinded study staff, CRO, or blinded Sponsor personnel involved with study conduct.** All measurements will be conducted using qualified assays. Specific details regarding all aspects of sample collection and processing can be found in the central laboratory Study Reference Manual.	Additional language added to state measures already in place to assure that quantitative antibody measurements could not be construed for treatment assignment inference.
3.9	Subjects may re-screen for the study if the reason for screen failure is no longer relevant.	Subjects may re-screen for the study if the reason for screen failure is no longer relevant**; a new informed consent form must be signed for re-screening**.	Procedural clarification
4.3.6	In the event that true hemolytic anemia develops, it will be considered an AE and/or an SAE depending on whether seriousness criteria are met.	In the event that true hemolytic anemia develops, it will be considered an AE and/or an SAE depending on whether seriousness criteria are met. **Hemolytic ARs are defined as temporally associated with the study drug within 7 days post infusion.**	Specific definition added to be consistent with comprehensive monitoring for potential hemolysis effects.

Sections	Change From:	Change To:	Rationale:
4.4.5	Events not listed for the particular drug under investigation in the IB or SPC are considered "unexpected" and those listed are considered "expected." When new AE information is received, it is the Sponsor's responsibility to determine whether the event is "unexpected" for Investigational New Drug (IND) safety reporting purposes.	Events not listed for the particular drug under investigation in the IB or SPC are considered "unexpected" and those listed are considered "expected." When new ~~AE information is~~ **Serious ADRs (Serious potentially-related AEs) are** received, it is the Sponsor's responsibility to determine whether the event**s** ~~is~~ **are** "unexpected" for ~~Investigational New Drug (IND)~~ **expedited** safety reporting purposes.	Text updated to reflect global clinical study
4.4.8	Variable #9 outcome and sequel (follow-up on AE) *Causality assessment will be only made when the AE occurs after the subject has initiated at least one infusion of the IP. AEs occurring before subject's exposure to IP will be always labeled as "unrelated".	Variable #9 outcome and sequel (follow-up on AE) *~~Causality assessment will be only made when the AE occurs after the subject has initiated at least one infusion of the IP.~~ AEs occurring before subject's exposure to IP will be always labeled as "unrelated".	Clarification provided to emphasize that while pre-IP AEs could not reasonably be attributed to study drug (never received) causality is always assessed
4.4.9	Grifols Global Drug Safety Email: [redacted] FAX (back-up only): [redacted]	Grifols Global ~~Drug Safety~~ **Pharmacovigilance** Email: [redacted] FAX (back-up only): [redacted] **(US/Canada)** **and** [redacted] **(International)**	Addition of international fax number

Sections	Change From:	Change To:	Rationale:
6	New Section Added – ADMINISTRATIVE 5.3 – Investigators, Other Study Personnel and External Committees	New Section Added **6 – ADMINISTRATIVE** ~~5.3~~ **6.1** – Investigators, Other Study Personnel and External Committees 1. **6.1.1 - Independent Safety Review Committee** **This study will utilize an Independent Safety Review Committee (ISRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. The clinical trial team will remain blinded to subject treatment assignment. The ISRC will review relevant safety information from the study as outlined in the ISRC Charter. At a minimum, after the first 20 subjects are enrolled and have completed half of the treatment period, the ISRC will conduct a safety review of the following data at a minimum:** • **AEs, SAEs, and discontinuations due to AEs and SAEs** • **Vital signs** • **Blood chemistry and hematology** • **Assessing for TEs** • **Assessing for hemolysis** **During the study, the Medical Monitor will review all relevant safety information from the study in order to protect subject welfare and preserve study integrity. Data to be reviewed include but are not limited to the following: eCRFs, listings from the clinical and safety databases, AEs/SAE reports, concomitant medications, laboratory data, vital signs, and physical examinations data.**	Addition of Independent Safety Review Committee to provide assurance of objective, regular and comprehensive safety data review at defined intervals; also included is further detail regarding medical monitoring activities.

Sections	Change From:	Change To:	Rationale:
9	Reference #37 Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: Assessment of responsiveness and longitudinal validity. Neurology 2005; 64: 1968-1970.	Reference #37 ~~Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: Assessment of responsiveness and longitudinal validity. Neurology 2005; 64: 1968-1970~~. **The evaluation of belimumab in myasthenia gravis (MG), [Internet], (2015) [updated 2015 Jun 25]. Available from: https://clinicaltrials.gov/ct2/show/NCT01480596?term=NCT01480596&rank=1**	Reference updates
Appendix 1	Study Week New assessment added New row added k. Hemolysis evaluation (laboratory parameters) and thromboembolism evaluation will be performed at Baseline prior to start of first IP loading infusion, at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of each designated maintenance dosage at Week 3 and Week 6 (Visit 2 and 3) and at Week 15 (Visit 6). Hemolysis evaluation includes hemoglobin (Hb), hematocrit, red blood cell count (RBC), blood smear, serum free-Hb, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), total and direct/indirect bilirubin, urine for urinary sediment and hemoglobinuria, hematuria.	Study Week **(or days post study drug infusion)** Additional assessment of **+7 days post** added to Study Weeks 0, 3, 6, and 15 k. Hemolysis evaluation (laboratory parameters) and thromboembolism evaluation will be performed at Baseline prior to start of first IP loading infusion, at the end of the first infusion of the loading dose, at the time when last loading infusion is complete, and at the completion of each designated maintenance dosage at Week 3 and Week 6 (Visit 2 and 3) and at Week 15 (Visit 6). Hemolysis evaluation includes hemoglobin (Hb), hematocrit, red blood cell count (RBC), blood smear, serum free-Hb, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), total and direct/indirect bilirubin, urine for urinary sediment and hemoglobinuria, **and** hematuria. **Hemolysis evaluation (laboratory parameters) will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post study drug infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance.
Appendix 8	New footnote added	New footnote added: **a. Hemolysis evaluation (laboratory parameters) will also be performed 7 days post loading dose infusion at Baseline (Week 0) and 7 days post study drug infusion at Weeks 3 (Visit 2), 6 (Visit 3), and 15 (Visit 6).**	Additional measure of laboratory parameters to assure comprehensive potential hemolysis surveillance.