Clinical Study Protocol

Protocol Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) as a Corticosteroid Sparing Agent in Corticosteroid Dependent Patients with Generalized Myasthenia Gravis
Investigational Product:	Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C)
Sponsor's Name and Address:	Grifols Therapeutics Inc. 79 T.W. Alexander Drive Research Triangle Park, NC 27709
Sponsor's Telephone Number:	919-316-2079
Study Number/Protocol Version Number/Date:	GTI1306/3.0/23 Dec 2016 Includes GTI1306/2.0/15 Jul 2015 and GTI1306/1.0/20 Aug 2014
EudraCT Number:	2013-005099-17
Development Phase:	Phase 2

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

Medical Monitor: PPD

Signature: PPD Date: 23 December 2016

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Summary of Changes for Amendment 2

Protocol Version	Date of Approval
3.0 Amendment 2 + Integrated Protocol	23 Dec 2016
2.0 Amendment 1 + Integrated Protocol	15 Jul 2015
1.0 Original	20 Aug 2014

Amendment 2

The protocol for GTI1306 (Version 2.0, dated 15 Jul 2015) has been amended and reissued as Protocol Amendment 2, Version 3.0, dated 23 Dec 2016. See Appendix 11 for a summary of changes for Amendment 2.

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 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) as a Corticosteroid Sparing Agent in Corticosteroid Dependent Patients with Generalized Myasthenia Gravis

Study Number

GTI1306

Phase:

2

Number of Subjects Planned:

Approximately 60 adult subjects will be randomized in this study.

Study Centers Planned:

Approximately 40 study centers

Study Objectives:

The primary objective of this study is to evaluate the efficacy of intravenous (IV) infusions of IGIV-C as compared to Placebo in reducing the maintenance dosage of corticosteroids in corticosteroid (CS)-dependent subjects with myasthenia gravis (MG) by assessing the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1).

The safety objective of this study is to evaluate the safety and tolerability of IGIV-C loading dose of 2 g/kg followed by 12 maintenance dosages of 1 g/kg every 3 weeks through Week 36 in CS-dependent subjects with MG.

Target Population:

Eligible participants for this study will include adult subjects with a confirmed diagnosis of generalized MG who have required systemic CS therapy for at least the preceding three months prior to Screening in order to control their signs and symptoms of MG. Subjects may be receiving immunosuppressive therapies within the confines stipulated in eligibility criteria and stable dosage of acetylcholinesterase inhibitors (e.g., pyridostigmine, neostigmine).

Overall Study Description:

Eligible subjects will be randomly allocated in a 1:1 ratio into IGIV-C treatment group and Placebo treatment group to receive either IGIV-C or matched Placebo every three weeks in a double-blinded fashion. Randomization will be stratified by baseline CS dose:

- 15 mg to 40 mg prednisone equivalent per day
- 41 mg to 60 mg prednisone equivalent per day

For those subjects randomized to receive IGIV-C, an initial loading dose of 2 g/kg will be administered at the Baseline/Week 0 Visit (Visit 1). The loading dose is divided over 2 days as standard infusion time (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]). The loading dosage is followed by maintenance doses of 1 g/kg administered every third week until Visit 13 (Week 36). The maintenance dosage is infused in 1 day as standard infusion (extensions are 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]). For those subjects randomized to receive Placebo, sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent will be infused at the Baseline/Week 0 Visit (Visit 1) in a manner that the blind is maintained. The volumes of Placebo will be equal to the volumes required for an initial loading dose of IGIV-C at the Baseline Visit (Visit 1) and subsequent maintenance doses will be administered every third week until Visit 13 (Week 36).

Tapering of the CS dose will not be initiated until the subject receives a total of 3 complete doses of the investigational product (IP), including the initial loading dose (Week 0 [Visit 1]) and the first two maintenance doses (Week 3 [Visit 2] and Week 6 [Visit 3]). The subject will begin a prescribed CS tapering regimen at Week 9 [Visit 4], coincident with receiving the fourth dose of IP. The tapering will be based on the CS dose (prednisone equivalent) as described under Study Phases below.

During the CS Tapering/IP Maintenance Phase, study visits will occur every three weeks while the subject continues his/her CS tapering and maintenance doses of IP. Implementation of the CS dose reductions will last a maximum of 27 weeks. The investigator will attempt to hold the non-CS therapy (e.g., pyridostigmine) of the subjects' MG medical regimen constant through the end of the study (Week 45 [Visit 16]) unless there are worsening symptoms or adverse effects due to other components of the subject's non-CS therapy.

During the CS Tapering Phase, the last CS dose reduction can occur at Week 36 (Visit 13). Week 39 (Visit 14) will constitute the time point for the primary endpoint, an opportunity to assess the effect of the final CS dose reduction made at Week 36 (Visit 13), and the initiation of the Safety/Follow-up Phase.

Subjects will receive 3 safety/follow-up visits following the last dose of IP (Weeks 39, 42, 45 corresponding to Visits 14, 15, 16, respectively). It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated.

Study Phases:

1. Screening Period

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

2. Investigational Product Run-in Phase:

Subjects will receive a total of 3 complete doses of the IP in the IP Run-In Phase, which includes the initial loading dose at the Baseline/Week 0 (Visit 1), and the first two maintenance doses at Weeks 3 and 6 (Visits 2 and 3). The CS dose will remain stable in this

phase. CS tapering will begin at Week 9 (Visit 4), coincident with the third maintenance dose of IP.

3. Corticosteroid Tapering/IP Maintenance Phase

After completion of the third maintenance dose at Week 9 (Visit 4), subjects will begin a prescribed tapering regimen of their CS dose as described below.

CS Tapering Regimen: CS dosage in subjects will be decreased at scheduled visits every three weeks during the CS Tapering Phase (Week 9 through Week 36 [Visit 4 through Visit 13], inclusive) as described in the tables below, provided that clinical status has not worsened.

Daily CS Dose Tapering (prednisone equivalent)

Daily CS Dose (mg/day)	Daily Dose Decrease (mg/day) every 3 weeks
> 40	10
≤ 40	5

The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.

Every Other Day CS Dose Tapering (prednisone equivalent)

Every Other Day CS Dose (mg/every other day)	Every Other Day Dose Decrease (mg/every other day) every 3 weeks
> 80 mg every other day	decrease by 20 mg on CS dosing days (every other day)
≤ 80 mg every other day	decrease by 10 mg on CS dosing days (every other day)

4. Follow-up Visits

Subjects will receive 3 safety/follow-up visits at Weeks 39, 42, 45 (corresponding to Visits 14, 15, 16, respectively). It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered clinically indicated.

Diagnosis and Main Eligibility Criteria: Eligible participants for this study will include adult subjects with a confirmed diagnosis of MG who have required systemic CS therapy for at least the preceding three months in order to control their signs and symptoms of MG. Subjects may be receiving immunosuppressive therapies within confines stipulated below and stable dosage of acetylcholinesterase inhibitors (e.g., pyridostigmine, neostigmine).

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 (AChR) antibody positive
3. Confirmed diagnosis of *generalized* MG *historically* meeting the clinical criteria for diagnosis of MG defined by the Myasthenia Gravis Foundation of America (MGFA) classification of Class II, III, IV, or V *historically* (Appendix 2).
4. At Screening, subjects may have symptoms controlled by CS (for example, only ocular [Class I] symptoms may be evident or there may be no symptoms) or be MGFA Class II-IVa inclusive (Class IVb and Class V excluded). *Note: Subjects who only have a history of ocular MG may not enroll.*
5. On systemic CS for a minimum period of at least three months and on a stable CS dose of ≥15 mg/day and ≤60 mg/day (prednisone equivalent) for the month prior to Screening. Individuals on alternate day CS dosing will be judged to be on a daily dose equivalent to half their alternate day dose (i.e., 40 mg/every other day = 20 mg/day)
6. The investigator feels that tapering the CS dose is currently appropriate (to be commenced as prescribed during this protocol)
7. At least one previous completed attempt to taper CS in order to minimize CS dose (lowest feasible dose based on observed MG signs and symptoms)
8. Subjects must be willing and able to provide written informed consent.
9. 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. Any dose change in concomitant immunosuppressant therapy, other than CS, in the prior six months
2. Any change in CS dose or acetylcholinesterase inhibitor (e.g., pyridostigmine) dose in the one month prior to Screening
3. A three-point change in Quantitative Myasthenia Gravis (QMG) score, increased or decreased, between the 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, or (at any time in the past) MC or hospitalization for MG exacerbation associated with a previous CS taper attempt
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 prior to Screening
7. Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months prior to Screening
8. History of non-response to intravenous immunoglobulin (IVIg) when used in maintenance therapy of the subject's MG, as judged by the investigator
9. Have received immune globulin treatment given by IV, subcutaneous, or intramuscular route within the last 3 months prior to Screening
10. Received plasma exchange (PLEX) performed within the last 3 months prior to Screening

11. Inadequate venous access
12. History of anaphylactic reactions or severe reactions to any blood-derived product
13. History of intolerance to any component of the IPs
14. Documented diagnosis of thrombotic complications to polyclonal IVIg therapy in the past
15. History of recent (within the last year) myocardial infarction or stroke
16. Uncontrolled congestive heart failure; embolism; or historically documented (within the last year) electrocardiogram (ECG) changes indicative of myocardial ischemia or atrial fibrillation
17. Current known hyperviscosity or hypercoagulable state
18. Currently receiving anti-coagulation therapy (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [e.g., fondaparinux]). Note that oral anti-platelet agents are allowed (e.g., aspirin, clopidogrel, ticlodipine)
19. History of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the Screening/Week -3 (Visit 0)
20. Active psychiatric illness that interferes with compliance or communication with health care personnel
21. Females of child-bearing potential who are pregnant, have a positive serum pregnancy test (human chorionic gonadotropin [HCG]-based assay), breastfeeding, or 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.)
22. 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.
23. Known Immunoglobulin A (IgA) deficiency and anti-IgA serum antibodies
24. 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)
25. 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.
26. Hemoglobin levels <9 g/dL
27. 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 Principal Investigator would compromise safety of the subject or the ability of the subject to complete the trial. No subject whose only MG treatment is CS alone may enroll, because in the blinded placebo arm this would mean that all MG treatment would be discontinued during CS taper, posing a substantial risk for the subject.

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 unblinded pharmacist or designee will prepare the IP to maintain the blind for all parties during infusions and study assessments.

The loading dose is 2 g/kg divided over 2 days starting after the randomization at Week 0 (Visit 1), followed by maintenance doses of 1 g/kg over 1 day every three weeks until Week 36 (Visit 13). IGIV-C will be infused intravenously. 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).

Placebo

Sterile 0.9% sodium chloride injection, USP (0.9% NaCl, USP) or equivalent will be used as Placebo. Placebo will be 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. Placebo will be infused intravenously.

Clinical Outcome Measures:

Primary Efficacy Variable:

The primary efficacy endpoint will be the percent of subjects in each arm achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1).

Secondary Efficacy Variables:

- Percent reduction in daily CS (prednisone or equivalent) dose from Baseline/Week 0 to Week 39 (Visit 14)
- Time to first episode of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Week 0 through Week 39 (Visit 1 through Visit 14)

Exploratory Variables:

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or

equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1)
- Percent of subjects CS-free at Week 39 (Visit 14)
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39 (Visit 14)
- Change from Baseline/Week 0 in fasting serum glucose at Week 39 (Visit 14)
- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14) compared to Baseline (Week 0)
- Percent of subjects experiencing MC (as defined in Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Number of episodes of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14)
- Change in 15-Item MG Quality-of-Life Instrument (MG-QOL) 15 from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change in Myasthenia Gravis-Activities of Daily Living (MG-ADL) from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change from baseline in serum Immunoglobulin (IgG) trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)
- Change from baseline in binding, blocking, and modulating AChR antibodies at Week 39 (Visit 14)
- Change from baseline in glycated hemoglobin A1c (HbA1c) at Week 39 (Visit 14)

Safety Study Variables

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
- 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 Assessments: 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)
- Hemolysis
- WHO-Five (WHO-5) Well-Being Index

Study Procedures:

Eligible subjects based on Screening evaluations will complete the Baseline assessments, thereby initiating the Treatment. Subjects will continue with assessments for 45 weeks, with scheduled assessments at Week 0 (Visit 1) (Baseline, post-Baseline, and loading infusion

over 2 days), followed by assessments and maintenance dosages every 3 weeks through Week 36 (Visit 13). The protocol-specified CS tapering will commence at Week 9 (Visit 4) and continue through Week 36 (Visit 13), inclusive, in conjunction with continued maintenance dosages of IP. Safety/Follow-up assessment visits are scheduled for Weeks 39, 42, and 45 (Visits 14, 15, and 16). Visits/procedures and assessments should be scheduled at the protocol specified study day ± 3 days.

Screening: Week -3 (Visit 0)

All subjects (or legally authorized representative) will start their participation in the study upon the signing of the informed consent form (ICF). Subjects will be assessed for study eligibility during the Screening Period. During Screening, subject numbers will also be assigned.

Subjects must hold 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 score.

The procedures and assessments conducted during Screening (Week -3, Visit 0) are listed in the full protocol text and Schedule of Study Procedures (Appendix 1).

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

Baseline, Prior to Randomization

Eligible subjects based on Screening evaluations will complete the Baseline assessments, thereby initiating the Treatment.

Subjects must hold 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 score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Baseline. 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 (20 mL/kg) given in divided doses over two days; 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).

The procedures and assessments conducted at Baseline/Week 0 (Visit 1) are listed in the full protocol text and Schedule of Study Procedures (Appendix 1). Baseline assessments will be immediately followed by randomization and initiation of IP loading infusions.

Randomization

Randomization will occur via Interactive Web Response System (IWRS) once all Baseline assessments are performed and eligibility is confirmed.

Post-Baseline/Post-Randomization Loading Dose Infusion

An unblinded Pharmacist or designee will prepare and dispense the IP per the randomization assignment and pharmacy manual. 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. The procedures and assessments conducted Post-Baseline/Post-Randomization are listed in the full protocol text and Schedule of Study Procedures (Appendix 1).

Investigational Product Run-in Maintenance Phase: Weeks 3 and 6 (Visits 2 and 3)

The first two maintenance dosages comprise the IP Run-In phase. An unblinded Pharmacist or designee will prepare and dispense the IP per the randomization assignment and pharmacy manual. For each infusion, documentation of total infusion volume prepared (as received from the pharmacist or designee), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation. Subjects must hold 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 score. The procedures and assessments performed at Week 3 and Week 6 (Visits 2 and 3) are listed in the full protocol text and Schedule of Study Procedures (Appendix 1).

Corticosteroid Tapering/IP Maintenance Phase: Week 9 to Week 36 (Visit 4 to Visit 13) Inclusive

Corticosteroid tapering will begin at Week 9 (Visit 4) after completion of the third maintenance IP dose. CS dosage in stable or improving subjects will be decreased at scheduled visits every three weeks during the CS Tapering phase (Week 9 through Week 36 [Visit 13]) predicated on current CS dose (prednisone equivalents): (a) if CS dosage > 40 mg/day, the dose decrease every 3 weeks is 10 mg/day; (b) if CS dosage is ≤ 40 mg/day, the dose decrease every 3 weeks is 5 mg/day. Commensurate dose changes are required for subjects receiving every other day CS dosing. Note that the rate of CS dose decrease is slower as subjects fall below the 40-mg per day threshold. During the CS Tapering phase, the last CS dose reduction can occur at Week 36 (Visit 13). The standardized CS tapering will continue unless there is worsening of MG (a priori per protocol definition). The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Weeks 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 visits to assure accurate assessment of the QMG score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow for accurate measurement of fasting serum glucose at Week 9 (Visit 4) and Week 24 (Visit 9). The procedures and assessments performed during the CS Tapering/IP Maintenance Phase are listed in the full protocol text and Schedule of Study

Procedures (Appendix 1).

After completion of IP infusion

- **Continue CS tapering as delineated in Section 3.3 (Week 36 [Visit 13] is last visit in which CS tapering occurs)**

Safety/Follow-up Phase: Week 39 to Week 45 (Visit 14 to Visit 16) Inclusive

Following the last step of the CS tapering at Week 36 (Visit 13), three additional visits will be performed at Weeks 39, 42, and 45 (Visits 14, 15, and 16). The primary efficacy endpoint is evaluated at Week 39 (Visit 14), given the long half-life of IP. Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Weeks 39, 42, and 45 visits (Visits 14, 15, and 16) to assure accurate assessment of the QMG score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Week 39 (Visit 14). It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated. The procedures and assessments performed during the Safety/Follow-up Phase are listed in the full protocol text and Schedule of Study Procedures (Appendix 1).

Definition and Management of MG Worsening:

During the study, MG worsening will be defined as:

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

During the CS Tapering phase, if a subject meets the definition of MG worsening as defined above, then the following increase in CS dose will occur as shown in the tables below:

***Daily* CS Dose Increase in Response to Worsening MG (CS Tapering Phase Only) (prednisone equivalent)**

CS Dose (mg/day) at Which Worsening Occurs	Dose Increase (mg/day)
≥ 15	20
< 15	15

***Every Other Day* CS Dose Increase in Response to Worsening MG (CS Tapering Phase Only) (prednisone equivalent)**

Every Other Day CS Dose (mg/every other day) at Which Worsening Occurs	Every Other Day Dose Increase (mg/every other day)
≥ 30	40
< 30	30

If an episode of MG worsening fails to improve with the above CS dose increase within 6 weeks (by the second subsequent visit), or if another specific episode requires a second dose increase at any time, the subject will be withdrawn from the study.

Special Note for subjects tapered to 0 mg CS per day: Some subjects with MG are uniquely sensitive to complete CS withdrawal (0 mg prednisone equivalent daily), and may become more vulnerable to MG triggers and sudden MG exacerbations. Therefore if a subject has tapered to 0 mg prednisone equivalent daily, any worsening MG signs or symptoms must be evaluated in clinic as soon as possible (recommended within 24 hours, allowed up to 48 hours) and treated aggressively with CS dose increase as delineated in the tables above. Once tapered to 0 mg CS per day, a 4-point QMG increase from Baseline/ Week 0 is not required for re-initiating CS because deterioration can be of greater severity and speed than expected and may be difficult to reverse.

Second Attempt to Taper CS:

Following a CS dose increase due to worsening MG as noted above, a second attempt at CS tapering may be made after the subject shows evidence of stabilization on the new CS dose for at least two visits (six weeks), and in the opinion of the investigator, there is no contraindication to resuming the tapering. This second attempt requires that there are still visits remaining in the CS Tapering phase.

Stabilization will be defined as a return to the subject's Baseline/Week 0 status prior to the episode of worsening, with QMG score ≤3 points relative to Baseline/Week 0, and return to

the baseline clinical symptom(s) that initially triggered the definition of worsening of MG as judged by physician.

On this second attempt to taper, the CS dose will be reduced in the same fashion as outlined in the above tables; however, the dose will not decrease below the last dose at which the subject was stable prior to their episode of MG worsening. During the CS Tapering phase, the last CS dose reduction can occur at Week 36 (Visit 13). An illustrative hypothetical example of three attempts to taper CS is provided in Appendix 10.

Statistical and Analytical Methods:

Determination of Sample Size

In order to provide 80% power to detect a 40% treatment difference (70% IGIV-C group versus 30% Placebo group) in the percent of subjects achieving a 50% or greater reduction in CS dosage at Week 39, alpha level = 0.05, a minimum of 24 subjects per treatment group is required. Assuming a discontinuation rate in the range of 20%, 60 subjects are planned to be randomized for the study. This is necessary to accommodate attrition anticipated.

Subject Populations for Analysis

- Intent-to-Treat (ITT) Population

The ITT population consists of all subjects who are randomized. Efficacy analyses will be performed on the ITT population.

- Safety Population

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

- Per Protocol Population

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in the per-protocol 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.

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

Primary Efficacy Analyses

The primary endpoint is the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1). The treatment comparison will be analyzed using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline CS dose (15-40 mg versus 41-60 mg). The null hypothesis (H0) and the alternative hypothesis (Ha) are:

$$H0: P1 = P2$$

$$Ha: P1 \neq P2$$

Where P1 and P2 represent the percent of subjects achieving a 50% or greater reduction in CS dose in the IGIV-C and the Placebo group, respectively.

Subjects who discontinued the study early due to the MG worsening will be considered as not achieving a 50% or greater reduction.

Primary efficacy analyses will be based on the ITT population. For sensitivity analysis, the

same analysis will be repeated using per-protocol population.

Secondary Efficacy Analyses

- Percent reduction in daily CS (prednisone or equivalent) dose from Baseline (Visit 1) to Week 39 (Visit 14)
  The percent daily CS dose reduction from baseline will be analyzed using analysis of covariance (ANCOVA). The ANCOVA model will include the percent daily CS dose reduction as dependent variable, treatment as fixed effect, and Baseline daily CS dose as a covariate.

- Time to first episode of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 through Week 39 (Visit 1 through Visit 14)

  Kaplan-Meier estimates will be provided for time to first episode of MG worsening for each treatment group. The treatment comparison will be performed using log-rank test adjusted for baseline CS dose (15 to 40 mg versus 41 to 60 mg).

Exploratory Efficacy Analyses

Exploratory efficacy variables that will be evaluated in this study include the following:

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1)
- Percent of subjects CS-free at Week 39 (Visit 14)
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39 (Visit 14)
- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14)
- Percent of subjects experiencing MC (as defined in Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Percent of subjects with 0, 1, or 2 episodes of MG worsening from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14) (in aggregate and by number of episodes/subject).

The following exploratory endpoints will be analyzed using the ANCOVA with treatment as main factor and baseline CS dose as covariate. In addition, the mixed model for repeated measurement (MMRM) will also be performed.

- Change from Baseline/Week 0 in fasting serum glucose at Week 39 (Visit 14)
- Change in 15-Item MG-QOL 15 from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change in MG-ADL from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change from baseline in serum IgG trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)

- Change from baseline in binding, blocking, and modulating AChR antibodies at Week 39 (Visit 14)
- Change from baseline in HbA1c at Week 39 (Visit 14)

Safety Analysis

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.

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.

TABLE OF CONTENTS

LIST OF APPENDICES

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
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
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
GBS	Guillain-Barré syndrome
HAV	Hepatitis A virus
Hb	Hemoglobin
HbA1c	Glycated hemoglobin A1c
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
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
IND	Investigational New Drug
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
ISRC	Independent Safety Review Committee
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVIg	Intravenous immunoglobulin
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
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 model for repeated measurement
NaCl	Sodium chloride
NAT	Nucleic acid testing
NINDS	National Institute of Neurological Disorders and Stroke
PE	Pulmonary embolism
PLEX	Plasma exchange
QMG	Quantitative myasthenia gravis
RBC	Red blood count
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
WHO-5	WHO-Five Well-Being Index

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 (AChRs) 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 anticholinesterase 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 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 above, 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). Corticosteroids are commonly a first choice drug when immunosuppressive drugs are necessary in MG (16). However, there are many important side effects including weight gain, fluid retention, hypertension, diabetes, anxiety/depression/insomnia/psychosis, glaucoma, cataract, gastrointestinal hemorrhage and perforations, myopathy, increased susceptibility to infections and avascular joint necrosis (16). Thus tapering the CS dose to the minimum effective dosage is good practice.

This is a multicenter, prospective, double-blind, placebo-controlled study to assess the efficacy and safety of IGIV-C in CS-dependent subjects with generalized MG and a history of Myasthenia Gravis Foundation of America (MGFA) clinical class II-V (34). The aim of the study is to demonstrate that IGIV-C (versus Placebo) may enhance feasibility of CS

tapering. The primary measure of efficacy for this study is the proportion of subjects achieving a ≥50% reduction in CS dosage at Week 39.

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 in this study will receive a loading IGIV-C dose of 2 g/kg of body weight followed by maintenance infusions at 3-week intervals at a dose of 1 g/kg of body weight. 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 of this study is to evaluate the efficacy of IV infusions of IGIV-C as compared to Placebo in reducing the maintenance dosage of corticosteroids in corticosteroid (CS)-dependent subjects with MG when given as an initial loading dose (2 g/kg) followed by 12 maintenance doses (1 g/kg) every 3 weeks through Week 36 by assessing the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1).

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 39 in the following:

- Percent reduction in daily CS (prednisone or equivalent) dose from Baseline to Week 39 (Visit 14)
- Time to first episode of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 through Week 39 (Visit 1 through Visit 14)

2.1.3 Exploratory Objectives

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

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1)
- Percent of subjects CS-free at Week 39 (Visit 14)
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39 (Visit 14)
- Change from Baseline/Week 0 in fasting serum glucose at Week 39 (Visit 14)
- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14) compared to Baseline (Week 0)
- Percent of subjects experiencing MC (as defined in Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Number of episodes of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14)
- Change in 15-Item MG Quality-of-Life Instrument (MG-QOL 15) from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change in MG Activities of Daily Living (MG-ADL) from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change from baseline in serum immunoglobulin G (IgG) trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)
- Change from baseline in binding, blocking, and modulating AChR antibodies at Week 39 (Visit 14)
- Change from baseline in glycated hemoglobin A1c (HbA1c) at Week 39 (Visit 14)

2.2 Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of one IGIV-C loading dose of 2 g/kg followed by 12 maintenance dosages of 1 g/kg every 3 weeks through Week 36 in CS-dependent 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 as a CS-sparing agent in CS-dependent MG. Approximately 60 adult subjects will be randomized in this study.

Subjects who have been dependent on systemic corticosteroids for at least the preceding three months and who have received a stable dose of CS for at least one month immediately prior to the Screening visit, will be randomly allocated in a 1:1 ratio into IGIV-C treatment group and Placebo treatment group to receive either IGIV-C or matched Placebo every three weeks in a double-blinded fashion. Randomization will be stratified by baseline CS dose:

- 15 mg – 40 mg prednisone equivalent per day
- 41 mg – 60 mg prednisone equivalent per day

For those subjects randomized to receive IGIV-C at the Baseline/Week 0 (Visit 1), an initial loading dose of 2 g/kg will be administered at the Baseline Visit (Visit 1). Note that the loading dosage is divided over 2 days as standard infusion time (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]). Loading dosage is followed by maintenance doses of 1 g/kg administered every third week until Visit 13 (Week 36). Note that the maintenance dosage is infused in 1 day as standard (extensions are 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]). For those subjects randomized to receive Placebo at the Baseline Visit (Visit 1), sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent will be infused in a manner that the blind is maintained. The volumes of Placebo will be equal to the volumes required for an initial loading dose at the Baseline Visit (Visit 1) and subsequent maintenance doses administered every third week until Visit 13 (Week 36).

Tapering of the CS dose will not be initiated until the subject receives a total of 3 complete doses of the investigational product (IP), which includes the initial loading dose (Visit 1 – Week 0) and the first two maintenance doses (Week 3 [Visit 2] and Week 6 [Visit 3]). The subject will begin a prescribed CS tapering regimen at Week 9 [Visit 4], coincident with receiving the fourth dose of IP. This regimen is described in "**CS Tapering Regimen**," Section 3.3.2. The tapering will be based on the CS dose (prednisone equivalent). If the CS dose is >40 mg/day the CS dose will be reduced in decrements of 10 mg at each visit (every 3 weeks); if the CS dose is ≤40 mg, the CS will be reduced in 5 mg decrements at each visit (every 3 weeks) in accordance with Table 3-1 and Table 3-2. Tapering will occur under the observation of the investigator. The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.

During the CS Tapering/IP Maintenance phase, study visits will occur every three weeks while the subject continues his/her CS tapering and maintenance doses of IP. Implementation of the CS dose reductions will last a maximum of 27 weeks. The investigator will attempt to hold the non-CS therapy (e.g., pyridostigmine) of the subjects' MG medical regimen constant through the end of the study (Week 45 [Visit 16]) unless there are worsening symptoms (defined in Section 3.3.3) or adverse effects due to other components of the subject's non-CS therapy.

During the CS Tapering phase, the last CS dose reduction can occur at Week 36 (Visit 13). Week 39 (Visit 14) will constitute the time point for the primary endpoint, an opportunity to assess the effect of the final CS dose reduction made at Week 36 (Visit 13), and the initiation of the Safety/Follow-up phase.

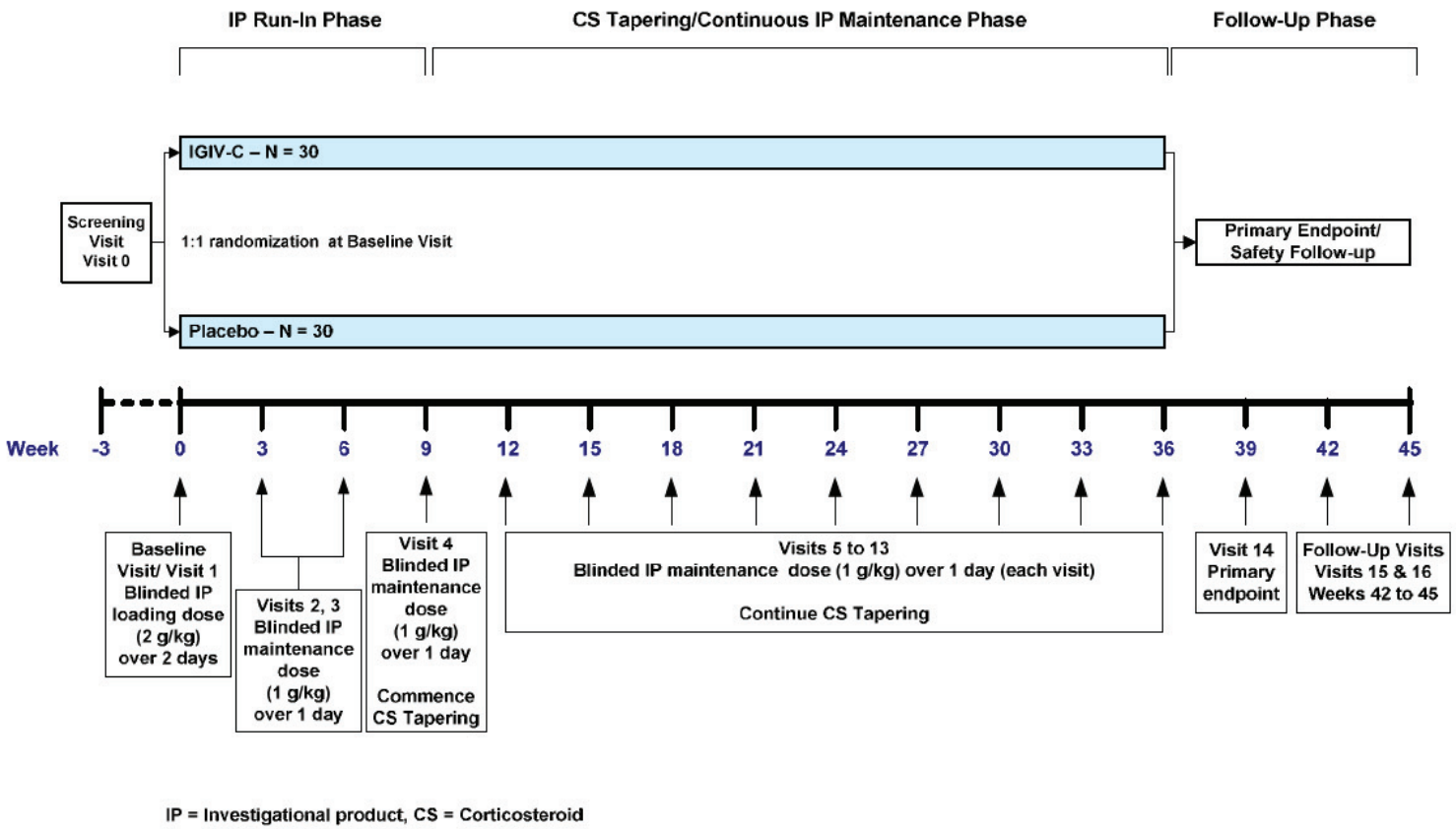
Subjects will receive 3 safety/follow-up visits (Weeks 39, 42, 45 corresponding to Visits 14, 15, 16, respectively). It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated.

A schematic of the overall study design and essential activities is shown in Figure 3-1, and a schedule of study procedures is provided in Appendix 1. Tools for assessing MG are provided in Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, and specific safety monitoring in Appendix 7, Appendix 8, and Appendix 9.

Worsening of MG symptoms

If at any point during the CS Tapering phase, the subject suffers a worsening of his/her MG symptoms, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," the CS dose will be increased by 20 mg if the CS dose (mg/day) at which worsening occurs is ≥15 mg/day or the dose will be increased by 15 mg/day if the CS dose (mg/day) at which worsening occurs is <15 mg/day in accordance with Table 3-3 and Table 3-4. The increased CS dose (prednisone equivalent) will be assessed over the next 2 consecutive visits (6 weeks). The subject's symptoms of MG must have re-stabilized while receiving this higher dose of CS for the subject to continue in the study. Stabilization is defined as a Quantitative Myasthenia Gravis (QMG) score increase of ≤3 points relative to Baseline/Week 0 and a return to baseline of clinical symptom(s) that triggered the definition of worsening of MG as judged by the physician investigator. If the episode of MG worsening fails to improve with the above CS dose increase within 6 weeks (by the second subsequent visit), the subject will be withdrawn from the study.

If the increased CS dose was successful in abating the QMG score worsening to within ≤3 points relative to Baseline/Week 0 and a return to baseline of clinical symptom(s) that triggered the definition of MG worsening as judged by the physician investigator, then a second attempt at tapering of the subject's new CS dose will be initiated according to Section 3.3.4. On this second attempt to taper, the CS dose will be reduced in the same fashion as outlined above; however, the dose will not decrease below the last dose at which the subject was stable prior to their episode of MG worsening. If the subject requires a second CS dose increase at any time, the subject will be withdrawn from the study. Also see Early Discontinuation Visit (Section 3.8.2.6) and Section 3.11.



IP = Investigational product, CS = Corticosteroid

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 MG who have required systemic CS therapy for at least the preceding three months in order to control their signs and symptoms of MG. Subjects may be receiving immunosuppressive therapies within confines stipulated below and stable dosage of acetylcholinesterase inhibitors (e.g., pyridostigmine, neostigmine).

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* meeting the clinical criteria for diagnosis of MG defined by the MGFA classification of Class II, III, IV, or V *historically* (Appendix 2).
4. At Screening, subjects may have symptoms controlled by CS (for example, only ocular [Class I] symptoms may be evident or there may be no symptoms) or be MGFA Class II-IVa inclusive (Class IVb and Class V excluded). *Note: Subjects who only have a history of ocular MG may not enroll.*
5. On systemic CS for a minimum period of at least three months and on a stable CS dose of ≥15 mg/day and ≤60 mg/day (prednisone equivalent) for the month prior to Screening. Individuals on alternate day CS dosing will be judged to be on a daily dose equivalent to half their alternate day dose (i.e., 40 mg/every other day = 20 mg/day)
6. The investigator feels that tapering the CS dose is currently appropriate (to be commenced as prescribed during this protocol)
7. At least one previous completed attempt to taper CS in order to minimize CS dose (lowest feasible dose based on observed MG signs and symptoms)
8. Subjects must be willing and able to provide written informed consent.
9. 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. Any dose change in concomitant immunosuppressant therapy, other than CS, in the prior six months
2. Any change in CS dose or acetylcholinesterase inhibitor (e.g., pyridostigmine) dose in the one month prior to Screening
3. A three-point change in QMG score, increased or decreased, between the Screening/Week -3 (Visit 0) and Baseline (Week 0 [Visit 1])
4. Any episode of MC in the one month prior to Screening, or (at any time in the past) MC or hospitalization for MG exacerbation associated with a previous CS taper attempt

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 prior to Screening
7. Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months prior to Screening
8. History of non-response to IVIg when used in maintenance therapy of the subject's MG, as judged by the investigator
9. Have received immune globulin treatment given by IV, subcutaneous, or intramuscular route within the last 3 months prior to Screening
10. Received plasma exchange (PLEX) performed within the last 3 months prior to Screening
11. Inadequate venous access
12. History of anaphylactic reactions or severe reactions to any blood-derived product
13. History of intolerance to any component of the IPs
14. Documented diagnosis of thrombotic complications to polyclonal IVIg therapy in the past
15. History of recent (within the last year) myocardial infarction or stroke
16. Uncontrolled congestive heart failure; embolism; or historically documented (within the last year) electrocardiogram (ECG) changes indicative of myocardial ischemia or atrial fibrillation
17. Current known hyperviscosity or hypercoagulable state
18. Currently receiving anti-coagulation therapy (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [e.g., fondaparinux]). Note that oral anti-platelet agents are allowed (e.g., aspirin, clopidogrel, ticlodipine)
19. History of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the Screening/Week -3 (Visit 0)
20. Active psychiatric illness that interferes with compliance or communication with health care personnel
21. Females of child-bearing potential who are pregnant, have a positive serum pregnancy test (human chorionic gonadotropin [HCG]-based assay), breastfeeding, or 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.)

22. 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.
23. Known Immunoglobulin A (IgA) deficiency and anti-IgA serum antibodies
24. 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)

25. 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.
26. Hemoglobin (Hb) levels <9 g/dL
27. 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 Principal Investigator would compromise safety of the subject or the ability of the subject to complete the trial. No subject whose only MG treatment is CS alone may enroll, because in the blinded placebo arm this would mean that all MG treatment would be discontinued during CS taper, posing a substantial risk for the subject.

3.3 Study Time Periods and Definitions

3.3.1 Investigational Product Run-in Phase

Subjects will receive a total of 3 complete doses of the IP in the IP Run-In phase, which includes the initial loading dose at the Baseline/Week 0 (Visit 1), and the first two maintenance doses at Weeks 3 and 6 (Visits 2 and 3). The CS dose will remain stable in this phase. CS tapering will begin at Week 9 (Visit 4), coincident with the third maintenance dose of IP.

3.3.2 Corticosteroid Tapering/IP Maintenance Phase

After completion of the third maintenance dose at Week 9 (Visit 4), subjects will begin a prescribed tapering regimen of their CS dose as described below.

CS Tapering Regimen: CS dosage in subjects will be decreased at scheduled visits every three weeks during the CS Tapering phase (Week 9 through Week 36 [Visit 4 through Visit 13], inclusive) as described in Table 3-1 and Table 3-2, provided that clinical status has not worsened as defined in Section 3.3.3 "**Definition and Management of MG Worsening**."

Table 3-1 *Daily* CS Dose Tapering (prednisone equivalent)

Daily CS Dose (mg/day)	Daily Dose Decrease (mg/day) every 3 weeks
> 40	10
≤ 40	5

The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.

Table 3-2 *Every Other Day* CS Dose Tapering (prednisone equivalent)

Every Other Day CS Dose (mg/every other day)	Every Other Day Dose Decrease (mg/every other day) every 3 weeks
> 80 mg every other day	decrease by 20 mg on CS dosing days (every other day)
≤ 80 mg every other day	decrease by 10 mg on CS dosing days (every other day)

3.3.3 Definition and Management of MG Worsening

During the study, MG worsening will be defined as:

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

During the CS Tapering phase, if a subject meets the definition of MG worsening as defined above, then the following increase in CS dose will occur as shown in Table 3-3 and Table 3-4:

Table 3-3 *Daily* CS Dose Increase in Response to Worsening MG (CS Tapering Phase Only) (prednisone equivalent)

CS Dose (mg/day) at Which Worsening Occurs	Dose Increase (mg/day)
≥ 15	20
< 15	15

Table 3-4 *Every Other Day* CS Dose Increase in Response to Worsening MG (CS Tapering Phase Only) (prednisone equivalent)

Every Other Day CS Dose (mg/every other day) at Which Worsening Occurs	Every Other Day Dose Increase (mg/every other day)
≥ 30	40
< 30	30

If an episode of MG worsening fails to improve with the above CS dose increase within 6 weeks (by the second subsequent visit), or if another specific episode requires a second dose increase at any time, the subject will be withdrawn from the study. Also see Early Discontinuation Visit (Section 3.8.2.6 and Section 3.11).

Special Note for subjects tapered to 0 mg CS per day: Some subjects with MG are uniquely sensitive to complete CS withdrawal (0 mg prednisone equivalent daily), and may become more vulnerable to MG triggers and sudden MG exacerbations. Therefore if a subject has tapered to 0 mg prednisone equivalent daily, any worsening MG signs or symptoms must be evaluated in clinic as soon as possible (recommended within 24 hours, allowed up to 48 hours) and treated aggressively with CS dose increase as delineated in the tables above. Once tapered to 0 mg CS per day, a 4-point QMG increase from Baseline/

Week 0 is not required for re-initiating CS because deterioration can be of greater severity and speed than expected and may be difficult to reverse.

3.3.4 Second Attempt to Taper CS

Following a CS dose increase due to worsening MG as noted in Section 3.3.3, a second attempt at CS tapering may be made after the subject shows evidence of stabilization on the new CS dose for at least two visits (six weeks), and in the opinion of the investigator, there is no contraindication to resuming the tapering. This second attempt requires that there are still visits remaining in the CS Tapering phase.

Stabilization will be defined as a return to the subject's Baseline/Week 0 status prior to the episode of worsening, with QMG score ≤3 points relative to Baseline/Week 0, and return to the baseline clinical symptom(s) that initially triggered the definition of worsening of MG as judged by physician.

On this second attempt to taper, the CS dose will be reduced in the same fashion as outlined in Table 3-1 and Table 3-2; however, the dose will not decrease below the last dose at which the subject was stable prior to their episode of MG worsening. During the CS Tapering phase, the last CS dose reduction can occur at Week 36 (Visit 13). An illustrative hypothetical example of three attempts to taper CS is provided in Appendix 10.

3.3.5 Myasthenic Crisis

Myasthenic (or MG) crisis will be defined as an episode of worsening (as defined in Section 3.3.3) which requires hospitalization. Hospitalizations solely for socioeconomic reasons would not fulfill criteria for MG crisis. Also see Early Discontinuation Visit (Section 3.8.2.6 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 IB.

The unblinded pharmacist or designee will prepare 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

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

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 over 2 days starting after the randomization at Week 0 (Visit 1), followed by maintenance doses of 1 g/kg over 1 day every three weeks until Week 36 (Visit 13). 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 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

IPs are 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 return or 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 Visit 13 (Week 36). 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 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 36 (Visit 13). 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 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]). 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.

- Immunoglobulin 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
- Subjects with PLEX within the last 3 months
- Anti-coagulation therapy at the time of Screening or Baseline (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], 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) that the subject was not already taking at Screening. Note: Methotrexate is allowed provided dose is stable for 6 months prior to Screening.
- Rituximab, belimumab, eculizumab, use of any monoclonal antibody for immunomodulation or any other investigational agent for treatment of myasthenia gravis
- Live viral vaccines (e.g., measles, mumps, rubella)
- PLEX

Treatments needed for myasthenic crisis or MG exacerbation requiring hospitalization are not restricted per protocol as this constitutes a real medical necessity and required interventions to assure subject safety are always allowed.

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 (other than CS) in the six months prior to Screening is not allowed for study eligibility. During the study, changes in concomitant immunosuppressant therapy are 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 in the one month prior to Screening is not allowed for study eligibility. During the study, changes in dosage are not allowed unless there is a real medical necessity for safety reasons in the investigator's opinion.

Use of medications known to potentially worsen myasthenia gravis is discouraged (unless medically required) including telithromycin, fluoroquinolones (e.g., Ciprofloxacin and Levofloxacin), Zithromax (azithromycin), aminoglycoside antibiotics, botulinum toxin, quinine, quinidine, procainamide, D-penicillamine, and β-blockers.

3.6 Efficacy Study Variables

3.6.1 Primary Variable

The primary efficacy endpoint will be the percent of subjects in each arm achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1).

3.6.2 Secondary Variables

Secondary efficacy variables assessed in this study are:

- Percent reduction in daily CS (prednisone or equivalent) dose from Baseline/Week 0 to Week 39 (Visit 14)
- Time to first episode of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Week 0 through Week 39 (Visit 1 through Visit 14)

3.6.3 Exploratory Variables

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

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1)
- Percent of subjects CS-free at Week 39 (Visit 14)
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39 (Visit 14)
- Change from Baseline/Week 0 in fasting serum glucose at Week 39 (Visit 14)

- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14) compared to Baseline (Week 0)
- Percent of subjects experiencing MC (as defined in Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Number of episodes of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14)
- Change in 15-Item MG-QOL 15 from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change in MG-ADL from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change from baseline in serum IgG trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)
- Change from baseline in binding, blocking, and modulating AChR antibodies at Week 39 (Visit 14)
- Change from baseline in HbA1c at Week 39 (Visit 14)

3.6.4 Quantitative Myasthenia Gravis (QMG) Score

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 score is easy to administer by clinical evaluators and/or physicians in approximately 30 minutes with minimal equipment to measure spirometry and muscle strength testing. A 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 score.

QMG score test items are attached 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 patients 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 Myasthenia Gravis-Activities of Daily Living (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 (42,43,44). 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 Myasthenia Gravis 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-QOL15 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) (45,46,47).

The MG-QOL15 and scoring are provided in Appendix 6.

3.7 Safety Study Variables

The following safety variables will be assessed in this study:

- AEs, suspected adverse drug reactions (suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
- 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 Assessments: 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)
- Hemolysis
- WHO-Five (WHO-5) Well-Being Index

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 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 completion of each maintenance dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 24 (Visit 9).

Procedures for the monitoring of TEs 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 at Baseline (prior to infusion), Day 1 (after the first loading infusion), at the time when the last loading infusion is complete, and at completion of each maintenance dosage at Week 3 (Visit 2), Week 6 (Visit 3), and Week 24 (Visit 9) for hemolysis detection. 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 24 (Visit 9).

Procedures for hemolysis detection are provided in Appendix 8.

3.7.3 WHO-Five (WHO-5) Well-Being Index

The WHO-5 Well-Being Index score will be used to measure CS side effects. This index is an easy to use 5-item questionnaire designed to measure current mental well-being (over the last 2 weeks) and may be a useful tool for reflecting mood (48,49,50,51). Cross cultural evaluation has been performed and the index has been utilized in clinical trials.

The WHO-5 Well-Being Index and scoring is provided in Appendix 9.

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 over 2 days starting after randomization. Maintenance infusions of blinded IP will be given at doses of 1 g/kg over 1 day every three weeks through Week 36 (Visit 13). 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).

The IP Run-in consists of the loading infusion and maintenance infusions received prior to Week 9 (Visit 4). After completion of the third maintenance dosage at Visit 4 (Week 9), subjects will begin the protocol-prescribed CS tapering which will continue from Week 9 (Visit 4) through Week 36 (Visit 13) provided that clinical status has not worsened as defined in Section 3.3.3, whilst continuing maintenance IP infusions at 3-week intervals. After

completion of the treatment period, there is a 9-week Safety/Follow-up period through Week 45 (Visit 16).

3.8.2 Observations and Measurements

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 Overall Study Schema (Figure 3-1) and 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).

Eligible subjects based on Screening evaluations will complete the Baseline assessments, thereby initiating the Treatment. Subjects will continue with assessments for 45 weeks, with scheduled assessments at Week 0 (Visit 1) (Baseline, post-Baseline, and loading infusion over 2 days), followed by assessments and maintenance dosages every 3 weeks through Week 36 (Visit 13). The protocol-specified CS tapering will commence at Week 9 (Visit 4) and continue through Week 36 (Visit 13), inclusive, in conjunction with continued maintenance dosages of IP. Safety/Follow-up assessment visits are scheduled for Weeks 39, 42, and 45 (Visits 14, 15, and 16). *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 hold 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 score. 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
- Subject number assigned
- Medical history including demographics and prior/concomitant diseases
- Prior and concomitant medications
- Record CS dose prescribed this visit; instruct subjects to document CS doses taken during the entire study
- Full physical exam (excluding breast and genitourinary areas) and waist circumference
- Vital signs including T, RR, HR, SBP, and DBP
- Inclusion/exclusion criteria review
- Height
- Weight (Screening will be used to calculate IP infusion dose for Visits 1-3)
- Laboratory assessments (see Section 3.8.3)
  - Blood

- Serum Pregnancy Test (β human chorionic gonadotropin [HCG]) (potential child-bearing females 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)

- TEs risk monitoring assessment
- QMG score
- MGFA Clinical Classification
- MG Composite Score
- AEs with onset after informed consent is signed

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

Subjects must hold 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. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Baseline. 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 (20 mL/kg) given in divided doses over two 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

- Laboratory assessments (see Section 3.8.3):
  - Urine
    - Urine sediment and measuring of hemoglobinuria/hematuria
  - 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
    - HbA1c
    - **Fasting** serum glucose (following which subject may eat)
    - Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies

    - Retain samples for virus safety testing as detailed in Table 3-5 (These retention samples will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], or parvovirus B19 [B19V] infection while participating in the study. These samples will be retained until all analyses in support of the study are complete.)
- TEs 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
- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken
- Full physical exam (excluding breast and genitourinary areas) and waist circumference. In addition, assess the following features as either absent (0) or present with grading indicated as mild (1), moderate (2), or severe (3) for each of the following:
  a. Moon face
  b. Centripetal obesity
  c. Dorsalcervical fat pad
  d. Thin skin/easy bruising
  e. Skin striae
  f. Hirsutism (women)
  g. Acne (both genders)

Changes in these graded parameters are not considered AEs.

- Vital signs including T, RR, HR, SBP, and DBP
- Inclusion/exclusion criteria review (e.g., QMG score relative to Screening [to be eligible must be within 3 points of Screening value])
- QMG score
- MG Composite
- MG-ADL
- MG-QOL 15
- MGFA Class
- WHO-5 Well-Being Index

RANDOMIZATION

- Randomization will occur via IWRS once all Baseline assessments are performed and eligibility is confirmed

POST-BASELINE/POST-RANDOMIZATION LOADING DOSE INFUSION

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and 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 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 medication
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post loading dose infusion

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

The first two maintenance dosages comprise the IP Run-In phase. *Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 3 and 6 (Visits 2 and 3) to assure accurate assessment of the QMG.* At Week 3 and Week 6 (Visits 2 and 3), the following will be performed:

- **Maintain stable CS dose**
- QMG score to be assessed pre-infusion
- MG Composite to be assessed pre-infusion
- Record complete vital signs including T and RR
- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and the 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 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
- Record CS dose prescribed at each visit; review subject's prior adherence; instruct subject to continue to document CS doses taken
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion

3.8.2.5 Corticosteroid Tapering/IP Maintenance Phase: Week 9 to Week 36 (Visit 4 to Visit 13) Inclusive

CS tapering will begin at Week 9 (Visit 4) after completion of the third maintenance IP dose. CS dosage in stable or improving subjects will be decreased at scheduled visits every three weeks during the CS Tapering phase (Week 9 through Week 36 [Visit 13]) predicated on current CS dose (prednisone equivalents): (a) if CS dosage is >40 mg/day, the dose decrease every 3 weeks is 10 mg/day; (b) if CS dosage is ≤40 mg/day, the dose decrease every 3 weeks is 5 mg/day. Commensurate dose changes are required for subjects receiving every other day CS dosing (Table 3-1 and Table 3-2). Note that the rate of CS dose decrease is slower as subjects fall below the 40-mg per day threshold. During the CS Tapering phase, the last CS dose reduction can occur at Week 36 (Visit 13). The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.

The standardized CS tapering will continue unless there is worsening of MG which is defined as:

- QMG score increase by ≥ 4 points relative to Baseline

During the CS Tapering phase, if a subject meets the definition of worsening then the CS dosage (prednisone equivalents) will increase based on the CS dosage at which worsening occurs. The CS dose increase will be 20 mg/day if the CS dosage (mg/day) at the time of worsening is ≥ 15 mg/day, or the CS dose increase will be 15 mg/day if the CS dosage (mg/day) at time of worsening is < 15 mg/day. Commensurate dose changes are required for subjects receiving every other day CS dosing (Table 3-3 and Table 3-4).

If an episode of MG worsening fails to improve with the above CS dose increase within 6 weeks (by the second subsequent visit), or if the specific episode requires a second dose increase at any time, the subject will be withdrawn from the study. Details are provided in Section 3.3.

Following a CS dose increase due to worsening MG, a second attempt at CS tapering may be made after the subject shows evidence of stabilization on the new CS dose for at least two visits (six weeks), and in the opinion of the PI, there is no contraindication to resuming the tapering. This second attempt requires that there are still visits remaining in the CS Tapering phase. Stabilization will be defined as a return to the subject's Baseline/Week 0 status prior to the episode of worsening, with QMG score ≤3 points relative to Baseline/Week 0, and return to the baseline clinical symptom(s) that initially triggered the definition of worsening of MG as judged by the physician.

On this second attempt to taper, the CS dose will be reduced in the same fashion as before; however, the dose will not decrease below the last dose at which the subject was stable prior to their episode of MG worsening. Appendix 10 provides an example of this scenario.

During the CS Tapering phase, assessments and maintenance IP infusions occur every 3 weeks. The assessments performed at the Week 9 (Visit 4) and Week 24 (Visit 9) are comprehensive and are nearly the same for both visits (with the exception that Week 24 [Visit 9] includes assessments for hemolysis and thrombosis risk); assessments at Week 12, 15, 18, 21, 27, 30, and 33 (Visits 5, 6, 7, 8, 10, 11, and 12) are identical though requiring fewer evaluations. The Week 36 (Visit 13) is the last visit which includes IP infusion and is the last time point for CS tapering.

STUDY WEEK 9 (VISIT 4)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 9 Visit to assure accurate assessment of the QMG score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Week 9 (Visit 4).

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

- Full physical exam (excluding breast and genitourinary areas) and waist circumference. In addition, assess the following features as either absent (0) or present with grading indicated as mild (1), moderate (2), or severe (3) for each of the following:
  a. Moon face
  b. Centripetal obesity
  c. Dorsalcervical fat pad
  d. Thin skin/easy bruising
  e. Skin striae
  f. Hirsutism (women)
  g. Acne (both genders)
- Weight (to be used to calculate IP infusion dosage for the scheduled visit and subsequent IP infusions until the next scheduled weight is measured).

  - Note: Subject weight collected at Visit 4 is used for IP dose calculations for Visits 4 to 8.
- Full vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments: Hematology, Chemistry (see Section 3.8.3)
- HbA1c
- Blood for IgG (trough)
- **Fasting** serum glucose (following which subject may eat)
- QMG score
- MG Composite
- MG-QOL 15
- MG-ADL
- WHO-5 Well-Being Index

IP infusion:

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

After completion of IP infusion

- **Initiate CS tapering as delineated in Section 3.3.**
- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

STUDY WEEK 12, WEEK 15, WEEK 18, WEEK 21 (VISITS 5 TO 8 INCLUSIVE)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 12, Week 15, Week 18, and Week 21 (Visits 5 to 8 inclusive) to assure accurate assessment of the QMG score.

Assessments to be performed pre-infusion:

- Full vital signs including T, RR, HR, SBP, and DBP
- QMG score
- MG Composite

IP infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual.
  - Note: Subject weight collected at Visit 4 (Week 9) is used for IP dose calculations for Visits 4 to 8 (Weeks 9 – 21).
- 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.
- 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

After completion of IP infusion

- Continue CS tapering as delineated in Section 3.3.
- Record corticosteroid dose prescribed at each visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

STUDY WEEK 24 (VISIT 9)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 24 (Visit 9) to assure accurate assessment of the QMG score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Week 24 (Visit 9).

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

- Full physical exam (excluding breast and genitourinary areas) and waist circumference. In addition, assess the following features as either absent (0) or present with grading indicated as mild (1), moderate (2), or severe (3) for each of the following:
  a. Moon face
  b. Centripetal obesity

c. Dorsalcervical fat pad
d. Thin skin/easy bruising
e. Skin striae
f. Hirsutism (women)
g. Acne (both genders)

- Weight (to be used to calculate IP infusion dosage for the scheduled visit and subsequent IP infusions until the next scheduled weight is measured).
- Full vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments: Hematology, Chemistry (see Section 3.8.3)
- HbA1c
- Blood for IgG (trough)
- **Fasting** serum glucose (following which subject may eat)
- Hemolysis evaluation (laboratory parameters: Hb, hematocrit, RBC (from hematology specimen), blood smear, ARC, serum free Hb, haptoglobin, LDH, DAT, total and indirect bilirubin (TBL from chemistry specimen); urine for urinary sediment and hemoglobinuria/hematuria), and Thromboembolism evaluation (Wells score and D-dimer) will be performed at the time when last maintenance infusion is complete. Appendix 7 and Appendix 8 provide details.
- QMG score
- MG Composite
- MG-QOL 15
- MG-ADL
- WHO-5 Well-Being Index

IP infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual.
  - Note: Visit 9 (Week 24) subject weight is used for IP dose calculations for Visits 9 to 13 (Weeks 24 – 36).
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note: 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.
- 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

After completion of IP infusion

- **Continue CS tapering as delineated in Section 3.3.**
- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken
- Additional hemolysis evaluation (laboratory parameters) will be performed 7 days post maintenance infusion

STUDY WEEK 27, WEEK 30, WEEK 33 (VISITS 10 TO 12 INCLUSIVE)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 27, Week 30, and Week 33 (Visits 10 to 12 inclusive) to assure accurate assessment of the QMG score.

Assessments to be performed pre-infusion:

- Full vital signs including T, RR, HR, SBP, and DBP
- QMG score
- MG Composite

IP infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual.
  - Note: Visit 9 subject weight is used for IP dose calculations for Visits 9 to 13.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). 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.
- 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

After completion of IP infusion

- **Continue CS tapering as delineated in Section 3.3**

- Record CS dose prescribed at each visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

STUDY WEEK 36 (VISIT 13)

The final maintenance IP dosage is administered during the Week 36 (Visit 13); this is also the final visit for the CS tapering adjustment. *Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Week 36 (Visit 13) to assure accurate assessment of the QMG score.*

Assessments to be performed pre-infusion:

- Full vital signs including T, RR, HR, SBP, and DBP
- QMG score
- MG Composite

IP infusion:

- Unblinded Pharmacist or designee, to prepare and dispense the IP per randomization assignment and Pharmacy Manual.
  - Note: Visit 9 subject weight is used for IP dose calculations for Visits 9 to 13.
- Administer the maintenance dosage (blinded active or placebo) of 1 g/kg over 1 day (per Pharmacy Manual). Note: 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.
- 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

After completion of IP infusion

- **Continue CS tapering as delineated in Section 3.3 (this is last visit in which CS tapering occurs)**
- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

3.8.2.6 Safety / Follow-up Phase: Week 39 to Week 45 (Visit 14 to Visit 16) Inclusive

Following the last step of the CS tapering at Week 36 (Visit 13), three additional visits will be performed at Weeks 39, 42, and 45 (Visits 14, 15, and 16). The primary efficacy endpoint is evaluated at Week 39 (Visit 14), given the long half-life of IP.

STUDY WEEK 39 (VISIT 14)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 39 (Visit 14) to assure accurate assessment of the QMG score. Additionally, subjects must fast for at least 8 hours (e.g., overnight) to allow accurate measurement of fasting serum glucose at Week 39 (Visit 14).

Assessments to be performed are the following:

- Full physical exam (excluding breast and genitourinary areas) and waist circumference. In addition, assess the following features as either absent (0) or present with grading indicated as mild (1), moderate (2), or severe (3) for each of the following:
  a. Moon face
  b. Centripetal obesity
  c. Dorsalcervical fat pad
  d. Thin skin/easy bruising
  e. Skin striae
  f. Hirsutism (women)
  g. Acne (both genders)

Changes in these graded parameters are not considered AEs.

- Weight
- Full vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments: Hematology, Chemistry (see Section 3.8.3)
- HbA1c
- Blood for IgG (trough)
- **Fasting** serum glucose (following which subject may eat)
- Quantitative/semi-quantitative binding, blocking, and modulating AChR antibodies
- QMG score
- MG Composite
- MG-QOL 15
- MG-ADL
- WHO-5 Well-Being Index
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Concomitant medications
- It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated.

- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

STUDY WEEK 42 (VISIT 15)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 42 (Visit 15) to assure accurate assessment of the QMG score.

Assessments to be performed are the following:

- Full vital signs including T, RR, HR, SBP, and DBP
- QMG score
- MG Composite
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Concomitant medications
- It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated.
- Record CS dose prescribed this visit; review subject's prior adherence; instruct subject to continue to document CS doses taken

STUDY WEEK 45 (VISIT 16)

Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to Week 45 (Visit 16) to assure accurate assessment of the QMG score.

This is the Final Study Visit. Assessments to be performed are the following:

- Full physical exam (excluding breast and genitourinary areas) and waist circumference
- Weight
- Full vital signs including T, RR, HR, SBP, and DBP
- Clinical laboratory assessments: Hematology, Chemistry (see Section 3.8.3)
- QMG score
- MG Composite
- MG-QOL 15
- MG-ADL
- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Concomitant medications
- Record CS dose prescribed this visit; review subject's prior adherence

It is suggested that the investigator consider an increase in CS dose after subjects complete the Week 39 (Visit 14) assessments if considered medically indicated.

EARLY DISCONTINUATION VISIT

The Early Discontinuation Visit includes the same assessments as the Week 45 visit with the exception of not including MG-QOL 15.

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 below 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 hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Early Discontinuation Visit to assure accurate assessment of the QMG score.*

The following procedures and assessments will be conducted at the Early Discontinuation Visit:

- AEs (includes clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Concomitant medications
- Record CS dose prescribed this visit; review subject's prior adherence
- Full physical exam (excluding breast and genitourinary areas) and waist circumference
- Weight
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.8.3):
  - Chemistry
  - Hematology
- QMG score
- MG Composite
- MG-ADL

Subjects who withdraw IP due to the occurrence of a treatment-emergent adverse event (TEAE) (or other reason) during the treatment period should be followed for safety by completing the two additional visits in the Follow-up Phase. Specifically subjects discontinuing during the IP Run-in maintenance and CS Tapering/IP Maintenance phases should complete assessments at the specified visit intervals for the Week 42 and Week 45 visits, which are 6 and 9 weeks post end-of-IP administration.

3.8.3 Description of Laboratory Tests and Procedures

Table 3-5 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), potassium, aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBL)	Central
Fasting serum glucose & HbA1c	Fasting serum glucose & HbA1c. HbA1c is produced by glycation of hemoglobin A, and reflects the mean blood glucose level over a period of one or two months before the blood sample is taken. Fasting serum glucose may reflect more immediate changes.	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 39 quantitative/semi-quantitative measurement of blinding, 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 (HCG) for females of child-bearing potential. Results must be negative to continue in the study.	Central
Viral Nucleic Acid Testing (NAT)	Retains [b]: Hepatitis A virus (HAV) RNA, Hepatitis B virus (HBV) DNA, Hepatitis C virus (HCV) RNA, Human immunodeficiency virus (HIV) RNA, Parvovirus B19 (B19V) DNA	Central
Viral Serology	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 will be collected at Baseline/Week 0 prior to randomization but will be tested *only* if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V 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 signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study.

3.8.3.1 Thromboembolic Events Risk Testing

Measurement of D-dimer blood levels and TEs 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 24 (Visit 9). 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) 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 24 (Visit 9). 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 24 (Visit 9). Appendix 8 provides details.

3.8.3.3 Virus Safety Testing

Viral NAT and viral serology retain samples 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 HAV, HBV, HCV, HIV, or B19V 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 HAV, HBV, HCV, HIV, or B19V 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 and Week 39.

Baseline and Week 39 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 validated 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 validated 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 randomization 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 (e.g., CS dosage subsequently stable and meeting protocol entry requirements); a new informed consent form must be signed for re-screening.

3.10 Removal of Subjects

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
- If an episode of MG worsening fails to stabilize with the CS dose increase as described in Sections 3.3.3 and 3.3.4 within 6 weeks (by the second subsequent visit), or if another specific episode of MG worsening requires a second dose increase at any time, the subject will be withdrawn from the study. MG crisis requiring hospitalization in accordance with Section 3.3.5 would also be grounds for study discontinuation.
- 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 Discontinuation Visit procedures (see Section 3.8.2.6) as soon as practical following decision to withdraw (at least within 14 days after the termination date) if the subject is willing. If discontinuation is due to a TEAE (or other reason) during the treatment period (which includes IP Run-in maintenance and CS Tapering/IP Maintenance phases) assessments specified for the two additional visits in the

Safety/Follow-up phase should be performed, i.e., Week 42 (Visit 15) and Week 45 (Visit 16) corresponding to time points 6 and 9 weeks after the last IP administration.

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 patients, 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 patients that blinded IGIV-C/Placebo can interfere with their immune response to live viral vaccines. Inform patients 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 assessments
- Blood chemistry and hematology
- TEs
- 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 Assessment

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. In addition to the routine physical exam, particular features will be evaluated as part of the physical exam performed at Baseline (Week 0), Visit 4 (Week 9),

Visit 9 (Week 24), and Visit 14 (Week 39) as an inventory of manifestations of steroid excess. Specifically, the following features will be assessed as either absent (0) or present with grading indicated as mild (1), moderate (2), or severe (3) for each of the following:

a. Moon face
b. Centripetal obesity
c. Dorsalcervical fat pad
d. Thin skin/easy bruising
e. Skin striae
f. Hirsutism (women)
g. Acne (both genders)

Changes in these graded parameters are not 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 Table 3-5).

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/Adverse Reaction

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 (52):

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 (53,54).

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 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 change 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 is unusual to be 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 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. Seriousness (not severity) is a medical term while severity is a subjective term.

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, Grifols Medical Monitor will routinely review reported AEs for possible hemolysis. Hemolysis will be recorded as an AE, and 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 an exacerbation of MG, or 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 medical 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 change 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

Email: CCI
FAX (back-up only): CCI (US/Canada)
and CCI (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 inferential tests are two-sided with alpha level at 0.05.

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. Efficacy analyses will be performed on the ITT population.

SAFETY POPULATION

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

PER-PROTOCOL POPULATION

The per-protocol population consists of all subjects in the ITT population without any major protocol deviation that 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 per-protocol 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 endpoint is the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1). The treatment comparison will be analyzed using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline CS dose (15-40 mg versus 41-60 mg). The null hypothesis (H_0) and the alternative hypothesis (H_a) are:

$$H_0: P_1 = P_2$$
$$H_a: P_1 \neq P_2$$

Where P1 and P2 represent the percent of subjects achieving a 50% or greater reduction in CS dose in IGIV-C and Placebo group, respectively.

Subjects who discontinued the study early due to the MG worsening will be considered as not achieving a 50% or greater reduction. In subjects who discontinue the study early due to other reasons, the last observation carried forward (LOCF) method will be used to compute the missing CS dose and drive the primary efficacy endpoint. Also, as a sensitivity analysis, the primary efficacy endpoint will be analyzed for all subjects who complete the CS dose up to Week 39 (Visit 14).

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

5.1.3.2 Secondary Efficacy Analyses

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

- Percent reduction in daily CS (prednisone or equivalent) dose from Baseline to Week 39 (Visit 14)
  The percent daily CS dose reduction from baseline will be analyzed using analysis of covariance (ANCOVA). The ANCOVA model will include the percent daily CS dose reduction as dependent variable, treatment as fixed effect, and Baseline daily CS dose as a covariate.

- Time to first episode of MG worsening, as defined in Section 3.3.3 "**Definition and Management of MG Worsening**," from Baseline/Week 0 through Week 39 (Visit 1 through Visit 14)
  Kaplan-Meier estimates will be provided for time to first episode of MG worsening for each treatment group. The treatment comparison will be performed using log-rank test adjusted for baseline CS dose (15 to 40 mg versus 41 to 60 mg).

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 with the same approach as the primary efficacy endpoint using the ITT population: In the situation where the CMH method is not appropriate due to the sparse events, the Fisher exact test will be used for treatment comparison.

Exploratory efficacy variables that will be evaluated in this study include the following:

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 (Visit 14) from Baseline/Week 0 (Visit 1)
- Percent of subjects CS-free at Week 39 (Visit 14)
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39 (Visit 14)
- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14)
- Percent of subjects experiencing MC (as defined in Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Percent of subjects with 0, 1, or 2 episodes of MG worsening from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14) (in aggregate and by number of episodes/subject).

The following exploratory endpoints will be analyzed using the ANCOVA with treatment as main factor and baseline CS dose as covariate. In addition, the mixed model for repeated measurement (MMRM) will also be performed.

- Change from Baseline/Week 0 in fasting serum glucose at Week 39 (Visit 14)
- Change in 15-Item MG-QOL 15 from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change in MG-ADL from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline to Week 42 and Week 45 (Visit 15 and Visit 16)
- Change from baseline in serum IgG trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)
- Change from baseline in binding, blocking, and modulating AChR antibodies at Week 39 (Visit 14)
- Change from baseline in HbA1c at Week 39 (Visit 14)

In addition, exploratory analyses of the correlation between CS dose reduction and blood pressure (hypertension), measures of glycemic control, weight, body habitus/Cushingoid features, and mood/emotional well-being will be explored.

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 (includes suspected ADRs), vital signs, physical assessments 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.

AEs will be coded and classified using MedDRA terms (system organ class and preferred terms).

AEs will be classified as TEAEs or non-TEAEs depending on the comparison of AE onset date/time with the start date/time of study treatment with the IP. 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, 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.

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 Assessment:

Physical Exam findings (normal and abnormal) will be listed for each clinical trial subject with the specific findings observed included in the listing. Abnormal findings judged as clinically relevant by the investigator in the context of the patient's medical history will be considered AEs. In addition, additional features related to CS side effects (graded as absent [0], mild [1], moderate [2], or severe [3]) will be listed and summarized.

Blood chemistry and hematology:

All clinical laboratory data for renal (creatinine, BUN, potassium), hepatic (ALT, AST, ALP, and TBL) and hematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subject. 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. 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.

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

In order to provide 80% power to detect a 40% treatment difference (70% IGIV-C versus 30% Placebo group) in the percent of subjects achieving a 50% or greater reduction in CS dosage at Week 39, alpha level = 0.05, a minimum of 24 subjects per treatment group is required. Assuming a discontinuation rate in the range of 20%, 60 subjects are planned to be randomized for the study. This is necessary to accommodate attrition anticipated.

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 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 presentation.

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10 APPENDICES

Appendix 1 Schedule of Study Procedures

Study Period / Procedures/Assessments	Screening	Baseline	Loading IP Dose over 2 Days		IP Run-In Maintenance				Corticosteroid Tapering/IP Maintenance										Safety/Follow-up		
Visit	**0**	**1**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**	**14**	**15**	**16**
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**	**18**	**21**	**24**	**+7 days post**	**27**	**30**	**33**	**36**	**39**	**42**	**45 [o]**
Informed Consent	X																					
Inclusion/Exclusion Criteria[a]	X	X																				
Randomization[b]		X																				
Serum Pregnancy Test[c]	X																					
Demographics/Medical History	X																					
Full Physical Exam and waist circumference[d]	X	X[d,e]							X[e]					X[e]						X[d]		X
Height	X																					
Weight[f]	X								X[e]					X[e]						X		X
Vital signs[g]	X	X	X		X		X		X	X	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		X
Fasting Serum Glucose & HbA1c[i]		X[e]							X[e]					X[e]						X		
QMG score[j]	X	X[e]			X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X	X	X
MG Composite	X	X[e]			X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]	X	X[e]	X[e]	X	X	X
MG-QOL 15		X[e]							X[e]					X[e]						X		X
MG-ADL		X[e]							X[e]					X[e]						X		X
WHO-5 Well-Being Index		X[e]							X[e]					X[e]						X		
MGFA Class	X	X[e]																				
Blood for IgG (trough)		X[e]							X[e]					X[e]						X		

Study Period / Procedures/Assessments	Screening	Baseline	Loading IP Dose over 2 Days		IP Run-In Maintenance				Corticosteroid Tapering/IP Maintenance										Safety/Follow-up		
Visit	**0**	**1**	**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**	**14**	**15**	**16**
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**	**18**	**21**	**24**	**+7 days post**	**27**	**30**	**33**	**36**	**39**	**42**	**45 [o]**
Blood for Anti- AchR Antibodies	X																					
Quantitative/Semi-quantitative Binding, Blocking, and Modulating AChR Antibodies		X[e]																		X		
Hemolysis Evaluation[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]						X[l]	X[l]							
Thromboembolism Evaluation (Wells Score and D-Dimers)[l]	X	X[l]	X[l]		X[l]		X[l]							X[l]								
AE Assessment/Review of Clinical Signs/Symptoms[k]	X	X	X		X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Prior & Concomitant Medications	X	X	X		X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Administration of IP		X[m]	X[m]		X[n]		X[n]		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]		X[n]	X[n]	X[n]	X[n]			
Corticosteroid Tapering									X	X	X	X	X	X		X	X	X	X			
Record corticosteroid dose prescribed	X	X	X		X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Review subject's adherence based on subject's documentation of CS doses taken	X	X	X		X		X		X	X	X	X	X	X		X	X	X	X	X	X	X

AChR = anti-acetylcholine receptor, CS = corticosteroid, HbA1c = hemoglobin A1c, IgG = immunoglobulin, 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 for subject to continue in the study.

[d] Excludes breast and genitourinary exam. At Baseline Visit (Week 0, prior to randomization), Visit 4 (Week 9), Visit 9 (Week 24), and Visit 14 (Week 39), full physical exam includes additional assessment of the following features as either absent (0) or present with grading indicated as mild (1), moderate (2), or

severe (3) for each of the following: (a) moon face, (b) centripetal obesity, (c) dorsalcervical fat pad, (d) thin skin/easy bruising, (e) skin striae, (f) hirsutism (women), (g) acne (both genders). Changes in these graded parameters are not considered AEs.

[e] Assessments to be performed pre-infusion on study visits during which IP dosage occurs.

[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. Screening subject weight is used to calculate the IP infusion dose for IP Visits 1-3, Visit 4 (Week 9) subject weight for IP Visits 4-8, and Visit 9 (Week 24) subject weight for IP Visits 9-13.

[g] Full vital signs including T, RR, HR, SBP, and 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 HAV, HBV, HCV, HIV, or B19V infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. See Section 3.8.3 and Table 3-5 for details.

[i] *Subjects must fast for at least 8 hours (e.g. overnight) to allow accurate measurement of fasting serum glucose.*

[j] *Subjects must hold their acetylcholinesterase inhibitor (e.g., pyridostigmine) dosage for 12 hours prior to the Visit to assure accurate assessment of the QMG score.*

[k] Includes clinical observation of signs and symptoms suggestive of any significant disease or condition (e.g., thrombosis, anemia etc)

[l] 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 24 (Visit 9). Hemolysis evaluation includes Hb, hematocrit, RBC, blood smear, serum free Hb, haptoglobin, LDH, DAT, ARC, total and 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 24 (Visit 9).

[m] Initiation of induction (loading) dose of IGIV-C 2.0 g/kg begins after all Baseline assessments are complete and subject 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 80 g/day [corresponding to 80 kg body weight]).

[n] Maintenance doses of 1 g/kg are administered over 1 day every three weeks through Week 36. 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]).

[o] **The Early Discontinuation Visit** will consist of the same assessments as Week 45 (Visit 16) with the exception of the MG-QOL 15 which is 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 Score Test Items

Subjects receiving cholinesterase inhibitors will be instructed not to take medication 12 hours prior to assessments such as QMG Score. Scores for each individual item are added together for total score (range 0-39).

TEST ITEMS WEAKNESS	***NONE***	***MILD***	***MODERATE***	***SEVERE***	***SCORE***
GRADE	**0**	**1**	**2**	**3**	
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous	
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing Choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Forced vital capacity	≥80%	65-79%	50-64%	<50%	
Rt hand grip: male (Kg) : female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4	
Left hand grip: male (Kg) : female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4	
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	
Right leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	
Left leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	

Appendix 4 MG Composite Scale

Ptosis, upward gaze (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 2	Immediate = 3
Double vision on lateral gaze, left or right (physician examination)	> 45 seconds = 0	11-45 seconds = 1	1-10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eyes closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, e.g. necessitating changes in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3[a]	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4[a]	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4[a]	Severe weakness = 5

[a]Moderate weakness for neck and limb items should be construed as weakness that equals roughly 50% ±15% of expected normal strength. Any weakness milder than that would be mild and any weakness more severe than that would be classified as severe.

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

Grade	0	1	2	3	Score (0, 1, 2, 3)
1. Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL score (items 1–8)	

Appendix 6 MG-Quality of Life (MG-QOL) 15

Please indicate how true each statement has been (over the past few weeks).

	Not at all	A little bit	Some-what	Quite a bit	Very much
	0	1	2	3	4
1. I am frustrated by my MG					
2. I have trouble using my eyes					
3. I have trouble eating because of MG					
4. I have limited my social activity because of my MG					
5. My MG limits my ability to enjoy hobbies and fun activities					
6. I have trouble meeting the needs of my family because of my MG					
7. I have to make plans around my MG					
8. My occupational skills and job status have been negatively affected by MG					
9. I have difficulty speaking due to MG					
10. I have trouble driving due to MG					
11. I am depressed about my MG					
12. I have trouble walking due to MG					
13. I have trouble getting around public places because of my MG					
14. I feel overwhelmed by my MG					
15. I have trouble performing my personal grooming needs					

MG-QOL15

Muscle and Nerve 2008;38:957-963.
Muscle and Nerve;2010;41:219-226.
Muscle and Nerve;2011;43:14-18

Total MG-QOL15 score

Appendix 7 Monitoring of Thromboembolic Events Risk

Subjects will be monitored for signs and symptoms of arterial and venous thromboembolic events (TE). Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases (ICD) [55]. 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.

TEs 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 24 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 [56] will be utilized to assess the clinical characteristics indicative of possible DVT or PE (Table 2);

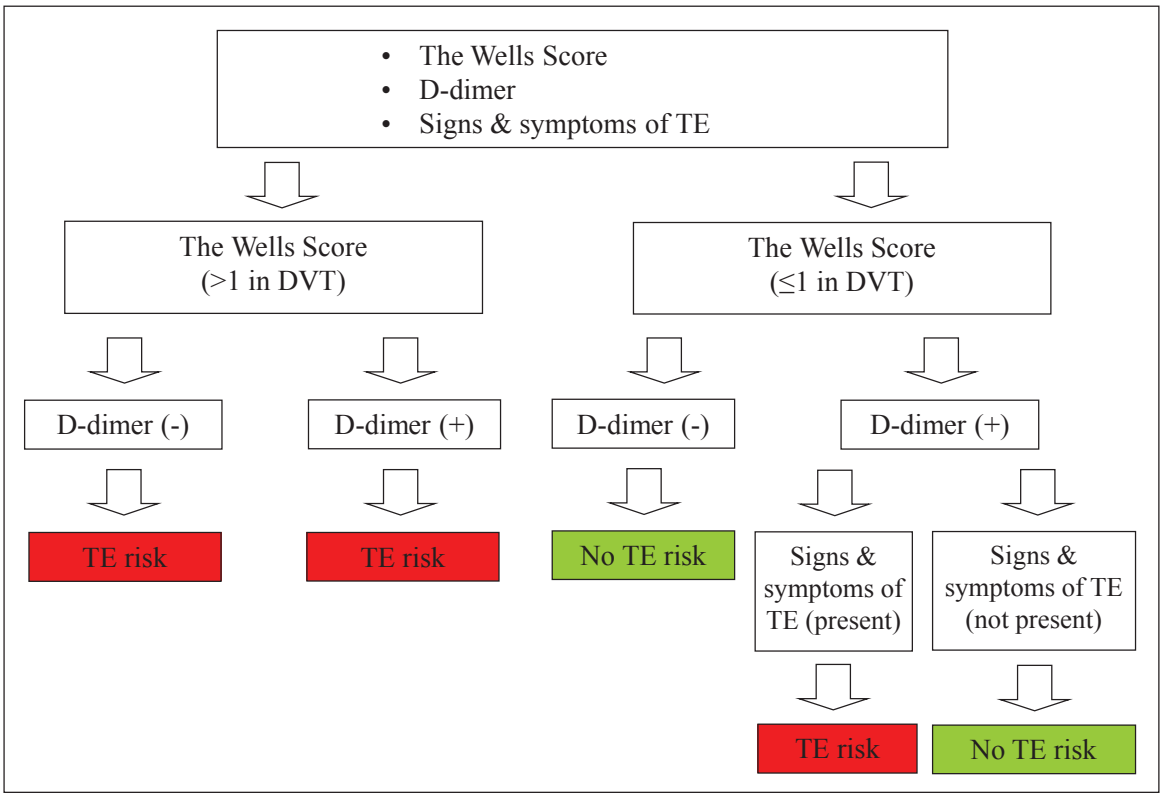
Measurement of D-dimer blood levels [57]; Evaluation of clinical signs and symptoms of arterial and venous TE as part of AEs assessment.

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:	

TEs risk will be assessed according to the following algorithm adapted from Wells [56] (Figure 1 and Figure 2):

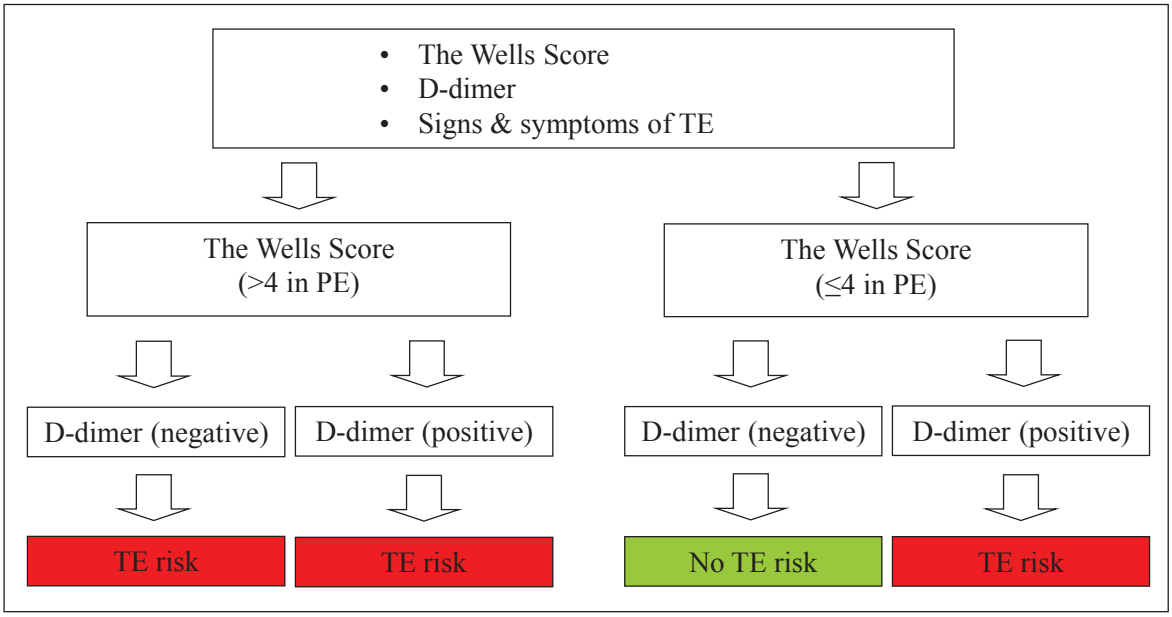
Figure 1. Algorithm to Assess Thromboembolic Events Risk for DVT



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 24 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 24 (Visit 9).

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 [58]. 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 [59,60]), iron-deficiency anemia, other drug-induced hemolytic anemia, or anemia associated with an underlying disease (e.g. autoimmune hemolytic anemia [61,62]).
- 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*	- hemoglobulemia
- 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 WHO-Five (WHO-5) Well-Being Index (1998 version)

WHO (Five) Well-Being Index (1998 version)

Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks. Notice that higher numbers mean better well-being.

Example: If you have felt cheerful and in good spirits more than half of the time during the last two weeks, put a tick in the box with the number 3 in the upper right corner.

	Over the last two weeks	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1	**I have felt cheerful and in good spirits**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2	**I have felt calm and relaxed**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3	**I have felt active and vigorous**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4	**I woke up feeling fresh and rested**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5	**My daily life has been filled with things that interest me**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Scoring:

The raw score is calculated by totalling the figures of the five answers. The raw score ranges from 0 to 25, 0 representing worst possible and 25 representing best possible quality of life.

To obtain a percentage score ranging from 0 to 100, the raw score is multiplied by 4. A percentage score of 0 represents worst possible, whereas a score of 100 represents best possible quality of life.

Interpretation:

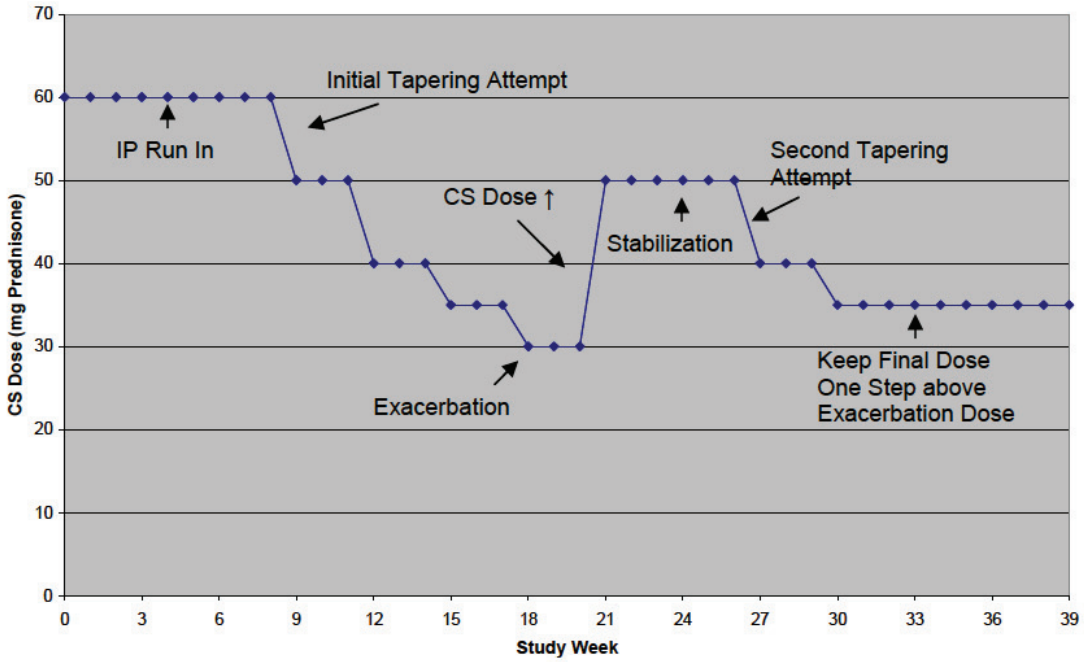
It is recommended to administer the Major Depression (ICD-10) Inventory if the raw score is below 13 or if the patient has answered 0 to 1 to any of the five items. A score below 13 indicates poor wellbeing and is an indication for testing for depression under ICD-10.

Monitoring change:

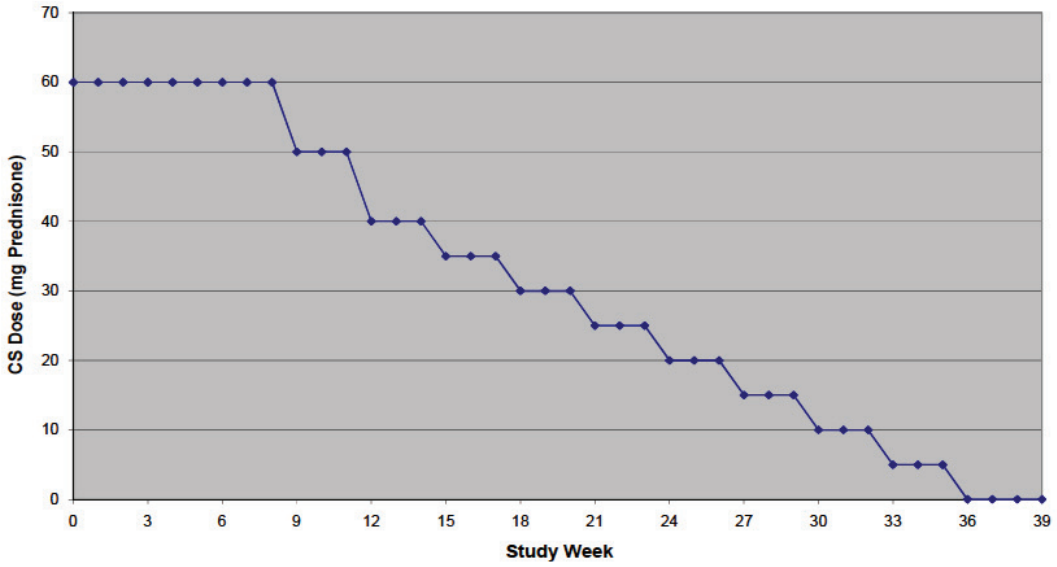
In order to monitor possible changes in wellbeing, the percentage score is used. A 10% difference indicates a significant change (ref. John Ware, 1995).

Appendix 10 Examples of CS Tapering with an Exacerbation/Second CS Tapering Attempt and Successful CS Tapering

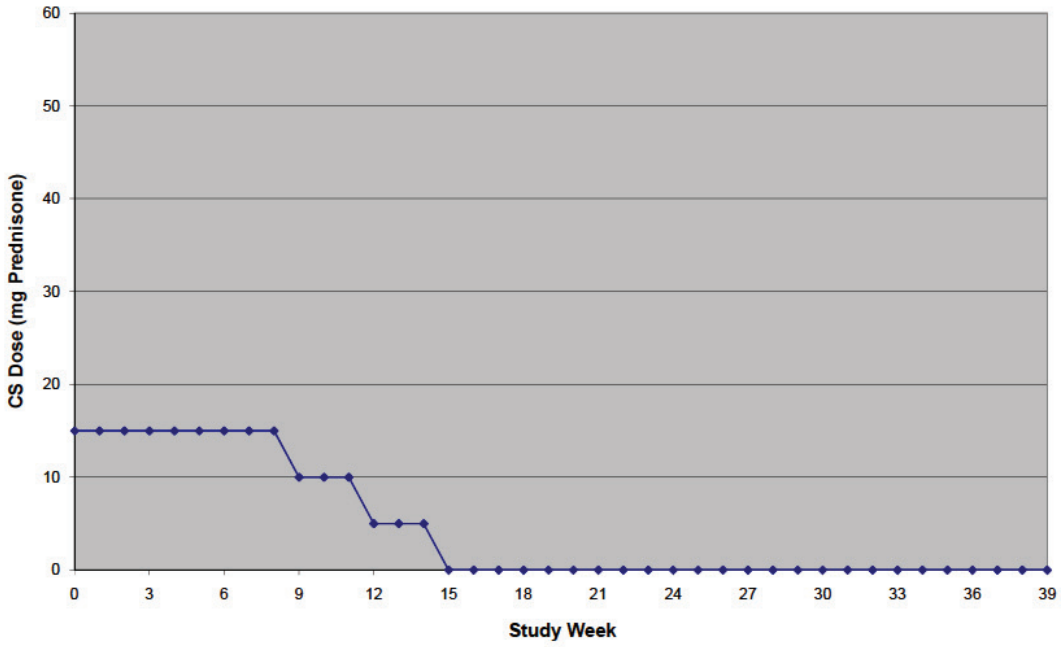
A. CS Tapering with an Exacerbation and Second CS Tapering



B. Successful CS Tapering



C. Successful CS Tapering



Appendix 11 Summary of Changes for Amendment 2

(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:
Synopsis; 3.1 Study Design and Plan; 3.3.2 Corticosteroid Tapering/IP Maintenance Phase; 3.8.2.5 Corticosteroid Tapering/IP Maintenance Phase: Week 9 to Week 36 (Visit 4 to Visit 13) Inclusive	Added text	**The final CS taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily is the Principal Investigator's decision and is not mandatory per protocol. The Principal Investigator may choose to taper to 0 mg prednisone equivalent daily based on best medical judgment for each subject given individual variability with regards to sensitivity to complete CS withdrawal and perceived MG exacerbation risk while CS-free.**	As safety measure Investigator discretion introduced for final taper step from 5 mg prednisone equivalent daily to 0 mg prednisone equivalent daily given unique, subtle sensitivities of MG subjects to complete CS withdrawal.
Synopsis	Added existing text from protocol Section 3.2 to Synopsis	**Eligible participants for this study will include adult subjects with a confirmed diagnosis of MG who have required systemic CS therapy for at least the preceding three months in order to control their signs and symptoms of MG. Subjects may be receiving immunosuppressive therapies within confines stipulated below and stable dosage of acetylcholinesterase inhibitors (e.g., pyridostigmine, neostigmine).**	This verbatim pre-existing text from Section 3.2 of protocol is now also included in Synopsis to emphasize scope of MG treatment at study entry.

Sections	Change From:	Change To:	Rationale:
Synopsis; 3.2.2 Exclusion Criteria	Added text to exclusion criteria	4. Any episode of myasthenic crisis (MC) in the one month prior to Screening, **or (at any time in the past) MC or hospitalization for MG exacerbation associated with a previous CS taper attempt** 27. 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 **Principal I**nvestigator would compromise **safety of the subject or** the ability of the subject to complete the trial. **No subject whose <u>only</u> MG treatment is CS alone may enroll, because in the blinded placebo arm this would mean that all MG treatment would be discontinued during CS taper, posing a substantial risk for the subject**.	Exclusion 4: As safety measure given 50% active: 50% placebo randomization, prior MC or hospitalization due to MG exacerbation associated with a previous CS taper attempt is exclusionary since CS tapering is a fundamental, integral part of GTI1306 study design. Exclusion 27: Clarification of original intention of eligibility criteria to assure this specific potential risk is fully appreciated when evaluating patients for possible study participation. If a patient is treated for MG solely with CS alone as the only MG medication, inclusion in protocol GTI1306 would not be appropriate, because all patients will be tapered off CS during study (primary efficacy measure), in the setting of 50% active: 50% placebo randomization. This text is introduced as a safety measure to prevent any misconception.

Sections	Change From:	Change To:	Rationale:
Synopsis; Section 3.3.3 Definition and Management of MG Worsening	Added text	**Special Note for subjects tapered to 0 mg CS per day:** **Some subjects with MG are uniquely sensitive to complete CS withdrawal (0 mg prednisone equivalent daily), and may become more vulnerable to MG triggers and sudden MG exacerbations. Therefore if a subject has tapered to 0 mg prednisone equivalent daily, any worsening MG signs or symptoms must be evaluated in clinic as soon as possible (recommended within 24 hours, allowed up to 48 hours) and treated aggressively with CS dose increase as delineated in the tables above. Once tapered to 0 mg CS per day, a 4-point QMG increase from Baseline/Week 0 is not required for re-initiating CS because deterioration can be of greater severity and speed than expected and may be difficult to reverse.**	As safety measure for subjects whose CS is tapered to 0 mg prednisone equivalent daily, new text added to assure rapid medical evaluation, CS re-initiation, and medical intervention because of vulnerability of some subjects to severe MG exacerbations which may be difficult to reverse. Some subjects on 0 mg prednisone equivalent daily (completely CS-free) require immediate increase in CS dose (and/or other interventions) because initially mild MG signs/symptoms may deteriorate with greater severity and speed than expected, even if QMG was previously improved or stable while on 0 mg CS relative to baseline QMG.
Section 3.5.2 Prohibited Concomitant Medications during the Study	Added text	**Treatments needed for myasthenic crisis or MG exacerbation requiring hospitalization are not restricted per protocol as this constitutes a real medical necessity and required interventions to assure subject safety are always allowed**.	To clarify that MG treatment measures for MG crisis or hospitalization for MG exacerbation are always allowed for emergent medical need.