Clinical Study Protocol

Protocol Title:	A multicenter, prospective, open-label, non-controlled clinical trial to assess the efficacy and safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in patients with Myasthenia Gravis exacerbations
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:	0034 935 710 700
Study Number/Protocol Version Number/Date:	GTI1305/ Version 4.0/30 Mar 2016 Includes GTI1305/Version 3.0/03 Sep 2015 GTI1305/Version 2.0/June 19, 2014 GTI1305/Version 1.0/February 27, 2014
EUDRACT Number:	2013-005098-28
Development Phase:	Phase 3

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

Medical Monitor: [redacted]

[redacted]

Date: 31 MAR 2016

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Summary of Changes for Amendment 3

Protocol Version	Date of Approval
4.0 Amendment 3 + Integrated Protocol	30 Mar 2016
3.0 Amendment 2 + Integrated Protocol	03 Sep 2015
2.0 Amendment 1 + Integrated Protocol	June 19, 2014
1.0 Original	February 27, 2014

Amendment 3

The protocol for GTI1305 (Protocol Amendment 2, Version 3.0, dated 03 Sep 2015) has been amended and reissued as Protocol Amendment 3, Version 4.0, dated 30 Mar 2016. See Appendix 8 for a summary of changes for Amendment 3.

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

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GLOSSARY AND ABBREVIATIONS

AAN	American Academy of Neurology
AChR	Acetylcholine receptor
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
B19V	Parvovirus B19
Breg	Regulatory B cell
BUN	Blood urea nitrogen
CBC	Complete blood count
CIDP	Chronic inflammatory demyelinating polyneuropathy
CRO	Clinical research organization
CS	Corticosteroid
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DVT	Deep venous thrombosis
ECG	Electrocardiogram
eCRF	electronic case report form
EFNS	European Federation of Neurological Societies
GBS	Guillain-Barré syndrome
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
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	Intravenous immunoglobulin
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IgM	Immunoglobulin M
IP	Investigational product
IRB/EC	Institutional review board/Ethics committee
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis-activities of daily living
MGFA	Myasthenia Gravis Foundation of America
MuSK	Muscle specific kinase
NAT	Nucleic acid testing
PE	Pulmonary embolism
PI	Primary immunodeficiency
PLEX	Plasma exchange
QMG	Quantitative myasthenia gravis scale
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
Treg	Regulatory T cell
ULN	Upper limit of normal

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 Exacerbations

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 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).

Myasthenic symptoms and signs may worsen or exacerbate. MG exacerbations are characterized by worsening muscle weakness resulting in swallowing difficulty, acute respiratory failure, or major functional disability responsible for the discontinuation of physical activity. These cases fall in the class IVb-V of the disease severity staging proposed by the Myasthenia Gravis Foundation of America (MGFA) (3). Particularly, MG crisis is the most severe phenotype (class V of MGFA classification) and commonly requires an effective and urgent life-saving treatment such as invasive or noninvasive mechanical ventilation due to respiratory failure (4).

The majority of patients have their first MG exacerbation within the first 2 years after disease onset (5), and about 20% of the patients develop crisis episodes within the first year (6). Infection or changes in medications (such as recent addition of a corticosteroid [CS], a dose reduction or overtreatment with acetylcholinesterase inhibitors) are common triggers for exacerbations of MG (7,8). Other recognized triggers for exacerbations in refractory MG include emotional stress, hot environment, sudden elevation of body temperature and hyperthyroidism, with autoimmune thyroid disease being a common association of myasthenia gravis (9). However, approximately 33 to 50% of patients with MG do not have an obvious cause for an exacerbation (7). Since identified causes can relate to infection or medications, physical examination, review of medications, chest X-ray, complete blood count (CBC), and blood as well as other cultures, depending on presentation, should be obtained (8).

1.2 Management of MG Exacerbations

Management for myasthenic exacerbations should be carried out in an intensive care unit (ICU) or general ward staffed with physicians who are experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy (1,10). After stabilizing the patient and securing the airway, respiration, and haemodynamics, options for specific treatment include use of acetylcholinesterase inhibitors, plasma exchange (PLEX), intravenous immunoglobulin (IGIV), and immunosuppressive drugs (such as CS), (11). Autoantibody activity in MG can be modulated by either removal from plasma by PLEX or selective immunoadsorption techniques or by the expansion of the immunoglobulin

pool by administering high-dose IGIV that interferes with the autoantibody activity by means of several and still poorly understood pathways (12). CS administration results in a gradual effect on symptoms, which starts after a few days and is clinically obvious after approximately 2 weeks, but maximum benefit may take months (13,14). Initial treatment with prednisone may lead to an exacerbation of MG in almost half of the patients attempted and it is recommended that initiation of CS should occur in a hospital setting where respiratory function can be monitored (15). Additionally, if patients experience an MG exacerbation and are already receiving CS, then CS use should not be discontinued while treating the exacerbation (15).

PLEX and IGIV are common treatment modalities for MG exacerbation. Their beneficial and symptom-relieving effect is regarded as well proven from several studies and from widespread clinical use. In contrast to most other treatment options, the clinical response is rapid and often with a dramatic effect (11). PLEX therapy produces its clinical effect by removing plasma containing acetylcholine receptor (AChR) antibodies. Although efficacious, PLEX has drawbacks, such as increased side-effects as compared to IGIV and the haemodynamics of PLEX (16). The mechanism by which IGIV exerts its clinical effect in MG is still unknown, 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 (17,18). Improvement in MG symptoms typically occurs in about 70% of patients, beginning during treatment or within a few days of initiating IGIV treatment and lasting for weeks to months (19).

Several studies comparing PLEX with IGIV have demonstrated equal efficacy, but significantly fewer or less severe side effects were noted for the IGIV treatment (20,21). These recommendations are also supported by the European Federation of Neurological Societies (EFNS) guidelines with IGIV and PLEX both being effective (recommendation level A) for the treatment of MG exacerbations (16). The Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology (AAN) recently released updated evidence-based guidelines that consider IGIV as an effective therapy for moderate-to-severe cases of MG, but also acknowledges the need for additional clinical trials (22). Importantly, IVIG can be used for management of MG exacerbations in patients with contraindications or who have experienced a lack of clinical response to PLEX (13,15).

A recent Cochrane Review (23) identified four trials in acute exacerbation or worsening MG in which IGIV was compared to placebo, CS or PLEX in a randomized, controlled manner. The placebo controlled trial showed some evidence for a positive effect of IGIV. A trial against CS, a commonly used immune modulator in MG, was underpowered and showed no difference in treatment effect between IGIV and CS. The two trials comparing IGIV to PLEX, both generally accepted therapies, also showed a similar treatment effect.

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 (PI), 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 IGIV concentrates are a safe and effective treatment option as a short term treatment for acute exacerbation of MG. Moreover, IGIV-C has demonstrated a positive treatment effect in clinical studies of MG exacerbations (24-26), but further clinical data are needed to confirm the effectiveness of IGIV-C in the treatment of MG exacerbations. The MGFA, Inc. Task Force on clinical research standards recommended that the Quantified Myasthenia Gravis Scale (QMG) be used in all prospective clinical trials in MG to assess clinical efficacy in MG (3).

This is a multicenter, prospective, open-label, non-controlled study to assess the efficacy and safety of IGIV-C in subjects with MG class IVb-V exacerbations according to the MGFA (3). The primary measure of efficacy for this study is the change in the QMG score from Baseline to Day 14.

1.4.2 Dose Rationale

The optimal dose of IGIV 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 (13,19). More recent studies in MG have evaluated the administration of a total IGIV 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 (24-26).

Likewise, in a study of subjects with Guillain-Barré syndrome (GBS), a total IGIV 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 (27).

Based on the above, subjects will receive a single, total IGIV-C dose of 2 g/kg of body weight that will be administered on 2 consecutive days (at a dose of 1 g/kg per day).

2 STUDY OBJECTIVES

2.1 Efficacy Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of an IV infusion of IGIV-C (total dose of 2 g/kg administered over 2 consecutive days at a dose of 1 g/kg per day) in subjects with MG exacerbations by assessing the change in score of MG symptoms as measured by the QMG from Baseline to Day 14.

2.1.2 Secondary Objectives

The secondary objectives of this study are to evaluate the efficacy of an IV infusion of IGIV-C (total dose of 2 g/kg administered over 2 days at a dose of 1 g/kg per day) in subjects with MG exacerbations by:

- Percentages of subjects who experience a clinical improvement assessed by QMG from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in QMG
- Percentages of subjects who experience a clinical improvement assessed by MG – Activities of Daily Living (MG-ADL) from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 2-point decrease in MG-ADL
- Percentages of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in the MG Composite

2.1.3 Exploratory Objectives

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

- Change in and percentage of subjects who experience a clinical improvement in QMG score from Baseline (Day 0) to Days 7, 21 and 28
- Change in and percentage of subjects who experience a clinical improvement in MG-ADL from Baseline (Day 0) to Days 7, 14, 21 and 28
- Change in and percentage of subjects who experience a clinical improvement in the MG Composite from Baseline (Day 0) to Days 7, 14, 21 and 28
- Change in AChR antibody (or muscle specific kinase [MuSK] antibody) levels from Baseline (Day 0) to Days 14 and 28
- Change in Immunoglobulin G (IgG) levels from Baseline (Day 0) to Day 1 (after completion of infusion), Days 7, 14, 21 and 28
- Length of ICU stay and length of intubation (if applicable)

2.2 Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of an IV infusion of IGIV-C (total dose of 2 g/kg administered over 2 consecutive days at a dose of 1 g/kg per day) in subjects with MG exacerbations.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Plan

This is a multicenter, prospective, open-label, non-controlled study to assess the efficacy and safety of an IV dose of 2 g/kg of IGIV-C in subjects with MG exacerbations. The study consists of a single dose course of IGIV-C treatment followed by 28-days of post-infusion assessments. The total duration of study participation for each subject is up to 28 ± 2 days. Approximately 50 subjects, ages 18 or greater, are planned to be enrolled in the study and receive a single, total dose of 2 g/kg of IGIV-C over 2 consecutive days (dose of 1 g/kg per day) across multiple centers in North America and Europe.

Informed consent will be obtained from subjects who experience an exacerbation of MG that is not attributable to an infection or change in medication. After obtaining informed consent, study eligibility will be determined by the Investigator using the protocol inclusion/exclusion criteria (See Section 3.2). Subjects must meet all inclusion/exclusion criteria prior to receiving IGIV-C at the Baseline Visit (Day 0 and Day 1). Throughout the course of the clinical study, assessments will consist of the following: QMG score (See Section 3.5.4), MG Composite Scale (See Section 3.5.5), MG-ADL (See Section 3.5.6), physical assessments, infusion vital signs monitoring, laboratory tests, recording of adverse events (AEs) and concomitant medications. Each MG assessment should be performed by the same clinical staff member whenever possible.

A schematic of the study design and essential activities is shown in Figure 3-1, and a schedule of procedures is provided in Appendix 1.

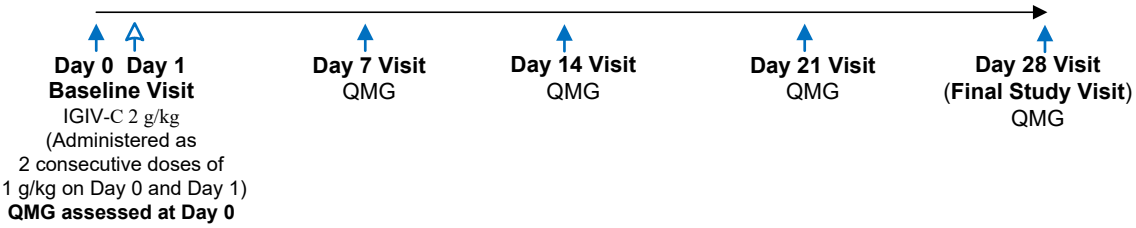

Figure 3-1 Overall Study Schema

3.2 Selection of Study Population

Study population will be made up of individuals with MG suffering from an exacerbation or crisis as defined by difficulty in swallowing, acute respiratory failure or major functional

disability responsible for the discontinuation of physical activity that is not attributable to an infection or change in medication.

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 aged ≥18 years.
2. Subjects must be willing and able to provide written informed consent (if applicable, a legally authorized representative may provide informed consent on behalf of the subject).
3. Subjects who meet the clinical criteria for diagnosis of MG with an exacerbation defined as worsening of MG symptoms as defined by an MGFA classification IVb or V (Appendix 2).
4. Subjects on long-term (8 weeks) corticosteroid treatment for MG.
5. Female subjects of child-bearing potential must have a negative test for pregnancy (human chorionic gonadotropin (HCG)-based assay).
6. Subjects must be willing to comply with all aspects of the clinical trial protocol, including blood sampling and long-term storage of extra samples, for the entire duration of the study.

3.2.2 Exclusion Criteria

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

1. Subjects who have received immune globulin treatment given by IV, subcutaneous or intramuscular route within the last 30 days.
2. Subjects with documentation of a lack of clinical response to IVIG therapy for MG.
3. Subjects documented positive for antibodies directed against MuSK.
4. Subjects with CS treatment initiated within the last 8 weeks or modified within the last 2 weeks.
5. Subjects with PLEX within the last 30 days.
6. Subjects with MG exacerbation attributable to change in medication or evident infection as defined by, but not limited to, the presence of at least one of the following diagnostic features: 1) axillary temperature ≥38°C, 2) positive blood culture of infective microorganism, 3) white blood cell count $>12\times10^9$/L and differential white blood cell count of >10% band neutrophils ($>1.2\times10^9$/L), and 4) pulmonary infiltrate with consolidation on chest X-ray. Alternatively, other signs and symptoms may be considered for the diagnosis of evident infection according to the Investigator's judgement.
7. Subjects with inadequate venous access.
8. Subjects with a history of anaphylactic reactions or severe reactions to any blood-derived product.
9. Subjects with a history of intolerance to any component of the investigational products (IPs).
10. Subjects with a documented diagnosis of thrombotic complications to polyclonal IVIG therapy in the past.

11. Subjects with a history of recent (within the last year) myocardial infarction, stroke or uncontrolled hypertension.
12. Subjects who suffer from uncontrolled congestive heart failure, embolism or documented electrocardiogram (ECG) changes indicative of myocardial ischemia or atrial fibrillation.
13. Subjects with current known hyperviscosity or hypercoagulable state.
14. Subjects currently receiving anti-coagulation therapy.
15. Subjects with a history of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the Baseline Visit.
16. Subjects with active psychiatric illness that interferes with compliance or communication with health care personnel.
17. Females who are pregnant, breastfeeding, or of child-bearing potential and 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.)
18. Subjects with 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.
19. Subjects currently receiving, or having received within 3 months prior to the Baseline Visit, any investigational medicinal product or device.
20. Subjects who are unlikely to adhere to the protocol requirements or are likely to be uncooperative or unable to provide a storage serum/plasma sample prior to the first IP infusion.
21. Subjects with a known Immunoglobulin A (IgA) deficiency and anti-IgA serum antibodies.
22. Subjects with 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).
23. Subjects with 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.
24. Subjects with haemoglobin levels <9 g/dL.

3.3 Treatments

3.3.1 Treatment to be administered

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

The IP provided by Grifols Therapeutics Inc. is marketed IGIV-C in glass vials. Detailed information regarding IGIV-C can be found in the IGIV-C IB.

3.3.1.2 Labeling of Investigational Product

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

3.3.1.3 Storage of Investigational Product

IP must be stored in a secure area accessible to study personnel authorized by the Investigator, such as the study staff responsible for the preparation and dispensing of investigative product.

IP must be stored at temperatures of 2°C to 8°C (36°F to 46°F). Do not freeze. Investigators, or designees, are responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the study monitor.

3.3.1.4 Preparation

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 total 2 g/kg dosage to be administered over 2 consecutive days at a dose of 1 g/kg per day. The IP will be prepared by the study site pharmacist or designee.

IP must be inspected visually before being prepared 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. The Investigator, or designee, is responsible for immediately reporting any discrepancies noted with IP to the study monitor.

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

3.3.1.5 Accountability for Investigational Product

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

The Investigator, or designee such as the study pharmacist, 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 Investigator or designee. The inventory must be made available for inspection by the 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 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.

IGIV-C vials may be supplied in the following vial sizes 10, 25, 50, 100, and 200 mL.

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

3.3.2.1 Selection of IGIV-C Dose and Interval in the Study

The optimal dose of IGIV for MG exacerbation is still unclear; however, recent studies have divided the total dose of 2 g/kg into 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 (24-26).

Based on the above, subjects will receive a single, total IGIV-C dose of 2 g/kg of body weight that will be administered on 2 consecutive days at a dose of 1 g/kg per day.

3.3.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, uncontrolled study; all subjects will receive the same IP (IGIV-C) via IV administration. Each subject's IGIV-C dose will be individualized based on the subject's weight and the protocol specified dose of 2 g/kg over 2 consecutive days. Therefore, each subject's infusion volume and duration of the infusion will vary from subject to subject.

3.3.3.1 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.

3.3.3.2 Blinding

This is an open-label study with no blinding.

3.3.3.3 Administration and Timing of Investigational Products for Each Subject

IGIV-C will be administered as a total dose of 2 g/kg given in two divided, daily doses of 1 g/kg over 2 consecutive days. The initial infusion will be on Day 0 followed by a second infusion on Day 1. All subjects will receive this single total dose of IGIV-C. Infusion administration, including infusion rate, is provided in the Pharmacy Manual.

Details regarding infusion preparation are located 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.

3.3.3.4 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.

3.4 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).

3.4.1 Prohibited Medications Prior to Study Participation

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

- Immune globulin treatment given by IV, subcutaneous or intramuscular route within the last 30 days
- CS treatment newly initiated within the last 8 weeks or modified within the last 2 weeks
- Subjects with PLEX within the last 30 days
- Any IP(s) within 3 months

3.4.2 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 IP(s) which are not part of this study
- Live viral vaccines (e.g., measles, mumps, rubella)
- PLEX
- Anti-coagulant therapy except when administered during hospitalization as prophylactic treatment as part of standard of care for deep venous thrombosis (DVT) prevention
- Systemic antibiotic therapy
  - Note: antibiotics are allowed for treatment of AEs where medically necessary according to the Investigator's opinion and for safety reasons.

3.4.3 Restricted Concomitant Medications during the Study

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

- Changes to routine therapy (such as CS, cholinesterase inhibitors or other immunosuppressants) to treat symptoms of MG, as described in the medical history prior to exacerbation, will not be permitted until Day 14 (after primary efficacy assessment) unless necessary according to the Investigator's opinion and for safety reasons.
- Except for the baseline visit, subjects receiving cholinesterase inhibitors will be instructed not to take medication 12 hours prior to assessment and for those receiving

slow-release cholinesterase inhibitors, the medication will be held 24 hours before the assessment.

3.5 Efficacy Study Variables

3.5.1 Primary Variable

The primary variable to assess efficacy in this study is the change in QMG score from Baseline (Day 0) to Day 14.

3.5.2 Secondary Variables

Secondary efficacy variables assessed in this study are:

- Percentages of subjects who experience a clinical improvement assessed by QMG from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in QMG
- Percentages of subjects who experience a clinical improvement assessed by MG-ADL from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 2 point decrease in MG-ADL
- Percentages of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in the MG Composite

3.5.3 Exploratory Variables

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

- Change and percentage of subjects who experience a clinical improvement in QMG score from Baseline (Day 0) to Day 7, Day 21 and Day 28
- Change and percentage of subjects who experience a clinical improvement in MG-ADL from Baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28
- Change and percentage of subjects who experience a clinical improvement in the MG Composite from Baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28
- Change in AChR antibodies (or MuSK antibodies) from Baseline (Day 0) to Day 14 and Day 28
- Change in IgG levels from Baseline (Day 0) to Day 1 (after completion of infusion), Day 7, Day 14, Day 21 and Day 28
- Length of ICU stay and length of intubation (if applicable)

3.5.4 Quantitative Myasthenia Gravis Scale (QMG)

The MGFA, Inc. Task Force on Clinical Research Standards recommends that the QMG be used in all prospective clinical trials in MG (3). The QMG is easy to administer by clinical evaluators and/or physicians in approximately 30 minutes with minimal equipment to measure spirometry and muscle strength testing. The QMG should be performed by the same

clinical staff member whenever possible. An average 3.5-point improvement in QMG score indicates clinical improvement (24).

QMG Test Items are attached in Appendix 3.

Since this study exclusively enrolls subjects with MGFA classification of IVb or V severity, a proportion of subjects may be intubated and otherwise compromised so that the QMG score may need to be performed in extenuating circumstances. Assessments may not be feasible in standard format, although still obtainable with minor modifications. As such, it is necessary to standardize the methodology employed so that consistent scoring is obtained across study centers for subjects in these extenuating circumstances.

A guideline for the QMG test for subjects in extenuating circumstances is available for these specific situations, which is located in the MG assessment binder provided to each site.

3.5.5 MG Composite Scale

The MG Composite scale takes less than five minutes to complete, is made up of three ocular, three bulbar, one respiratory, one neck, and two limb items (29,30). The MG Composite scale should be performed by the same clinical staff member whenever possible.

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 (28).

A guideline for administering the MG Composite Scale is available in the MG assessment binder provided to each site. The MG Composite items are listed in Appendix 4.

3.5.6 MG-ADL

The MG-ADL is an 8-item, patient reported questionnaire that is completed to assess the symptoms and activities in MG (31). A 2-point improvement in the MG-ADL indicates clinical improvement (31). The MG-ADL should be performed by the same clinical staff member whenever possible.

The questionnaire and scoring is provided in Appendix 5.

3.6 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. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs. Clinically relevant changes as determined by the Investigator in vital signs (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure

[SBP] and diastolic blood pressure [DBP]) during infusions will be considered AEs temporally associated to the infusion.
- Physical Assessments. Physical exams, excluding the breast and genitourinary areas, will be recorded as normal or abnormal, according to the physician's judgment criteria. Abnormal findings judged by the Investigator as clinically relevant will be considered AEs.
- Blood biochemistry and Haematology. Laboratory results out of the normal range that are judged by the Investigator as clinically relevant will be considered AEs.
- Thromboembolic events (TEs) risk.
- Hemolysis detection.

3.6.1 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 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 Day 0 (prior infusion), Day 1 (after the infusion), Day 7 ± 1 and Day 28 ± 2.

Procedures for the monitoring of TEs risk are provided in Appendix 6.

3.6.2 Hemolysis Detection

Blood assessments including whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), red blood count (RBC), hematocrit, total bilirubin (TBL), indirect bilirubin, blood smear, and urinalysis including urinary sediment and hemoglobinuria will be conducted at Day 0 (prior infusion), Day 1 (after the infusion), Day 7 ± 1 and Day 28 ± 2 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 Day 0 (prior infusion) and Day 1 (after the infusion), Day 7 ± 1 and Day 28 ± 2.

Procedures for hemolysis detection are provided in Appendix 7.

3.7 Assessments

3.7.1 Assessment Periods

The study consists of a single treatment with a 28 ± 2 days assessment period. The expected duration of a study subject's participation will be approximately 28 ± 2 days.

3.7.2 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 Procedures in Appendix 1 for a summary of study visits and the procedures conducted at each visit.

3.7.2.1 Treatment and Post-infusion Follow-up Phase

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

Eligible subjects will complete the Baseline (Day 0) visit, thereby initiating the Treatment. Subjects will continue with assessments for 28 days, with scheduled visits and assessments at Days 7, 14, 21, and 28. Visits/procedures and assessments should be scheduled at the protocol specified study day ± 1 day from Day 7 to Day 14, ± 2 days for visits at Day 21 and Day 28.

BASELINE VISIT

The Baseline Visit will occur after the subject is stabilized according to the Investigator's judgment. Local laboratory results and assessments related to the inclusion and exclusion criteria must be available prior to the investigational product infusion at Day 0.

For eligible subjects, IGIV-C will be administered as a total dose of 2 g/kg (20 mL/kg) given in divided doses of 1 g/kg per day over two days. The initial infusion will be on Baseline (Day 0) followed by a second infusion on Day 1.

The following procedures and assessments will be conducted during the Baseline (Day 0) Visit.

Prior to the investigational product infusion (Day 0)

- Informed consent prior to the initiation of screening procedures
- Subject number assigned
- Medical history including demographics and concomitant diseases
- AE, concomitant medication
- Physical exam (excluding breast and genitourinary areas)
- Vital signs including T, RR, HR, SBP, and DBP
- Inclusion/exclusion criteria review
- Height
- Weight (Note: The recorded weight will be used to calculate the IP infusion dose)
- Laboratory assessments (see Section 3.7.3):
  - Urine collection (**within 8 hours prior to the IP infusion on Day 0**)
    - Urine Pregnancy Test (*potential child-bearing females only; results must be negative for the subject to continue in the study*)
    - Hemolysis (urine sediment and measuring of hemoglobinuria). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.

- Blood collection (**within 8 hours prior to IP infusion on Day 0**)
  - Biochemistry
  - Haematology
  - D-dimer
  - Hemolysis (whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smear). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.
  - AChR antibodies (or MuSK antibodies, if negative for AChR antibodies; See Section 3.7.3.4)
  - IgG levels
  - Retain samples for future biomarker testing (These samples will be collected and retained for future biomarker testing *only for subjects who provide consent for this portion of the study*)
  - Retain samples for virus safety testing as detailed in Table 3-1 (These retention samples will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete.)
- Thromboembolic events risk monitoring (Appendix 6) (**prior to IP infusion on Day 0**)
- Hemolysis detection assessment (Appendix 7) (**prior to IP infusion on Day 0**)
- QMG score
- MG Composite
- MG-ADL

<u>During and Post-completion of the IP infusion (Day 0)</u>

- Pharmacist, or designee, to prepare and dispense the IP per Pharmacy Manual
- Administer the infusion (Per Pharmacy Manual)
- During the infusion, vital signs (including T, RR, HR, SBP, and DBP) will be monitored and recorded 1) within 15 ± 5 minutes before the beginning of each infusion; 2) every 30 ± 10 minutes during the first hour of each infusion; and 3) at 30 ± 10 minutes post-completion of each infusion. **Note**: Any clinically significant vital sign will be recorded as an AE in the eCRF.
- <u>Documentation of total infusion volume prepared (as received from pharmacist or designee</u>), total time to infuse, total volume infused, and, if necessary, any infusion interruption with explanation
- AE, concomitant medication

STUDY VISIT AT DAY 1

- Pharmacist, or designee, to prepare and dispense the IP per Pharmacy Manual
- Administer the infusion (Per Pharmacy Manual)
- During the infusion, vital signs (including T, RR, HR, SBP, and DBP) will be monitored and recorded 1) within 15 ± 5 minutes before the beginning of each infusion; 2) every 30 ± 10 minutes during the first hour of each infusion; and 3) at 30 ± 10 minutes post-completion of each infusion. **Note**: Any clinically significant vital sign will be recorded as an AE in the eCRF.
- Laboratory assessments (see Section 3.7.3):
  - Urine collection (**between 8 and 24 hours post-completion of the IP infusion on Day 1**)
    - Hemolysis (urine sediment and measuring of hemoglobinuria). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.
  - Blood collection (**at 30 minutes post-completion of the IP infusion on Day 1**)
    - IgG levels
  - Blood collection (**between 8 and 24 hours post-completion of the IP infusion on Day 1**)
    - D-dimer
    - Hemolysis (whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smear). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.
- Thromboembolic events risk monitoring (Appendix 6) (**post-completion of the IP infusion on Day 1**)
- Hemolysis detection assessment (Appendix 7) (**post-completion of the IP infusion on Day 1**)
- 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
- AE, concomitant medication

STUDY VISIT AT DAY 7

The following procedures and assessments will be conducted during the visit at Day 7 ± 1 day:

- AE, concomitant medication
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.7.3):
  - Urine collection
    - Hemolysis (urine sediment and measuring of hemoglobinuria). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is

unable to perform any of the assessments, the central laboratory may be utilized.
  - Blood collection
    - D-dimer
    - Hemolysis (whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smear). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.
    - IgG levels
    - Retain samples for future biomarker testing (These samples will be collected and retained for future biomarker testing *only for subjects who provide consent for this portion of the study*)
- Thromboembolic events risk monitoring (Appendix 6)
- Hemolysis detection assessment (Appendix 7)
- QMG score
- MG Composite
- MG-ADL

STUDY VISIT AT DAY 14

The following procedures and assessments will be conducted during the visits at Day 14 ± 1 day:

- AE, concomitant medication
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.7.3):
  - Blood collection
    - AChR antibodies (or MuSK antibodies will be assessed, if subject tested negative for AChR antibodies and tested positive for MuSK antibodies at the Baseline Visit; See Section 3.7.3.4)
    - IgG levels
    - Retain samples for future biomarker testing (These samples will be collected and retained for future biomarker testing *only for subjects who provide consent for this portion of the study*)
- QMG score
- MG Composite
- MG-ADL

STUDY VISIT AT DAY 21

The following procedures and assessments will be conducted during the visit at Day 21 ± 2 days:

- AE, concomitant medication
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.7.3):
  - Blood collection
    - IgG levels
    - Retain samples for future biomarker testing (These samples will be collected and retained for future biomarker testing *only for subjects who provide consent for this portion of the study*)
- QMG score
- MG Composite
- MG-ADL

FINAL STUDY (DAY 28)/EARLY DISCONTINUATION VISIT

Subjects will return to study site at Day 28 ± 2 days for a Final Study Visit. 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.

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

- AE, concomitant medication
- Physical exam
- Vital signs including T, RR, HR, SBP, and DBP
- Laboratory assessments (see Section 3.7.3):
  - Urine collection
    - Urine Pregnancy Test (*potential child-bearing females only)*
    - Hemolysis (urine sediment and measuring of hemoglobinuria). Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.
  - Blood collection
    - Biochemistry
    - Haematology
    - D-dimer
    - Hemolysis (whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smearAChR antibodies (or MuSK antibodies will be assessed, if subject tested negative for AChR antibodies and tested positive for MuSK antibodies at the Baseline Visit; See Section 3.7.3.4)
    - IgG levels
    - Retain samples for future biomarker testing (These samples will be collected and retained for future biomarker testing *only for subjects who provide consent for this portion of the study*)
    - Retain samples for virus safety testing as detailed in Table 3-1 (These retention samples will be tested *only* if the subject exhibits clinical signs and

symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete.)

- Thromboembolic events risk monitoring (Appendix 6)
- Hemolysis detection assessment (Appendix 7)
- QMG score
- MG Composite
- MG-ADL

3.7.3 Description of Laboratory Tests and Procedures

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

Test Panel	Description	Location [a]
Haematology [b]	Haemoglobin, haematocrit, platelets, RBC count, including RBC morphology, white blood cell count with differential	Local
Biochemistry [b]	Creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBL)	Local
Hemolysis [c]	Blood: Whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smear	Local
	Urine: Urine sediment and measuring of hemoglobinuria	
Thromboembolic events risk	D-dimer	Local
AChR (or MuSK) Antibody [b]	Acetylcholine Receptor Antibody (if negative, then test for MuSK antibody. Please see Section 3.7.3.4 for details)	Central
IgG levels	Immunoglobulin G levels	Central
Urine pregnancy [b]	Urine pregnancy test for females of child-bearing potential. Results must be negative to continue in the study.	Local
Viral Nucleic Acid Testing (NAT)	Retains [d] - 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 [d] 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
Blood for biomarkers	Plasma and cellular pellet samples to be frozen and retained up to 5 years after the end of the study for possible future analysis [f]	Central

[a] Central laboratory results may not be provided to sites.

[b] 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.

[c] Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.

[d] Blood samples for viral NAT and viral serology will be collected at the Baseline (Day 0) Visit, prior to infusion, and the Study Visit Day 28/Early Discontinuation Visit but will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. Additional blood samples for viral NAT and viral serology may be collected and tested during the study *only* if the subject exhibits signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV or parvovirus B19 infection while participating in the study.

[e] At specific study sites due to logistical limitations, See Section 3.7.3.6.

[f] To be collected only for subjects who provide consent for this portion of the study.

3.7.3.1 Thromboembolic Events Risk Testing

Measurement of D-dimer blood levels will be performed at Day 0 (prior infusion), Day 1 (after the infusion), Day 7 ± 1 and Day 28 ± 2 for TEs risk testing.

3.7.3.2 Hemolysis Testing

Laboratory assessments (whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, TBL, indirect bilirubin, and blood smear) will be conducted on Day 0 (prior infusion), Day 1 (after infusion), Day 7 ± 1 and Day 28 ± 2 for hemolysis detection. Note: Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.

3.7.3.3 Virus Safety Testing

Viral NAT and viral serology retain samples will be collected at the Baseline (Day 0) Visit, prior to infusion, and at the Study Visit Day 28/Early Discontinuation Visit, but will be tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. Additional blood samples for viral NAT and viral serology may be collected and tested *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV or parvovirus B19 infection while participating in the study. If samples collected for laboratory analyses are non-analyzable due to various factors (*i.e.*, lost, quantity not sufficient, laboratory error), they will need to be recollected by contacting the subject and arranging for re-sampling.

3.7.3.4 AChR Antibody (or MuSK) Testing

AChR (or MuSK) antibody levels will be measured in all subjects at specified visits based on the following:

- If AChR antibody test is positive at the Baseline Visit, then AChR antibody testing will be conducted at Day 14 and Day 28
- If AChR antibody test is negative at the Baseline Visit, then MuSK antibody testing will be conducted as described below.
  - If MuSK antibody test is positive at the Baseline Visit, then MuSK antibody testing will be conducted at Day 14 and Day 28
  - If MuSK antibody test is negative at the Baseline Visit, then no further antibody testing will be conducted during the study.

All measurements will be conducted using validated assays. Specific details regarding all aspects of sample collection and processing can be found in the Laboratory Manual at each site. Information regarding contact details of central laboratories for sample collection and handling purposes can also be found in the Laboratory Manual at each site.

3.7.3.5 IgG Concentration Measurements

Serum total IgG concentrations will be measured in all subjects at specified visits. All measurements will be conducted using validated assays. Specific details regarding all aspects of sample collection and processing can be found in the Laboratory Manual at each site. Information regarding contact details of central laboratories for sample collection and handling purposes can also be found in the Laboratory Manual at each site.

3.7.3.6 Biomarker Testing

Samples will be collected and retained (up to 5 years after study completion) for future biomarker testing at all study sites (*only for subjects who provide consent for this portion of the study*). Specific details regarding all aspects of sample collection and processing can be found in the Laboratory Manual at each site. Information regarding contact details of central laboratories for sample collection and handling purposes can also be found in the Laboratory Manual at each site.

3.8 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment at the Baseline visit. Subjects who fail to meet eligibility criteria during screening evaluations will be considered screen failures and will not participate in the study.

3.9 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 (Day 0) Visit based on local 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
- 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.

3.10 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 Final Study/Early Discontinuation Visit procedures as close as practical to 28 days after their last administration of the IP.

3.11 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 overdosage 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 in this study is 1 g/kg, no cardiovascular events are expected.

4.1.2 Preparation and Handling

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

4.1.3 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 IGIV-C

can interfere with their immune response to live viral vaccines. Inform patients to notify their healthcare professional/immunizing physician of recent therapy with IGIV-C and this 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 biochemistry and haematology
- Thromboembolic events risk
- 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 all IP infusions, vital signs (T, RR, HR, SBP and DBP) will be monitored by the Investigator or study staff. Monitoring will be routinely performed within 15 ± 5 minutes before the beginning of infusion as well as every 30 ± 10 minutes during the first hour of infusion. Thereafter, vital signs will be monitored and recorded at 30 ± 10 minutes post completion of infusion.

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 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. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs.

4.3.4 Blood Biochemistry and Haematological Parameters

All clinical laboratory data for renal (creatinine, BUN), hepatic (ALT, AST, ALP and TBL) and haematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subject (See Table 3-1).

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.

Laboratory results out of the normal range judged by the Investigator as clinically relevant will be considered AEs.

4.3.5 Thromboembolic Events Risk

Procedures for the monitoring of TEs risk are provided in Appendix 6.

All TEs will be recorded as an AE.

4.3.6 Hemolysis

Procedures for hemolysis detection are provided in Appendix 7.

Hemolysis will be recorded as AEs.

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 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. However, MG exacerbations defined as inclusion criteria will not be considered an AE.

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

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

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 (32):

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 (33,34).

When an AE is classified, assessing causal relationship by the Investigator, as definitive, probable, possible or doubtful/unlikely, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an AR. When the

causal relationship is labeled “Unrelated”, then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.

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

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

AEs occurring during the two-day infusion period (i.e., from the initiation of the IP infusion on the first day to the completion of the total dose of IP on the last day) and within 72 hours following the completion of the infusion of the total dose 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 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 resolve 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 unusually is 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 current criteria 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 SPC).

Events not listed for the particular drug under investigation in the IB or SPC are considered “unexpected” and those listed are considered “expected.” When 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 Serious Adverse Event Management

An MG exacerbation would not be considered an SAE in any of the following scenarios:

- The patient arrives at the hospital with an MG exacerbation class IVb or V present (Inclusion Criterion 3).
- The patient arrives at the hospital with an MG exacerbation class IVb and the exacerbation worsens to class V ***prior to*** receiving treatment with IGIV-C (Inclusion Criterion 3).

If the patient arrives at the hospital with an MG exacerbation class IVb and the exacerbation worsens to class V ***after*** receiving treatment with IGIV-C, the MG exacerbation should be considered an SAE if the event results in any of the outcomes presented in Section 4.4.6.

4.4.6.2 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 exacerbation defined as inclusion criteria.

On the other hand, if the AE or suspected ADR results in a prolongation of the hospitalization beyond what is considered part of the clinical practice (according to the Investigator's criteria) for the treatment of the MG exacerbation defined as inclusion criteria, then the AE or suspected ADR will be considered "serious".

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 and reported accordingly.

4.4.7.2 Hemolysis

Subjects will be monitored for signs and symptoms of hemolysis. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible hemolysis. Hemolysis will be recorded as an AE and reported accordingly.

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

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

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related

signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible. It is responsibility of the Investigator to ensure that AEs are appropriately recorded.

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

1. the verbatim term (a diagnosis is preferred)
2. date/time of onset
3. date/time of resolution
4. intensity (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 resolve 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 clinical research organization (CRO) according to the Medical Dictionary for Regulatory Activities (MedDRA®).

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 EDC system or when 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 EDC system or when EDC system is not available, reported to:

Grifols Global Pharmacovigilance

Email: [redacted]
FAX (back-up only): [redacted]
and [redacted]

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 Plans

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.

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

5.1.1 Subject Population(s) for Analysis

Safety Population

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

Evaluable Population

The evaluable population consists of all subjects who received the entire dose of IP (2 g/kg over 2 consecutive days) and had valid Baseline and Day 14 QMG Score measurements.

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in each of these two populations (safety and evaluable) 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 additional protocol deviations are identified which justify removing a subject from any 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

Efficacy data will be summarized by visit on evaluable population and safety population (if different).

5.1.3.1 Primary Efficacy Analyses

The primary efficacy variable is the change from Baseline in QMG score at Day 14. The primary efficacy variable will be summarized. A paired t-test (comparison between the pre and post) will be used to test for the treatment effect. The hypothesis test is to test the null hypothesis: H_0: $\mu_d = 0$ versus alternative hypothesis Ha: $\mu_d \neq 0$ where μ_d is the mean change from Baseline to Day 14.

If the assumptions for parametric test are not met, the non-parametric test (Wilcoxon signed rank test) will be used.

5.1.3.2 Secondary Efficacy Analyses

The following secondary efficacy variables will be summarized for evaluable population:

- Percentage of subjects who experience a clinical improvement assessed by QMG from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in QMG
- Percentage of subjects who experience a clinical improvement assessed by MG-ADL from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 2 point decrease in MG-ADL
- Percentage of subjects who experience a clinical improvement assessed by the MG Composite from Baseline (Day 0) to Day 14 where clinical improvement is defined as at least 3 point decrease in the MG Composite

5.1.3.3 Exploratory Efficacy Analyses

Summary statistics will be provided and paired t-test or Wilcoxon signed rank test will be used for testing the treatment effect at different visits for:

- Change in QMG score from Baseline (Day 0) to Day 7, Day 21 and Day 28
- Change in MG-ADL from Baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28

- Change in MG Composite from Baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28
- Change in AChR antibodies (or MuSK antibodies) from Baseline (Day 0) to Day 14 and Day 28
- Change in IgG levels from Baseline (Day 0) to Day 1 (after completion of infusion), Day 7, Day 14, Day 21 and Day 28

The number and percentage of subjects who experience a clinical improvement based on the following measures and at the following timepoints will be summarized.

- Clinical improvement in QMG score from Baseline (Day 0) to Day 7, Day 21 and Day 28 where clinical improvement is defined as at least 3 point decrease in QMG score
- Clinical improvement in MG-ADL from Baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28 where clinical improvement is defined as at least 2 point decrease in MG-ADL
- Clinical improvement in MG Composite from baseline (Day 0) to Day 7, Day 14, Day 21 and Day 28 where clinical improvement is defined as at least 3 point decrease in MG Composite

The number of subjects who need ICU admission, the length of ICU stay, need for intubation, and length of intubation will be collected and summarized.

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.

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

Adverse events will be classified as TEAEs or non-TEAEs 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 1st 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 to 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. Abnormal vital signs judged as clinically relevant by the Investigator will be considered AEs. 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.

- Physical Assessment:
  Physical Exam findings (normal and abnormal) will be listed for each clinical trial subject. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs.

- Blood biochemistry and hematology:
  All clinical laboratory data for renal (creatinine, BUN), hepatic (ALT, AST, ALP, and TBL) and haematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subject. Laboratory results out of the normal range judged by the Investigator as clinically relevant will be considered AEs.

- Lab tests for TEs and hemolysis:
  The D-dimer for TE assessment and the laboratory tests for detecting hemolysis (including whole blood hemoglobin, serum or plasma free hemoglobin, 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

The data analysis from the single center study by Zinman et al (24) indicated that the SD for change from Baseline to Day 14 in QMG score is in the range of 2.74 – 3.48. To be

conservative considering multi-national study, the SD of 6.0 for QMG score change from Baseline to Day 14 is assumed, with 2-sided test, 33 subjects are needed to have 90% power to detect a clinically significant improvement of 3.5 in mean change in QMG (24). Fifty subjects are planned to be enrolled for the study.

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).

6.2 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 Sponsor by the Investigator site.

Written ICF must be obtained before any study specific procedure takes place. Considering the nature of this emergency indication, potential subjects may receive information regarding the study in advance of experiencing an MG exacerbation. However, when experiencing an MG exacerbation, the subject or legally authorized representative will be informed again and will sign the written ICF prior to any study specific procedure being conducted.

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

All subjects participating in the study will have insurance coverage by the Sponsor, which is in line with 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 (*eg,* pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, IRB/EC or Regulatory Authorities may inspect their medical records to verify the information collected and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

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

8 USE OF DATA AND PUBLICATION

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

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or Investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
- Within said thirty (30) day period, Grifols shall:
  - Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and other applicable privacy laws;
  - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
  - By written notice to the Investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and

  - By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
- Institution and/or Investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

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10 APPENDICES

Appendix 1 Schedule of Study Procedures

Visit Type	Baseline Visit		Study Visit	Study Visit	Study Visit	Final Study /Early Discontinuation Visit
Study Day	**Day 0**	**Day 1**	**Day 7 [a]**	**Day 14 [a]**	**Day 21 [a]**	**Day 28 [a]**
Informed Consent	X					
Subject Number Assigned	X					
Inclusion/Exclusion Criteria	X					
Medical History [b]	X					
Physical Exam [c]	X					X
Height	X					
Weight [d]	X					
Vital Signs [e]	X	X	X	X	X	X
Viral NAT/Serology	X [k, n]					X [n]
Urine Pregnancy Test [f]	X					X
Biochemistry and Hematology	X [k]					X
Thromboembolic events risk monitoring	X [k]	X [m]	X			X
Hemolysis assessment [g]	X [k]	X [m]	X			X
Biomarker Retains (*only for subjects who provide consent for this portion of the study*)	X [k]		X	X	X	X
AChR (or MuSK) Antibody testing (See Section 3.7.3.4 for details)	X [k]			X		X
QMG scale	X [k]		X	X	X	X
MG-Composite Scale	X [k]		X	X	X	X
MG-ADL	X		X	X	X	X
IgG levels	X [k]	X [l]	X	X	X	X
Preparation/Dispensing of IP [h]	X	X				
IP Infusion [i]	X [j]	X				
AE Assessment	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X

Note: Each MG assessment should be performed by the same clinical staff member whenever possible.

[a] A ± 1 day window is allowed for Study Visits at Days 7 and 14. A ± 2 day window is allowed for study visits at Days 21 and 28

[b] Includes demographics and concomitant diseases

[c] Excludes breast and genitourinary exam

[d] The recorded weight will be used to calculate the IP infusion dose at the Baseline (Day 0, Day 1) Visit

[e] Vitals signs will be monitored per standard site/caregiver procedures; any clinically significant vital sign will be recorded as an AE in the eCRF

[f] Potential child-bearing females only; results must be negative for subject to continue in the study

[g] Local laboratory is to be utilized for testing and reporting. If the local laboratory is unable to perform any of the assessments, the central laboratory may be utilized.

[h] To be performed by a pharmacist, or designee, per the Pharmacy Manual

[i] 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. Please refer to Section 3.7.2.1 to review monitoring vital signs during the two consecutive infusions on Day 0 and Day 1

[j] Inclusion/exclusion criteria must be satisfied before the subject receives the first IP infusion

[k] Samples (or assessments) to be collected (or conducted) within 8 hours prior to IP infusion on Day 0

[l] Sample to be collected 30 ± 10 minutes post-completion of the IP infusion on Day 1.

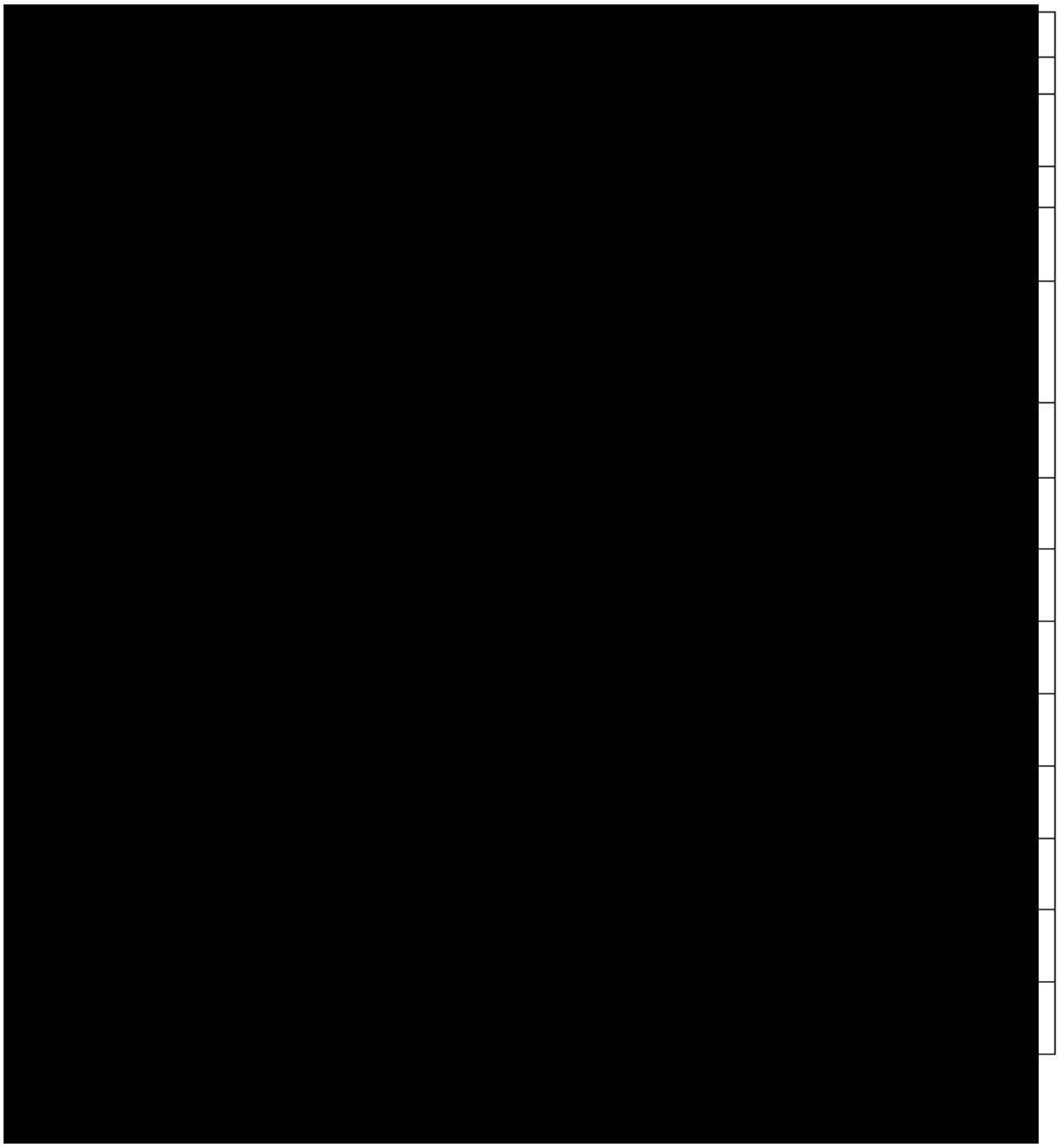
[m] Samples (or assessments) to be collected (or conducted) between 8 and 24 hours post-completion of IP infusion on Day 1

[n] Collect samples but test only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study; These samples will be retained until all analyses in support of the study are complete; see Table 3-1.

Appendix 2 MGFA Clinical Classification

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

Appendix 3 QMG Test Items



Appendix 4 MG Composite Scale

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

Appendix 6 Monitoring of Thromboembolic Events Risk

Subjects will be monitored for signs and symptoms of arterial and venous thromboembolic (TE) events. Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases (ICD) [35]. Such events include, but are not limited to, deep vein thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction, cerebral infarction, acute ischemic heart disease, embolism or thrombosis of arteries of lower extremities, sagittal sinus thrombosis, portal vein thrombosis and injury of mesenteric artery.

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

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

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

Table 1. Schedule of Monitoring of Thromboembolic Events Risk

Study visit	Wells score	D-dimer	Signs & symptoms of DVT and PE*
Day 0 (prior IP infusion)	X	X (within 8 hours prior IP infusion)	X
Day 1 (post-completion IP infusion)	X	X (between 8 and 24 hours post-completion of IP infusion)	X
Day 7 (±1 day)	X	X	X
Day 28 (±2 days)	X	X	X

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

Monitoring of thromboembolic events risk may be performed later, once laboratory results are available, blood collection for the D-dimer testing as well as the Wells score and evaluation signs and symptoms of DVT and PE must be performed as stated in the schedule of procedures.

Thromboembolic events risk will be determined using the **following** assessments:

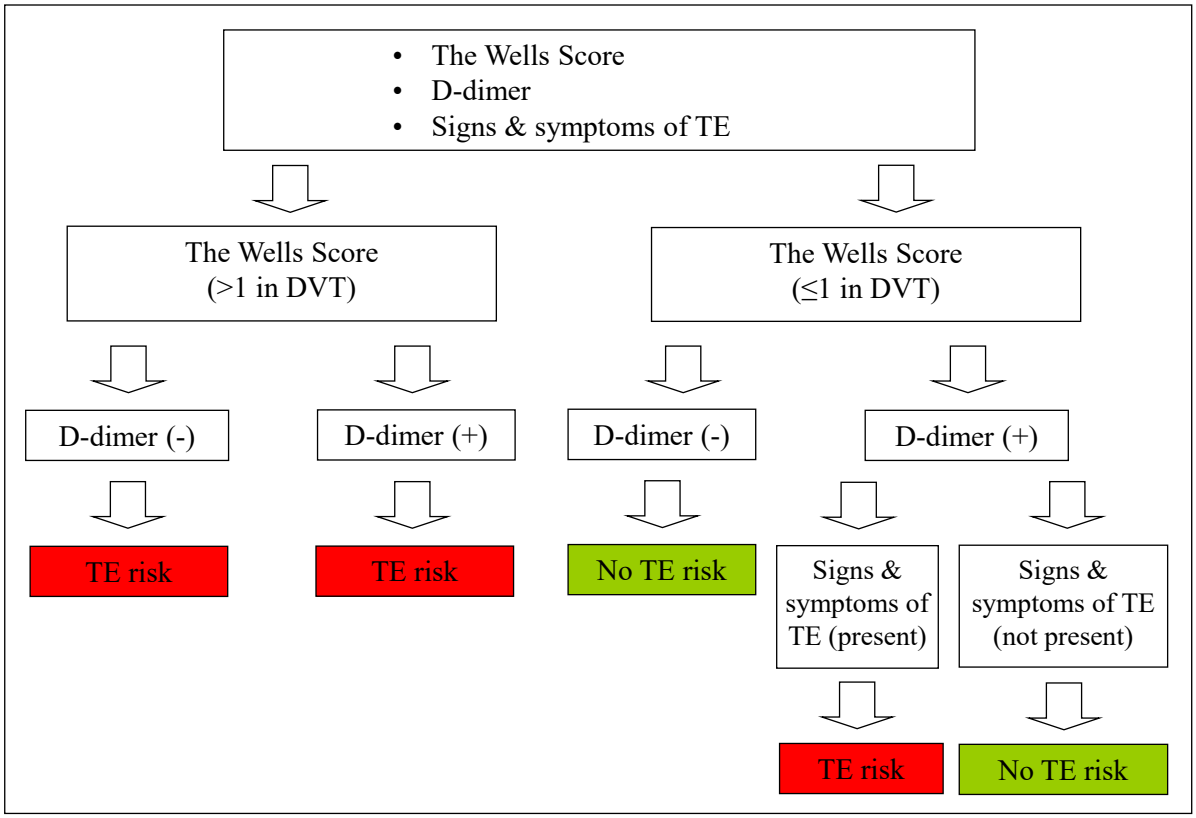
1. The Wells Score [36] will be utilized to assess the clinical characteristics indicative of possible DVT or PE (Table 2);
2. Measurement of D-dimer blood levels [37];
3. Evaluation of clinical signs and symptoms of arterial and venous TE as part of AEs assessment.

Table 2. Schedule of Monitoring of Thromboembolic Events Risk

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

Thromboembolic events risk will be assessed according to the following algorithm adapted from Wells [36] (Figure 1 and Figure 2):

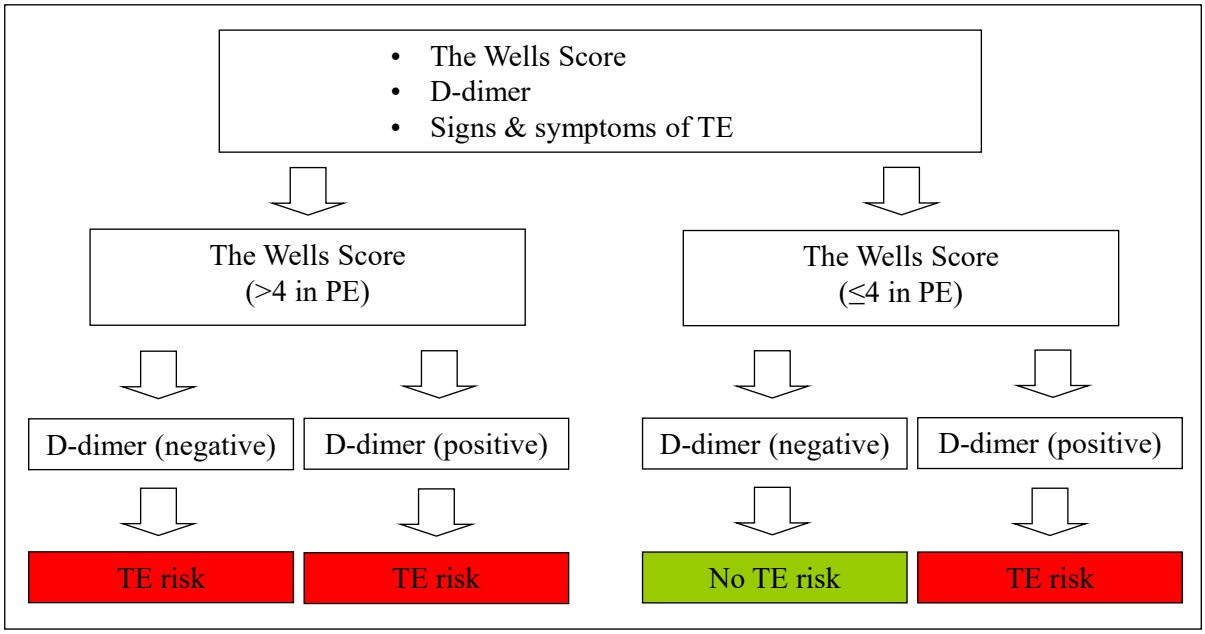
Figure 1. Algorithm to Assess Thromboembolic Events Risk for DVT



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 and 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 and 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 7 Hemolysis Detection

Schedule of the Procedures:

Study visit	Blood collection	Urine collection	Clinical parameters	Hemolysis detection assessment
Day 0 (prior IP infusion)	X (within 8 hours prior IP infusion)	X (within 8 hours prior IP infusion)	X	X
Day 1 (post-completion of IP infusion)	X (between 8 and 24 hours post-completion of IP infusion)	X (between 8 and 24 hours post-completion of IP infusion)	X	X
Day 7 (± 1 day)	X	X	X	X
Day 28 (± 2 days)	X	X	X	X

Assessment of hemolysis detection may be performed later, once laboratory results are available, blood and urine collection as well as the evaluation of clinical parameters must be performed as stated in the schedule of procedures.

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 hemoglobin, serum or plasma free hemoglobin, 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:

In this clinical trial, an IVIG-associated hemolytic reaction is one in which there is evidence of a new hemolytic process within 7 days of the first IGIV administration [38]. The following laboratory signs must be present:

1. Drop in whole blood hemoglobin 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	

*Changes from the previous blood testing i.e. from Day 0 to Day 1, from Day 1 to Day 7 (±1 day) and from Day 7 (±1 day) to Day 28 (±2 days).

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 hemoglobin and hematocrit levels for patients admitted to an internal medicine service [39-40]), iron-deficiency anemia, other drug-induced hemolytic anemia, or anemia associated with an underlying disease (e.g. autoimmune hemolytic anemia [41-42]).
- Negative DAT.
- Absence of other inclusion criteria, in particular absence of evidence for hemolysis.

Appendix 8 Summary of Changes for Amendment 3

(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: (Strikethrough is added to highlight deleted text):	Change To: (Underline is added to highlight new text)	Rationale:
3.2.2 – Exclusion Criteria	15. Subjects with a history of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the ~~Screening~~ Visit. 19. Subjects currently receiving, or having received within 3 months prior to the ~~Screening~~ Visit, any investigational medicinal product or device. 24. Subjects with haemoglobin levels <9~~m~~g/dL.	15. Subjects with a history of chronic alcoholism or illicit drug abuse (addiction) in the 12 months preceding the **Baseline** Visit. 19. Subjects currently receiving, or having received within 3 months prior to the **Baseline** Visit, any investigational medicinal product or device. 24. Subjects with haemoglobin levels <9g/dL.	Clarification provided as there is no Screening Visit in this study. Haemoglobin units corrected.