STATISTICAL ANALYSIS PLAN

GTI1408

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
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0.2	26JUN2017	[redacted]	Updates from sponsor comments. Key changes: mITT instead of ITT as primary population for efficacy Efficacy analyses based on both LOCF and OC Removal of multiplicity adjustment Exposure and Compliance to consider dosage across multiple infusion days Additional lab test summaries Table summary for physical examination
0.3	24Jul2017	[redacted]	Updates from sponsor comments: Key changes: Abbreviations mITT instead of SAF for medical history and medication summaries Additional lab test and vital sign summaries
1.0	04Aug2017	[redacted]	Updates from sponsor comments: Key changes: Duration of infusion in hours instead of minutes

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AChR	Acetylcholine Receptor Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CFB	Change From Baseline
CS	Corticosteroid
DAT	Direct Antiglobulin
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IP	Investigational Product
ISRC	Independent Safety Review Committee
ITT	Intent-to-Treat
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis – Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QOL 15	Myasthenia Gravis Quality-of-Life Instrument
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures
NAT	Nucleic Acid Amplification Technology
OC	Observed Case
PP	Per Protocol
PT	Preferred Term
QMG	Quantitative Myasthenia Gravis
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard Deviation
SI	Standard International
SOC	System Organ Class
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal

Abbreviation	Term
USP	United States Pharmacopeia
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol GTI1408. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated 15 July 2015.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SECONDARY OBJECTIVES

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

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

2.3. EXPLORATORY OBJECTIVES

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

- Percentage of subjects who experience a clinical improvement in QMG total score (at least a 3-point decrease) at Weeks 6, 9, 12, 15, 18, and 21
- Time to first clinical improvement in QMG total score (at least a 3-point decrease)

- Time to Treatment Failure based on QMG total score definition (see Section 3.1 of this analysis plan and protocol Section 3.3.3)
- Change from Baseline (CFB) (Week 0) in QMG total score to Weeks 6, 9, 12, 15, 18, and 21
- Percentage of subjects who experience a clinical improvement in the MG Composite (at least a 3-point decrease) to Weeks 6, 9, 12, 15, 18, and 21
- CFB in MG Composite to Weeks 6, 9, 12, 15, 18, 21, and 24
- Percentage of subjects who experience a clinical improvement in MG-ADL (at least a 2-point decrease) to Weeks 9 and 15
- CFB in MG-ADL to Weeks 9, 15, and 24
- CFB in the 15-item MG Quality-of-Life Instrument (MG-QOL 15) to Weeks 9, 15, and 24
- Myasthenia Gravis Foundation of America (MGFA) post-interventional change in status at Week 24 relative to Baseline

2.4. SAFETY OBJECTIVES

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

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

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

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

- Regimen includes **ONLY cholinesterase inhibitors**

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

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

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

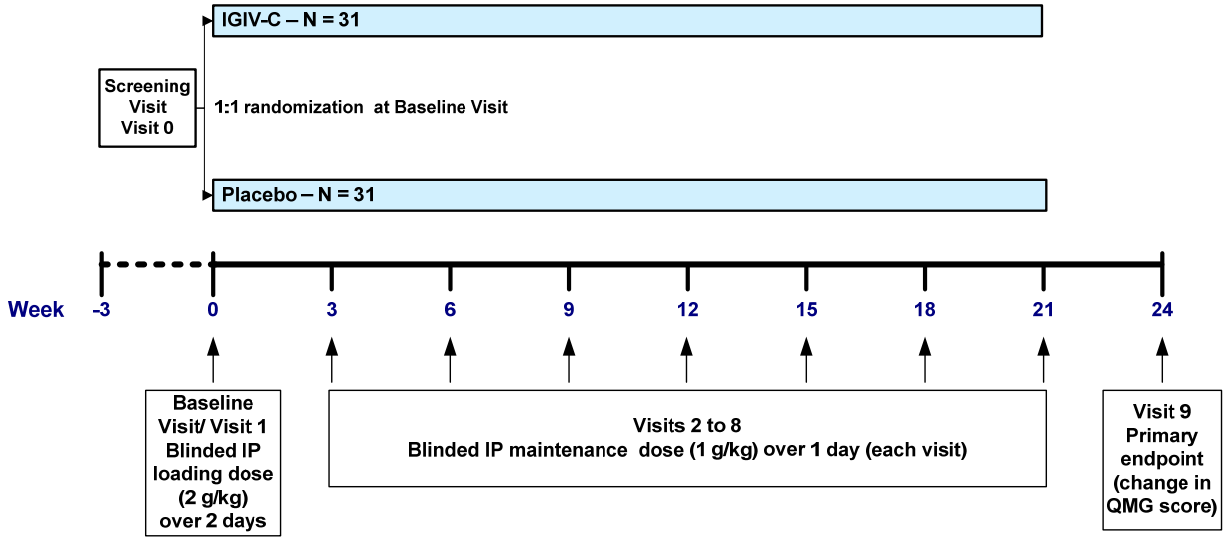
The investigators will hold the subjects' current background medical regimen constant from Screening through the end of the study (Week 24, Visit 9), unless there is a compelling emergent medical need to make medication adjustments, the subject discontinues the study because criteria for treatment failure are met as defined below (after End of Study visit assessments are complete), or adverse effects due to other components of the subject's therapy become untenable.

MG worsening is defined as a QMG increase by ≥4 points relative to Baseline/Week 0. If a subject experiences worsening in QMG total score fulfilling the criterion at or after Week 9, and this worsening (increase in QMG of 4 points or more) is confirmed at the next scheduled consecutive visit, the subject will be considered a treatment failure and will be discontinued from the study (at completion of the visit where confirmation of worsening is demonstrated). If a subject experiences worsening in QMG total score fulfilling the criterion above at Week 3 (Visit 2) or Week 6 (Visit 3) and the QMG increase by ≥ 4 points relative to Baseline is confirmed at the next scheduled visit (i.e., confirmation at Week 6 [Visit 3] or Week 9 [Visit 4], respectively), and this ≥ 4-point QMG worsening is maintained through Week 9 (Visit 4), the subject will be considered a treatment failure. A subject will not be discontinued from the study for reasons of treatment failure until the Week 9 Visit or later.

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

A schematic of the overall study design and essential activities is shown in Figure A.

Figure A: Overall Study Schema



IP = Investigational product, QMG score = Quantitative myasthenia gravis score

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Appendix 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

In the protocol, efficacy analyses were to be based on the intent-to-treat (ITT) population, consisting of all subjects who were randomized. In this analysis plan, the primary efficacy analysis population has been changed to the modified intent-to-treat (mITT) population, consisting of all subjects who were randomized and received at least one dose of study medication.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

There was no DMC for this study. The study did utilize an Independent Safety Review Committee (ISRC) whose members (from Grifols) reviewed relevant safety information. The ISRC did not evaluate any efficacy data, nor were efficacy analyses performed. Review by ISRC was limited to listings of safety parameters (adverse events [AEs], serious adverse events [SAEs], discontinuations due to AEs, and laboratory data) evaluated in a blinded fashion unless unblinding became necessary for an individual subject (urgently) for critical medical interpretation. Throughout study conduct, the clinical trial team members remained blinded to any knowledge of subject treatment assignment stemming from ISRC activities.

4.2. INTERIM ANALYSIS

No interim analysis for this study was planned.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Quintiles Biostatistics following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each population will be conducted prior to the unblinding of the study.

5.1. ALL SUBJECTS SCREENED POPULATION

The all subjects screened population will contain all subjects who provide informed consent for this study.

5.2. INTENT-TO-TREAT POPULATION [ITT]

The intent-to-treat population (ITT) will contain all subjects who were randomized to study medication. Subjects will be classified according to randomized treatment.

5.3. MODIFIED INTENT-TO-TREAT POPULATION [mITT]

The modified intent-to-treat population (mITT) will include all subjects who were randomized and received at least one dose of study medication. This is the primary population for efficacy analysis. Subjects will be classified according to randomized treatment.

5.4. PER PROTOCOL POPULATION [PP]

The Per Protocol population (PP) will contain all subjects in the mITT population who did not experience any major protocol violations impacting the primary efficacy data.

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in the PP population will be assessed at a blinded review meeting that will take place before unblinding/finalizing the database. The review meeting will review the protocol deviation list, as well as data listings. If protocol deviations are identified which justify removing a subject from the PP population, then these decisions will be documented.

5.5. SAFETY POPULATION [SAF]

The safety population (SAF) will contain all randomized subjects who receive any amount of study medication. Subjects will be classified according to treatment received.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear as the available values in

the listings, and any values for study day or corresponding durations will be missing.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the date/time of the first dose of study medication (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, unless a particular assessment (such as abbreviated vital signs) or specific laboratory draws (e.g., end of infusion laboratory draws) are designated as post baseline. Medications commencing on the reference start date will be considered either pre-baseline or post-baseline depending on start date and specific start time in relation to the date/time of IP infusion.

For subjects randomized but not treated, baseline is defined as the last non-missing measurement taken on or before the baseline (Visit 1) visit date.

6.3. DERIVED TIMEPOINTS

Imputation for missing values will be applied to continuous efficacy endpoints using the last observation carried forward (LOCF) method. For subjects who experience treatment failure (defined in protocol Section 3.3.3) or MG crisis (defined in protocol Section 3.3.4), the value at time of confirmation of failure or at time of MG crisis will be carried forward to impute values for all remaining visits. For subjects who discontinued the study early due to any other reasons, the last non-missing on-treatment value (including scheduled, unscheduled, and early termination) will be carried forward. In addition, any intermittent missing values up to the last visit will be imputed by the closest previous non-missing value. Note that if a subject has missing values immediately after baseline, the baseline observation will not be carried forward and these values will be left as missing.

For the same efficacy endpoints above that utilize the LOCF algorithm, separate analyses will also be performed using observed data only without imputing any missing data. This non-imputation method will be referred to as the observed case (OC).

Missing values for the binary endpoints (e.g., whether or not the subject experienced clinical improvement) will be handled similarly as for the continuous endpoints. First, the LOCF algorithm above will be used to impute the (continuous) missing values. The imputed values will then be used to derive the binary endpoints. The binary endpoints will also be analyzed with the OC approach.

Efficacy analyses will be performed on the mITT population using both the LOCF and OC approaches with regards to the missing data, which should allow for more robust assessments of efficacy. See Section 16 for the set of analyses using each of the two approaches. The LOCF endpoint row in by-visit listings will indicate the value that was used in the LOCF efficacy analysis.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/worst case value where required (e.g. shift table). Unscheduled visits may also contribute to QMG at time of treatment

failure or MG crisis in terms of both LOCF and time to treatment failure analyses. It is also possible that unscheduled visits may be used for time to first clinical improvement if the visit timing is appropriate for earliest change.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Early termination data will not be mapped to the next available visit number for by-visit summaries; instead, they will be summarized under a separate "Early Termination" visit. By-visit summaries will only present those visits where an assessment is scheduled to be collected. Early termination data will be eligible for the LOCF endpoint but will not be mapped for OC analysis.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study. Summaries and statistical analyses will be based on scheduled (i.e., nominal visit) data. Listings will include scheduled, unscheduled, retest and early termination data.

6.6. STATISTICAL TESTS

Unless otherwise noted, all statistical inference will be tested as 2-sided with α=0.05.

6.7. COMMON CALCULATIONS

For quantitative measurements, CFB will be calculated as:

- Test Value at Visit X – Baseline Value

6.8. SOFTWARE VERSION

All analyses will be conducted using Statistical Analysis Software (SAS) version 9.4 or higher. The actual SAS version used to perform the analyses will be documented in the Clinical Study Report.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline value
- Treatment group (IGIV-C, Placebo)
- Standard of Care Treatment Regimen at the time of randomization (only cholinesterase inhibitors, CS as the only immunosuppressant/immunomodulator, any non-CS immunosuppressant/immunomodulator)
- Protocol specified visits (Week 3, Week 6, Week 9, Week 12, Week 15, Week 18, Week 21, Week 24)
- Treatment-by-visit interaction

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country or center. The number of subjects per center is expected to be small. Data from this study will be summarized for all centers combined. No center effect will be considered in the statistical models.

7.3. MISSING DATA

Refer to Section 6.3 of this analysis plan on detailed approaches for missing data handling. Sensitivity analyses for missing data are described in section 16.1.4 of this analysis plan.

In the calculation of total scores, if one or more items are missing at a given assessment, the total score will be set to missing.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There will be no adjustment for multiple comparisons/multiplicity in this Phase 2 proof of concept study. All secondary and exploratory endpoints will be evaluated statistically and will have the corresponding results presented with 95% confidence intervals and nominal p-values.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The following subgroups will be assessed and described within the exploratory analysis sections:

- Stratification categories in terms of Baseline standard of care MG treatment regimen at the time of randomization:
  - Only cholinesterase inhibitors
  - CS as the only immunosuppressant/immunomodulator
  - Any non-CS immunosuppressant/immunomodulator
- Baseline QMG categories in relation to the median Baseline QMG across all subjects:
  - < median
  - ≥ median
- Sex:
  - Female
  - Male
- Age (years):
  - <65
  - ≥65
- Geographic Region:
  - North America (United States, Canada)
  - Europe (Czech Republic, France, Germany, Hungary, Estonia, Lithuania, Poland, Belgium)
- MGFA classification at randomization
  - Class IIa
  - Class IIb
  - Class IIIa
  - Class IIIb
  - Class IVa

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and reasons for discontinuation will be provided for the All Subjects Screened population. The list of protocol deviations (as defined in section 5.3), including inclusion and exclusion

criteria, will be presented for the All Subjects Screened population.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the mITT population.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex
- Race
- Ethnicity
- Geographic Region
- Screening Weight (kg)
- Height (cm)
- Screening Body Mass Index (BMI) (kg/m^2)
- Time since diagnosis (years) - calculated relative to date of consent
- Tests performed to confirm MG
- MGFA classification at time of diagnosis
- MGFA classification at screening
- MGFA classification at randomization
- MG treatment used during last six months
- Thymectomy history (yes/no)
- Standard of Care Treatment Regimen at randomization

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

11. MEDICAL HISTORY

Medical History information will be presented for the mITT population.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1, and presented by System Organ Class (SOC) and Preferred Term (PT).

12. CONCOMITANT ILLNESSES

All Concomitant Illnesses will be reported as medical history or as adverse events, as appropriate, and will contribute to the corresponding summaries.

13. MEDICATIONS

Medications will be presented for the mITT population and coded using World Health Organization (WHO) Drug Dictionary Enhanced 01MAR2015. Medications will be summarized by Anatomical Therapeutic Chemical (ATC) Class Level 2 and Medication Sub-Class ATC Level 4. If the ATC Level 2 or 4 term is missing, the higher level term will be used in the medication summary tables and data listing.

See Appendix 2 for handling of partial dates and times for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.

- 'Concomitant' medications are medications which:

  - started prior to, on or after the first dose of study medication,
  - AND ended on or after the date and time of first dose of study medication or were ongoing at the end of the study.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in weeks will be presented for the Safety population.

The date of first study medication administration will be taken as the earliest start date of infusion from the electronic Case Report Form (eCRF) Study Drug Infusion form. The date of last study medication will be taken as the latest stop date from the eCRF Study Drug Infusion form.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

The total number of dosages, the total number of days of infusions, and the total volume infused (in mL) will be summarized on a per-subject basis. Note that subjects can have more than one infusion day per treatment visit. The initial loading dosage (2 g/kg) will be divided on 2 consecutive days with extension

of up to 4 consecutive days to account for tolerability and/or weight >80 kg. The subsequent 7 maintenance dosages (1 g/kg) will be infused in one day with an extension to 2 consecutive days (divided dosages) to account for tolerability and/or weight >80 kg. For both loading and maintenance dosages the limit for blinded IGIV-C infusion is no more than 80 g/day, corresponding to an 80-kg body weight for a 1 g/kg per diem dosage.

In addition, the following variables will be derived and summarized separately for the loading dosage and the maintenance dosages:

On a per-subject basis:

- Number of dosage(s) received

On a per-dosage basis:

- Dosage in grams
- Dosage in g/kg
- Number of infusion days

On a per-infusion basis:

- Duration of infusion in hours

14.1. DERIVATIONS

Duration of exposure (weeks) = (date of last study medication administration – date of first study medication administration + 21)/7. The addition of 21 days is to take into account total exposure time to the study medication since the dosages are administrated every 3 weeks. Based on this derivation, the minimum exposure for any treated subject is 21 days.

In the below derivations, a dosage includes all infusion days within a given treatment visit.

Number of dosage(s) received will be determined directly from entries in the eCRF Study Drug Infusion form.

Dosage (g) = Total volume infused for the indicated dosage (mL) x Concentration of 0.1 (g/mL).

Dosage (g/kg) = Dosage (g) / Weight (kg), using the most recently available weight for the indicated treatment visit.

Number of infusion days will be determined directly from entries in the eCRF Study Drug Infusion form.

Duration of infusion in minutes will be calculated for each infusion day as: Stop time of infusion – Start time of infusion. Duration of infusion in hours will be calculated as: Duration of infusion in minutes / 60. If the time portion of either start or stop date/time is missing, then the duration will be missing for that infusion.

15. STUDY MEDICATION COMPLIANCE

Compliance to study medication, displayed as treatment compliance, infusion compliance, and overall compliance, will be presented for the Safety population.

15.1. DERIVATIONS

Treatment compliance will be calculated as the total volume infused divided by the total volume prepared, expressed as a percentage. The total volume prepared and dispensed by the pharmacist is the intended dose volume a subject should be given based on the body weight. This total volume prepared is recorded on the eCRF Study Drug Infusion form.

Infusion compliance will be calculated as the actual number of infusions received divided by the expected number of infusions, expressed as a percentage. Note that the number of days of infusions is a function of investigator choice based on both tolerability and weight. Subjects weighing > 80 kg will need to have infusions divided over more than 1 day as the limit for blinded study drug administration is 80 g/day. However, should a subject weigh more than 80 kg, the investigator may choose to divide the loading dose (2 g/kg) over 3 or 4 days as 3 or 4 daily infusions. For maintenance doses (1 g/kg) every 3 weeks, the choice is 1 or 2 days based on either tolerability or weight, given the mandatory dose limit of no more than 80 g/day. For the purpose of infusion compliance calculation, each loading or maintenance dose is counted as a single infusion (i.e., a single dosage). The expected number of infusions during the study is equal to 8 for subjects who complete the study. The total number of expected infusions for those who discontinue early is equal to the number of dosing visits, including completion of loading dose, up to the time of discontinuation. (For example, if a subject discontinues between weeks 6 and 9, the number of expected infusions is 3: one loading dose at Baseline, one maintenance dose at Week 3, and one maintenance dose at Week 6.)

Overall compliance will be calculated as treatment compliance multiplied by infusion compliance.

See calculations below.

- Treatment Compliance (%) to study medication will be calculated as follows:

$$\frac{[\text{Total Actual Volume Infused at 1st IP dose}]+\cdots+[\text{Total Actual Volume Infused at last IP dose}]}{[\text{Total Volume Prepared for Infusion at 1st IP dose}]+\cdots+[\text{Total Volume Prepared for Infusion at last IP dose}]} \times 100$$

- Infusion Compliance (%) to study medication will be calculated as follows:

$$\frac{[\text{Total Number of Dosages Received During the Study}]}{[\text{Total Number of Expected Dosages During the Study}]} \times 100$$

- Overall Compliance (%) to study medication will be calculated as follows:

(Treatment Compliance x Infusion Compliance) / 100

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the mean change in QMG total score from Baseline (Week 0) to Week 24.

The QMG total score consists of 13 individual items. Each item is scored from 0 (none) to 3 (severe). The results of the QMG test items are entered on the eCRF. The QMG Test Items are listed in Appendix 3.

The QMG total score is the sum of all 13 items and ranges from 0 to 39. If one or more individual items are missing, the QMG total score will be set to missing. Note that total scores are reported on the eCRF and in general will not be recalculated. The CFB for the QMG total score and for each individual item will be calculated and summarized. No statistical analysis will be performed on the individual items.

The CFB is calculated as indicated in section 6.7.

16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

For subjects who do not have QMG total score at Week 24, the LOCF will be used to impute the CFB to Week 24. For subjects who experience treatment failure (defined in protocol Section 3.3.3) or MG crisis (defined in protocol Section 3.3.4) the value at time of confirmation of failure or at time of MG crisis will be carried forward to impute values for all remaining visits. For subjects who discontinue the study early due to any other reasons, the last non-missing on-treatment value (including scheduled, unscheduled, and early termination) will be carried forward.

Subjects with no post-baseline QMG total score available will be excluded from analysis.

Refer to section 16.1.4 for analyses on sensitivity to missing data.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to test the null hypothesis that the mean change in QMG total score from Baseline to Week 24 (mean CFB) in the IGIV-C group is equal to the mean CFB in the Placebo group ($\mu_1=\mu_2$). The alternative hypothesis (H_a) is that the mean CFB in the IGIV-C group is not equal to the mean CFB in the Placebo group ($\mu_1\neq\mu_2$).

The primary efficacy analysis will be performed for the mITT population.

The primary efficacy variable will be analyzed using analysis of covariance (ANCOVA). The ANCOVA model will include CFB in QMG total score as the dependent variable, with treatment and Baseline

standard of care treatment regimen as fixed factors and Baseline QMG total score as a covariate (Dobson, 2002). Refer to section 7.1 for categorical levels of the fixed factors.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

Sensitivity analyses will be performed to assess the robustness of the primary analysis.

Sensitivity to population:

- The primary analysis described in section 16.1.3 will be repeated for the PP population.

Sensitivity to missing data assumptions:

- An analysis of subjects with non-missing QMG total score at Week 24 will be performed. Subjects with missing values will be excluded from this sensitivity analysis and the analysis will be performed on the mITT population using OC data only. The same ANCOVA model described in section 16.1.3 will be used.
- To assess the longitudinal measurements of QMG total score at various time points, the treatment effects will be explored by using the mixed-effect model repeated measures (MMRM.) The MMRM model will include CFB as the repeated dependent variable, with treatment, Baseline standard of care treatment regimen, protocol-specified visits, and treatment-by-visit interaction as fixed effects, with Baseline QMG value as a covariate, and with measures within-subject at each visit as a repeated measure (McCulloch, 2001). An unstructured covariance matrix will be used to model the within-subject error. If the fit of the unstructured covariance structure fails to converge, a compound symmetry covariance structure will be used. Parameters will be estimated using restricted maximum likelihood with the Kenward-Roger method for calculating the denominator degrees of freedom. For the MMRM, all available data will be utilized and no missing data will be imputed. Data collected starting at the Week 3 visit and up to the Week 24 visit is included in this analysis.
- Sensitivity analyses will be performed for the mITT population and repeated for the PP population.

16.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the mITT population using both the LOCF and OC approaches for missing data handling.

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Percentage of Subjects with a Clinical Improvement Assessed by QMG Total Score at Week 24

The QMG total score is calculated as described in section 16.1.1.

Clinical improvement is defined as at least a 3-point decrease in QMG total score from Baseline to Week 24.

16.2.1.2. Percentage of Subjects with a Clinical Improvement Assessed by MG Composite at Week 24

The MG Composite scale consists of 10 individual items. The results of the MG Composite items are entered on the eCRF. The MG Composite scale is shown in Appendix 4.

The MG Composite total score is the sum of all 10 items and ranges from 0 to 50. Higher item values represent greater severity of illness. If one or more individual items are missing, the MG Composite total score will be set to missing. Note that total scores are reported on the eCRF and in general will not be recalculated.

Clinical improvement is defined as at least a 3-point decrease in the MG Composite total score from Baseline to Week 24.

16.2.1.3. Percentage of Subjects with a Clinical Improvement Assessed by MG-ADL at Week 24

The MG-ADL is an 8-item questionnaire. Each item grade ranges from 0 to 3. The results of the MG-ADL items are entered on the eCRF. The MG-ADL profile is shown in Appendix 5.

The MG-ADL total score is the sum of all 8 items. Higher item values represent greater severity of illness. If one or more individual items are missing, the MG-ADL total score will be set to missing.

Clinical improvement is defined as at least a 2-point decrease in MG-ADL total score from Baseline to Week 24. Note that total scores are reported on the eCRF and in general will not be recalculated.

16.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

Missing values for the secondary binary endpoints will be handled similarly as for the continuous endpoints. First, the LOCF algorithm will be used to impute the (continuous) missing values. The imputed values will then be used to derive the binary endpoints.

The binary endpoints will also be analyzed with the OC approach, i.e., missing data will not be imputed.

16.2.3. Analysis of Secondary Efficacy Variables

16.2.3.1. Analysis of Clinical Improvement

All three clinical improvement variables will be analyzed using the same method. The effect of treatment on the percentage of subjects with clinical improvement will be tested using the Cochran-Mantel-Haenszel method (Mantel, 1963), adjusted for Baseline standard of care treatment regimen. The hypothesis test will be based on the General Association statistic.

16.3. EXPLORATORY EFFICACY

16.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

16.3.1.1. Percentage of Subjects with a Clinical Improvement Assessed by QMG Total Score at Weeks 6, 9, 12, 15, 18, and 21

Clinical Improvement as assessed by QMG total score is defined in the same way as in Section 16.2.1.1.

16.3.1.2. Time to First Clinical Improvement in QMG Total Score

Clinical Improvement as assessed by QMG total score is defined in the same way as in Section 16.2.1.1. Time to first clinical improvement is calculated as the date of first assessment with clinical improvement – date of Baseline visit + 1. The date of first assessment with clinical improvement will be used regardless of whether subsequent visits also demonstrate improvement. Subjects who never experience clinical improvement will be censored at the date of their last non-missing QMG total score assessment.

16.3.1.3. Time to Treatment Failure Based on QMG Total Score

Treatment failure due to MG worsening is defined as at least a 4-point increase in QMG total score from Baseline at two consecutive visits after Week 9. To qualify, the 4-point increase in QMG total score must be confirmed at next consecutive visit. Time to treatment failure is calculated as the date of the first of the two consecutive assessments meeting MG worsening – date of Baseline visit + 1. Subjects who never experience treatment failure will be censored at the date of their last non-missing QMG total score assessment.

16.3.1.4. CFB in QMG Total Score at Weeks 6, 9, 12, 15, 18, and 21

The CFB in QMG total score is defined in the same way as defined in section 16.1.1.

16.3.1.5. Percentage of Subjects with a Clinical Improvement Assessed by MG Composite Score at Weeks 6, 9, 12, 15, 18, and 21

Clinical Improvement as assessed by MG Composite score is defined in the same way as in Section 16.2.1.2.

16.3.1.6. CFB in MG Composite at Weeks 6, 9, 12, 15, 18, 21, and 24

MG Composite total score is defined in the same way as defined in section 16.2.1.2. The CFB is calculated as indicated in section 6.7.

16.3.1.7. Percentage of Subjects with a Clinical Improvement Assessed by MG-ADL Score at Weeks 9 and 15

Clinical Improvement as assessed by MG-ADL score is defined in the same way as in Section 16.2.1.3.

16.3.1.8. CFB in MG-ADL at Weeks 9, 15, and 24

MG-ADL total score is defined in the same way as in section 16.2.1.3. The CFB is calculated as indicated in section 6.7.

16.3.1.9. CFB in the 15-item MG-QOL 15 at Weeks 9, 15, and 24

The MG-QOL 15 is made up of 15-items. All individual items related to degree of disease-related impairment are rated on a Likert scale ranging from “not at all” (score 0 points) to “very much” (score 4 points), with higher scores indicating worse disease. The results of the MG-QOL 15 items are entered on the eCRF. The MG-QOL 15 is shown in Appendix 6.

The MG-QOL 15 total score is the sum of all 15 items. If one or more individual items are missing, the MG-QOL 15 total score will be set to missing. Note that total scores are reported on the eCRF and in general will not be recalculated.

The CFB is calculated as indicated in section 6.7.

16.3.1.10. MGFA Post-interventional Change in Status at Week 24 Relative to Baseline

An MGFA post-interventional change in status relative to Baseline will be evaluated at Week 24. The Investigator will classify the subject as: (I) Improved, defined as a substantial decrease in pre-treatment clinical manifestations of MG, QMG decrease ≥ 3 points; (U) Unchanged, defined as no substantial change in pre-treatment clinical manifestations of MG; (W) Worse, defined as a substantial increase in pre-treatment clinical manifestations of MG, QMG increase ≥ 3 points. The status value provided by the investigator will be used as the variable for analysis.

16.3.1.11. Subgroup Analysis of Primary Efficacy Variable

The primary efficacy variable defined in Section 16.1.1 will be analysed for the subgroups mentioned in Section 7.5.

16.3.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLES

16.3.2.1. Analyses of Clinical Improvement

Missing values for the exploratory binary endpoints will be handled using both the LOCF and the OC approaches. With the LOCF approach, first the missing total scores at the weeks indicated will be imputed using the LOCF approach for continuous endpoints as detailed in Section 6.3. The imputed scores will then be used to derive whether subjects met the clinical improvement criteria. With the OC approach, the analysis will be based on observed non-missing data only and subjects with missing total scores at the indicated visits will be excluded from the analysis.

16.3.2.2. Time to Clinical Improvement and Time to Treatment Failure

Subjects with no post-baseline data will be censored at Day 1. Subjects with missing data for at least one but not all scheduled visits will be censored at the last visit with non-missing data, unless they experience the event based on the assessments available. Both scheduled and unscheduled visits are considered in identifying the last visit with non-missing data.

16.3.2.3. CFB in QMG, MG Composite, MG-ADL, or MG-QOL 15

For subjects who do not have a total score at the week indicated, the same method as in section 16.1.2 will be used. As additional sensitivity analyses, the OC approach for handling missing data will also be used.

16.3.2.4. MGFA Post-interventional Change in Status

Subjects with missing results will be excluded from analysis.

16.3.2.5. Subgroup Analysis of Primary Efficacy Variable

For subjects who do not have a total score at Week 24, the same method as in section 16.1.2 will be used. As additional sensitivity analyses, the OC approach for handling missing data will also be used.

16.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

Exploratory efficacy analyses will be based on the mITT population. Both the LOCF and the OC approaches for handling missing data will be used. P-values presented for exploratory analyses are for information purposes only.

16.3.3.1. Analyses of Clinical Improvement

The same method described in section 16.2.3.1 will be used.

16.3.3.2. Time to Clinical Improvement and Time to Treatment Failure

For the time to event variables, Kaplan-Meier estimates (Kaplan, 1958) will be provided and the treatment comparison will be performed using a log-rank test, stratified by Baseline standard of care treatment regimen.

16.3.3.3. CFB in QMG, MG Composite, MG-ADL, or MG-QOL 15

The same ANCOVA method described in Section 16.1.3 will be used. The MMRM method described in section 16.1.4 will also be used to assess longitudinal measurements for the other parameters.

16.3.3.4. MGFA Post-interventional Change in Status

MGFA post-interventional change in status at Week 24 relative to Baseline will be summarized by

treatment group.

16.3.3.5. Subgroup Analysis of Primary Efficacy Variable

The observed and CFB values will be presented for each visit, including week 24, as well as for the LOCF endpoint used in the primary analysis, as described in section 16.1. Presentation by subgroups will not include any statistical testing.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety population.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 17.1.

Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the beginning of the first infusion of study medication and prior to the final study visit.

See Appendix 2 for handling of partial or missing dates/times for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

Listings will include TEAEs and Non-TEAEs. Subjects with deaths, serious adverse events (SAEs), suspected adverse drug reactions (ADRs) and AEs leading to premature discontinuation from the study will be listed.

An overall summary of number of subjects and number of events within categories of interest will be provided as specified in the templates.

17.1.1. ALL TEAES

Incidence of TEAEs and of suspected ADRs will be presented by SOC and PT and also broken down further by intensity and causal-relationship to study medication. Non-TEAEs will be summarized separately from TEAEs.

Summaries presented by PT will also be provided for the total number of events, the rate per dosage, and the rate per exposure week. The rate per dosage, where a dosage includes all infusion days within a given treatment visit, will be calculated as:

Total number of events / Total number of dosages received

The rate per exposure week will be calculated as:

Total number of events / Total duration of exposure in weeks

17.1.1.1. Intensity

Intensity (severity) is classed as mild/ moderate/ severe (increasing severity). The subject incidence of TEAEs by intensity and the subject incidence of TEAEs and suspected ADRs by maximum intensity will be summarized. The incidence of TEAEs and suspected ADRs will also be presented by SOC/PT; if a subject reports a TEAE more than once within that SOC/PT, the AE with the worst case severity will be included for the relevant SOC/PT.

17.1.1.2. Causal-Relationship to Study Medication

Causality to study drug, as indicated by the Investigator, is classed as "unrelated", "doubtful/unlikely", "possible", "probable", or "definite" (increasing level of relationship). The subject incidence of TEAEs and ADRs by relationship will be summarized. The incidence of TEAEs will also be summarized by relationship; if a subject reports the same AE more than once within that SOC/PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. AEs classified as "definite", "probable", "possible" or "doubtful/unlikely" will be defined as suspected ADRs. ADRs will be presented by SOC and PT. A suspected ADR with a causal relationship of "definite" will be defined as an adverse reaction (AR).

17.1.2. TEAEs Leading to Discontinuation From the Study

TEAEs leading to permanent discontinuation of study medication will be identified based on the eCRF response to the question 'Did subject withdraw from the study as a result of this event?' TEAEs leading to discontinuation will be presented in a listing.

17.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared. A listing will also be presented.

17.1.4. Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. AEs leading to death will be presented in a listing.

17.1.5. Infusional Adverse Events

Infusional AEs, including infusional suspected ADRs, are those temporally associated with the infusion of the IP and are defined as TEAEs that occur from the initiation of the IP infusion and within 72 hours following the completion of the infusion of the total dosage of IP. These will be summarized by presenting infusional events and subject incidences and percentage. A corresponding listing will also be presented. 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.

17.1.6. ADVERSE EVENTS OF SPECIAL INTEREST

Summaries of Thromboembolic or Hemolysis events will be presented by SOC and PT. Thromboembolic and Hemolysis Events are indicated on the eCRF.

17.2. LABORATORY EVALUATIONS

17.2.1. CHEMISTRY, HEMATOLOGY, HEMOLYSIS, ACETYLCHOLINE RECEPTOR ANTIBODY (ACHR), AND IMMUNOGLOBULIN G (IGG)

Results from the central laboratory will be included in the reporting of this study for clinical laboratory assessments (chemistry and hematology) parameters.

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and CFB by visit (for quantitative measurements)
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements with normal ranges)

Results out of normal range will be flagged in the listings.

For selected analytes, tabular summaries and listings will be provided for treatment-emergent laboratory abnormalities, utilizing the following thresholds of interest. Note that thresholds are in some cases relative to the established reference range (multiples of lower limit of normal [LLN] or upper limit of normal [ULN]) and in other cases are relative to an absolute value threshold:

- Hemoglobin: treatment-emergent (TE) value 8.9 g/dL or less AND a decrease of 1 g/dL from Baseline
- Absolute Neutrophils will have two thresholds:
  - TE Neutrophils <750/mm3
  - TE Neutrophils < 500/mm3
- Creatinine: TE > 2.5 x ULN (reference range specific to gender/age)
- Alanine aminotransferase [ALT]: TE > 3 x ULN (reference range specific to gender/age)
- Total bilirubin: TE > 3 x ULN (reference range specific to gender/age)
- Haptoglobin: < LLN

Quantitative/semiquantitative binding, blocking, and modulating Acetylcholine Receptor Antibody (AChR) antibodies, hemolysis labs, and trough Immunoglobulin G (IgG) level results from the central

laboratory will also be analyzed with methods similar to routine chemistry and hematology labs.

A listing of subjects with positive direct antiglobulin (DAT) test results will be provided. Subjects with positive DAT results are defined as those having a positive result for at least one of IgG and C3 from Screening through end of study. The listing will include all DAT results for any subject with at least one positive DAT value and will also include all hemoglobin, absolute reticulocyte count, serum free hemoglobin, haptoglobin, lactate dehydrogenase, and total and indirect bilirubin values at corresponding time points. Blood smear results (specifically "RBC morphology" whether there is presence of spherocytosis) and "urine blood" with any corresponding entries for "urine RBC/HPF" on urinalysis will also be included.

17.2.2. D-DIMER AND WELLS SCORE

D-dimer and Wells Score are collected for thromboembolism evaluation. D-dimer results are included in the laboratory data. The Wells Score data is collected on the eCRF. D-dimer and total scores of the Wells Score for Deep Vein Thrombosis and Pulmonary Embolism will be summarized with number of subjects, mean, standard deviation (SD), median, minimum, and maximum values. Summaries will be presented for actual and CFB by treatment and visit. All D-dimer and Wells Score data will also be presented in data listings.

17.2.3. VIRUS SAFETY TESTING

Blood samples for virus safety (viral nucleic acid amplification technology [NAT] and viral serology) testing will be collected at Baseline/Week 0 (Visit 1) prior to randomization, but will be tested only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or parvovirus B19 infection while participating in the study. These samples will be retained until all analyses in support of the study are complete. 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 any virus safety testing was conducted, all available results will be listed.

17.2.4. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in standard international (SI) units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

17.3. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)

Weight (kg) will be presented in listings and summarized with other vital signs.

The following summaries will be provided for vital signs data:

- Actual and CFB by visit

17.4. PHYSICAL EXAMINATION

Full physical assessment findings will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once. Physical assessment change findings will be summarized with numbers and percentages per category of the change findings. Physical examination findings (normal and abnormal) with specific findings observed will be listed for each subject.

18. REFERENCES

Dobson, Annette J. *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC, 2002.

Kaplan EL, Meier P. "Nonparametric estimation from incomplete observations." *Journal of the American Statistical Association* 53 (1958): 457-481.

Mantel, N. "Chi-square tests with one degree of freedom; extensions of the Mantel Haenszel procedure." *Journal ofthe American Statistical Association* 58 (1963): 690-700.

McCulloch CE, Searle SR. *Generalized, Linear, and Mixed Models*. New York: John Wiley and Sons, 2001.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

QUINTILES OUTPUT CONVENTIONS

Outputs will be presented according to the following output conventions.

1. ABBREVIATIONS

ASCII American standard code for information interchange file format

CGM Computer graphics metafile

ODS Output Delivery System

RTF Rich text file format

PDF Portable Document Format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures.

3. OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14_3_01_1_disp.RTF)

4. PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States.

The page orientation should be landscape.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.

The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.

5. FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining, italics or subscripting should be permitted. Super-scripts will be avoided. Single spacing should be used for all text.

6. HEADER INFORMATION

Headers should be defined as follows:

• The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing

• The protocol number and treatment should appear in row 1, left-aligned, and the page number (in the format of Page X of Y) should appear as right-aligned

• The indication should appear in row 2, left-aligned, and the customer name should be right-aligned

• Row 3 should be blank

• The output identification number should appear in row 4, centered

• The output title should start in row 5, centered

• The output population should appear in row 6, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.

• Row 7 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)

• Row 8 should be a blank line

• Mixed case should be used for titles

• The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg CFB) e.g. Vital Signs – CFB.

• Titles should not contain quotation marks or footnote references

• The column headings should be underlined with a row of underscores ('_')

• Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered

• Column headings containing numbers should be centered

• Column headings should be in sentence case

• In general, the population count should appear in the column header in the form "(N=XXX)"

• “Statistic” should be the column header over n, Mean, SE, n (%) etc.

• As a rule, all columns should have column headings.

7. TABLE AND LISTING OUTPUT CONVENTIONS

General:

• The first row in the body of the table or listing should be blank

• The left hand column should start in column 1. No indenting or centering of the output should occur.

• Rounding should be done with the SAS function ROUND.

• Numbers in tables should be rounded, not truncated.

• Alphanumeric output should be left aligned.

• Numbers should be decimal point aligned.

• Whole numbers should be right aligned.

• Text values should be left aligned.

• The first letter of a text entry should be capitalized

• Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order within subject, with earliest adverse event, medication or history coming first.

• The study drug should appear first in tables with treatments as columns

• In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization.

• If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.

• All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).

• Do not use superscripts and subscripts

• All variables that are output in the eCRF (which have data present) should appear in the listings

• The width of the entire output should match the linesize

Univariate Statistics:

• Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)

• Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up.

• If the original data has N decimal places, then the summary statistics should have the following decimal places:

Minimum and maximum: N

Mean and median: N + 1

SD and CV: N + 2

CV%: N, but with a maximum number of 1 decimal place

The maximum number of decimal places should be 4 for statistics other than CV%.

Frequencies and percentages (n and %):

• Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)

50 (64.9%)

0 (0.0%)

Confidence Intervals:

• As a rule confidence intervals are output to one place more than the raw data. Standard errors are output to two places more than the raw data.

• Boundary values of confidence intervals should be separated by a comma.

• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.

• Boundary value of -0.00 should be presented as 0.00.

• An example is given below:

(-0.12, -0.10)

(9.54, 12.91)

P-values:

• P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

• Ratios should be reported to one more decimal place than the original data.

Spacing:

• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number “n”.

• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

• A “0” should be used to indicate a zero frequency.

• A blank will be used to indicate missing data in an end-of-text table or subject listing.

8. FOOTNOTE INFORMATION

Footers should be defined as follows:

• A continuous line of underscores (‘_’) will follow the body of the table or listing prior to any footnotes at the bottom of the page

• Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table

• The program path and name should appear as footnote 1 at the bottom of the page, followed on the same line by the date/time stamp

• Footnotes should be left-aligned.

• Footnotes should be in sentence case.

• Only “typewriter” symbols are permitted – eg “*”, “$”, “#”, “@”, “&” and “+”.

• The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.

• If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

Ordering of footnotes should be as follows:

1.) Abbreviations and definitions

2.) Formulae

3.) Symbols

4.) Specific notes

• Common notes from table to table should appear in the same order.

• The symbols should appear in the same order as what they are defined in the table or listing, from left

to right.

10. PROGRAMMING INSTRUCTIONS

Programming instructions, if required, must appear in blue font at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words “Programming Note” followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY/HH:MM.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings and Graphs
Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) loading dose of 2 g/kg followed by 7 maintenance dosages of 1 g/kg every 3 weeks	IGIV-C
Matched Placebo	Placebo
Total	Total

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order. Where necessary to uniquely identify data records, additional time points will be included in the outputs.

Long Name (default)	Short Name
Screening	Scr
Baseline	BL

Long Name (default)	Short Name
Week 3	WK3
Week 6	WK6
Week 9	WK9
Week 12	WK12
Week 15	WK15
Week 21	WK21
Week 24	WK24
Early Termination	ET

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group (or treatment received if it's a safety output), first by active and then placebo
- center-subject ID,
- date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

AE START DATE TIME	STUDY MEDICATION START DATE TIME	ACTION
Known	**Known**	If start date/time < study med start date/time, then not TEAE If start date/time >= study med start date/time, then TEAE
Partial or Missing	**Known**	If start date < study med start date, then not TEAE If start date > study med start date, then TEAE If start date = study med start date, then impute AE start time to the latest possible time (i.e. 23:59 if hours and minutes are missing, or 59 minutes past the hour if only minutes are missing). If this imputed date/time is after AE stop date/time, then use AE stop date/time as the imputed AE start date/time. Then: If imputed start date/time < study med start date/time, then not TEAE If imputed start date/time >= study med start date/time, then TEAE
Known	**Partial or Missing**	If start date < study med start date, then not TEAE If start date > study med start date, then TEAE If start date = study med start date, then impute study med start time as the earliest possible time (i.e. 00:00 if hours and minutes are missing, or 00 minutes past the hour if only minutes are missing). Then: If start date/time < imputed study med start date/time, then not TEAE If start date/time >= imputed study med start date/time, then TEAE

AE START DATE TIME	STUDY MEDICATION START DATE TIME	ACTION
Partial or Missing	**Partial or Missing**	If start date < study med start date, then not TEAE If start date > study med start date, then TEAE If start date = study med start date then impute AE start time to the latest possible time (i.e. 23:59 if hours and minutes are missing, or 59 minutes past the hour if only minutes are missing). If this imputed date/time is after AE stop date/time, then use AE stop date/time as the imputed AE start date/time. Also impute study med start time as the earliest possible time (i.e. 00:00 if hours and minutes are missing, or 00 minutes past the hour if only minutes are missing). Then: If imputed start date/time < imputed study med start date/time, then not TEAE If imputed start date/time >= imputed study med start date/time, then TEAE (e.g. cases of fully missing times on the same date will be assumed TEAE)

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

Any imputed concomitant medication stop date/time will only be used to determine whether a medication is prior or concomitant. The start and stop dates/times reported on the eCRF will be presented in the listings.

NON-STUDY MED STOP DATE TIME	STUDY MED START DATE TIME	ACTION
Known	Known	If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant

NON-STUDY MED STOP DATE TIME	STUDY MED START DATE TIME	ACTION
Partial	Known	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown) with latest possible time (i.e. 23:59 if hours and minutes are missing, or 59 minutes past the hour if only minutes are missing), then: If stop date/time < study med start date/time, assign as prior If stop date/time >= study med start date/time, assign as concomitant
Missing	Known or Partial	Year can only be missing in stop date for ongoing medication. If entire stop date including year is missing, assign as concomitant.
Known	Partial or Missing Time	If stop date < study med start date, assign as prior If stop date > study med start date, assign as concomitant If start date = study med start date, then impute study med start time as the earliest possible time (i.e. 00:00 if hours and minutes are missing, or 00 minutes past the hour if only minutes are missing). Then: If stop date/time < imputed study med start date/time, assign as prior If stop date/time >= imputed study med start date/time, assign as concomitant

NON-STUDY MED STOP DATE TIME	STUDY MED START DATE TIME	ACTION
Partial	Partial or Missing Time	If stop date < study med start date, assign as prior If stop date > study med start date, assign as concomitant If start date = study med start date, impute stop date as latest possible date (i.e. last day of month if day unknown, or 31st December if day and month are unknown) with latest possible time (i.e. 23:59 if hours and minutes are missing, or 59 minutes past the hour if only minutes are missing). Also impute study med start time as the earliest possible time (i.e. 00:00 if hours and minutes are missing, or 00 minutes past the hour if only minutes are missing). Then: If imputed start date/time < imputed study med start date/time, assign as prior If imputed start date/time >= imputed study med start date/time, assign as concomitant

APPENDIX 3. **QMG TEST ITEMS**

[redacted]

APPENDIX 4. **MG COMPOSITE SCALE**

[redacted]

APPENDIX 5. **MG-ADL PROFILE**

[redacted]

APPENDIX 6. **MG-QOL 15**

[redacted]