STATISTICAL ANALYSIS PLAN

GTI1306

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

AUTHOR: PPD

VERSION NUMBER AND DATE: FINAL V2.0, 12APR2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final 2.0 (Dated 12Apr2019) for Protocol GTI1306.

	Name	Signature	Date
Author:	PPD	PPD	Apr 12. 2019
Position:	PPD		
Company:	CCI		

	Name	Signature	Date
Author:	PPD	P P	12th April 2019
Position:	PPD		
Company:	CCI		

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.

	Name	Signature	Date
Approved By:	PPD	PPD	April 15, 2019
Position:	PPD		
Company:	Grifols Therapeutics LLC.		
Approved By:	PPD	PPD	15 APR2019
Position:	PPD		
Company:	Grifols Therapeutics LLC.		
Approved By:	PP	PPD	15 April 2019
Position:	PPD		
Company:	Grifols Therapeutics LLC.		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	29May2018	PPD	Not Applicable – First Version
0.2	24Sep2018	PPD	Incorporate feedback from Sponsor on WOCF, average daily CS dose derivation, etc.
1.0	28Sep2018	PPD	Incorporate feedback from Sponsor
1.1	27Feb2019	PPD	Perform both unstratified and stratified analyses using exact methods for the primary analysis to handle the case of sparse events (frequency <5 in at least one cell). Similar updates are made for other binary endpoints.
2.0	12Apr2019	PPD	Incorporate feedback from Sponsor on average CS dose calculation.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AChR	Acetylcholine Receptor
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
CMH	Cochran-Mantel-Haenszel
CS	Corticosteroid
DAT	Direct Antiglobulin
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HbA1c	hemoglobin A1c
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
IV	Intravenous
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MC	Myasthenic Crisis
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis – Activities of Daily Living
MG-QOL 15	15-Item MG Quality-of-Life Instrument
MGFA	Myasthenia Gravis Foundation of America
mITT	Modified Intent-to-Treat
MMRM	Mixed-effect 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

Abbreviation	Term
SI	Standard International
SOC	System Organ Class
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-5	WHO-Five Well-Being Index
WOCF	Worst Observation Carried Forward

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol GTI1306. 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 3.0 (Amendment 2), dated 23 December 2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate the efficacy of IGIV-C as compared to placebo from baseline through Week 39 in the following:

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

2.3. EXPLORATORY OBJECTIVES

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

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

- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39 (Visit 14)
- Percent of subjects experiencing Myasthenic Crisis (MC; as defined in protocol Section 3.3.5) or episode of MG worsening requiring inpatient care from Baseline/Week 0 (Visit 1) through Week 39 (Visit 14)
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45 (at Visit 14 and Visit 16)
- Number of episodes of MG worsening, as defined in protocol Section 3.3.3, from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14)
- Change in 15-Item MG Quality-of-Life Instrument (MG-QOL 15) from Baseline/Week 0 to Week 39 (Visit 1 to Visit 14), and from Baseline to Week 45 (Visit 16)
- Change in MG Activities of Daily Living (MG-ADL) from Baseline/Week 0 to Week 39 (Visit 14), and from Baseline Week 45 (Visit 16)
- Change from baseline in serum immunoglobulin G (IgG) trough at Week 9 (Visit 4), Week 24 (Visit 9), and Week 39 (Visit 14)
- Change from baseline in binding, blocking, and modulating Acetylcholine Receptor (AChR) antibodies at Week 39 (Visit 14)
- Change from baseline in glycated hemoglobin A1c (HbA1c) at Week 39 (Visit 14)

2.4. SAFETY OBJECTIVES

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

3. 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 as a CS-sparing agent in CS-dependent MG. Approximately 60 adult subjects will be randomized in this study.

Subjects who have been dependent on systemic CS for at least the preceding three months and who have received a stable dose of CS for at least one month immediately prior to the Screening visit, will be randomly allocated in a 1:1 ratio into IGIV-C treatment group and Placebo treatment group to receive

either IGIV-C or matched Placebo every three weeks in a double-blinded fashion. Randomization will be stratified by baseline CS dose level:

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

For those subjects randomized to receive IGIV-C at the Baseline/Week 0 (Visit 1), an initial loading dose of 2 g/kg will be administered at the Baseline Visit (Visit 1). Note that the loading dosage is divided over 2 days as standard infusion time (extensions up to 4 days are allowed for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]). Loading dosage is followed by maintenance doses of 1 g/kg administered every third week until Visit 13 (Week 36). Note that the maintenance dosage is infused in 1 day as standard (extensions are allowed for divided dosage over 2 days for tolerability issues or higher weight, i.e., limit for IGIV-C infusion is no more than 80 g/day [corresponding to 80 kg body weight]). For those subjects randomized to receive Placebo at the Baseline Visit (Visit 1), sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent will be infused in a manner that the blind is maintained. The volumes of Placebo will be equal to the volumes required for an initial loading dose at the Baseline Visit (Visit 1) and subsequent maintenance doses administered every third week until Visit 13 (Week 36).

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

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

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

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

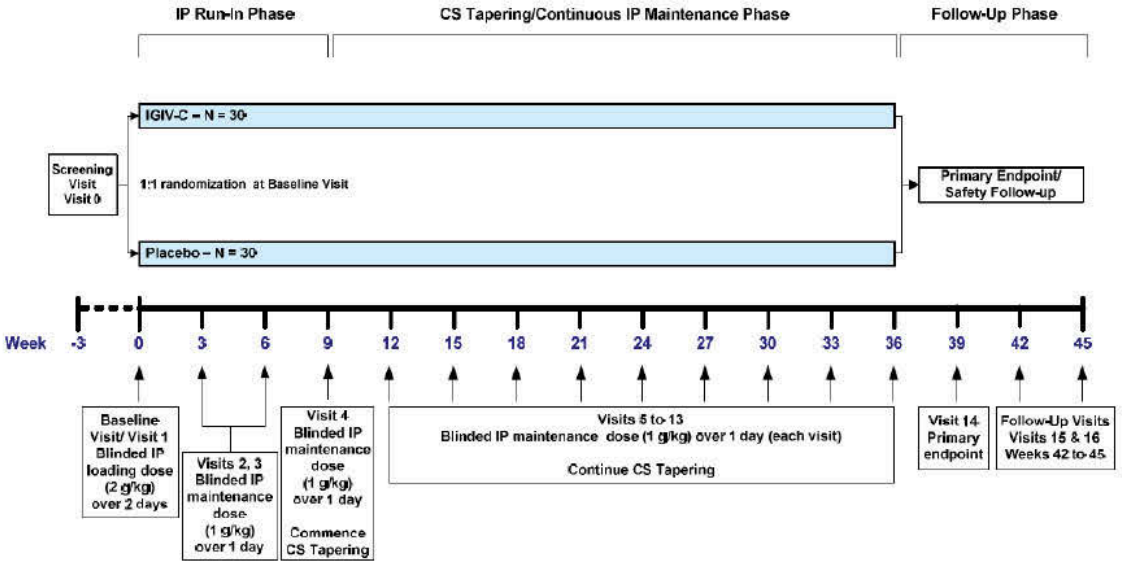
MG worsening is defined as a Quantitative Myasthenia Gravis (QMG) score increase by ≥4 points relative to Baseline/Week 0. If at any point during the CS Tapering phase, the subject suffers a worsening of

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

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

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

Figure A: Overall Study Schema



IP = investigational product, CS = Corticosteroid

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 CCI 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).

- 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).

The study day will appear in every listing where an assessment date or event date appears. 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.

Baseline CS dose level for stratification (categorical variable) will be taken directly from the ELIG page of the electronic Case Report Form (eCRF). Baseline CS dose (continuous variable) will be derived based on the Prescribed CS dose specified on the CS Use eCRF page at the Screening and Baseline visits, calculated as the average daily prednisone equivalent dose from Week -3 to Week 0 (See Section 16.1.1 for derivation details).

6.3. DERIVED TIMEPOINTS

Treatment phase starts at the start date/time of the first dose of study medication and stops at the

date/time of the end of study medication exposure, which is defined as three weeks after the stop date/time of the last dose, given the dosages are administrated every three weeks. The treatment phase includes two periods: IP run-in period (from the start date/time of the first dose of study medication to immediately before the start date/time of the Week 9 dose), and CS tapering/IP maintenance period (from the start date/time of the Week 9 dose to the date/time of the end of study medication exposure). Observations and measurements will be considered as in screening phase if they take place before the start date/time of the first dose of study medication, and in follow-up phase if they are after the date/time of the end of study medication exposure.

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 baseline, last observation carried forward (LOCF; defined in Section 7.3) and the best/worst case value where required. Unscheduled visits will also contribute to the analyses of all CS dosage variables (See Section 16.1.1 for derivation details).

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 (discontinuation) visit 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 1” 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/worst observation carried forward (WOCF; defined in Section 7.3) endpoint but will not be mapped for observed case (OC; defined in Section 7.3) analysis.

Subjects who discontinued during the treatment phase will be those who did not complete the study, i.e. “No” for Item 1 reported on the End of Study page of the eCRF, and did not reach the scheduled Week 39 visit. These subjects should return for two additional visits in the follow-up phase, i.e., Week 42 (Visit 15) and Week 45 (Visit 16) corresponding to time points 6 and 9 weeks after the last IP administration. If an early discontinued subject returned for two follow-up visits, they will be summarized under separate “Early Termination 1” visit and “Early Termination 2” visit, respectively.

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. Listings of CS doses will include all add entry fields for Prescribed CS dose for a given visit (both scheduled and unscheduled).

6.6. STATISTICAL TESTS

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

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 daily CS dose (prednisone or equivalent) level (15-40 mg, 41-60 mg); as a categorical variable
- Baseline value
- Treatment group (IGIV-C, Placebo)
- Protocol specified visits (Week 0, Week 3, Week 6, Week 9, Week 12, Week 15, Week 18, Week 21, Week 24, Week 27, Week 30, Week 33, Week 36, Week 39, Week 42, Week 45)
- 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

Imputation for missing values will be applied to continuous efficacy endpoints using the LOCF or the WOCF method.

Primary efficacy endpoint of CS dose:

For the primary efficacy endpoint of CS dose, the WOCF method will be applied to subjects who discontinued early from the study with adverse outcomes related to MG, defined as those subjects who met ALL criteria below:

- The primary reason for discontinuation is one of the following: "Adverse Event", "Death", "Discontinuation due to MG crisis requiring hospitalization", or "MG worsening (CS-unresponsive or 2nd episode)"
- The subject had at least one adverse event (AE) with preferred term (PT) of either "Myasthenia gravis crisis" or "Myasthenia gravis"
- The AE is serious, with the reason for seriousness being "Required/Prolonged Hospitalization" or "Resulted in Death"
- The onset date/time of the AE is on or after the start date/time of the first infusion of study medication, i.e., the AE is treatment-emergent

For these subjects, the worst values, i.e., the highest average daily CS dose available among all eligible visits [including the Baseline visit, all post-baseline scheduled visits, and the Early Termination visit(s)], will be carried forward to impute the missing CS dose for all remaining visits.

For subjects who discontinued the study early due to any other reasons, the LOCF method will be used to impute the missing values, i.e., the last non-missing post-baseline CS dose value available among all eligible visits [including all post-baseline scheduled visits and the Early Termination visit(s)] will be carried forward to impute missing values for all remaining visits.

Note for the primary efficacy endpoint of CS dose, the values to be considered as candidates for carrying forward are the derived average daily CS dose at the relevant scheduled visits, incorporating potential changes in the prescribed CS dose within the prior 3 weeks (see section 16.1.1 for derivation details).

Other continuous efficacy variables:

For all other continuous efficacy variables and for all subjects who discontinued the study early, regardless of the reason, the LOCF method will be used to impute the missing values, i.e., the last non-missing post-baseline value (including scheduled, unscheduled, and early termination) will be carried forward to impute missing values for all remaining visits.

All continuous efficacy variables:

In addition, for all efficacy variables, 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, with the exception of the primary efficacy variable of CS dose, for which the baseline value is eligible for the WOCF algorithm only.

For the same efficacy endpoints above that utilize the LOCF/WOCF 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 OC.

Missing values for the binary endpoints (e.g., whether or not the subject experienced CS dose reduction) will be handled similarly as for the continuous endpoints. First, the LOCF/WOCF 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/WOCF 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/WOCF endpoint row in by-visit listings will indicate the value that was used in the LOCF/WOCF efficacy analysis.

The total scores of QMG, MG Composite, MG-QOL 15, MG-ADL and World Health Organization – Five Well Being Index (WHO-5; see Section 16.3.1.14) are calculated and reported in the eCRF. 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 CS dose level at the time of randomization:
  - 15 mg – 40 mg per day
  - 41 mg – 60 mg per day
- 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 (Belgium, Czech Republic, France, Germany, Hungary, Estonia, Lithuania, Poland)

- Myasthenia Gravis Foundation of America (MGFA) classification at randomization
  - Class I
  - 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 CCI .

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 5.4), 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)
- Baseline Total scores of QMG, MG composite, MG-QOL15, MG-ADL and Wells scores
- Baseline Fasting serum glucose, serum IgG trough, AChR antibodies, HbA1c
- 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)
- Baseline daily CS dose (prednisone equivalent) (mg, prescribed)
- Baseline daily CS dose (prednisone equivalent) level (15 – 40 mg, 41 – 60 mg)

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 are reported on the Concomitant Medications page of the eCRF. They 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.

The CS use will be analyzed as efficacy outcomes as described in Section 16. The prescribed and the actual use will also be presented in a listing.

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 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 12

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 (one dosage/treatment visit may include multiple infusion days):

- Dosage in grams
- Dosage/body weight 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 (Week 0, Week 3, Week 6, Week 9, Week 12, Week 15, Week 18, Week 21, Week 24, Week 27, Week 30, Week 33, and Week 36). Based on this derivation, the minimum exposure for any treated subject is 21 days, or 3 weeks.

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/body weight (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 dosage. The expected number of dosages during the study is equal to 13 for subjects who complete the study. The total number of expected dosages 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 dosages 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 × Infusion Compliance) / 100

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

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

The prescribed CS dose (mg) is reported under item 3 on the CS Use page of the eCRF. Prednisone equivalent dose is also collected on the eCRF if prednisone is not the prescribed CS. The prednisone dose (if prednisone is the prescribed CS) or prednisone-equivalent dose (if prednisone is not the prescribed CS) will be used for primary analysis. The frequency of prescribed dose (Item 4) is reported as either "total daily" or "every other day". For analyses "every other day" doses will be normalized to daily doses as described in the protocol ([every other day dose]/2 = daily dose). All CS use data will be presented in a listing.

At each scheduled visit, a subject was to enter all prescribed CS doses that were in effect since the date of the last scheduled visit up to the date of the current scheduled visit on the CS Use page of the eCRF, including all changes to the prescribed CS doses that occurred during this time period. In some instances an unscheduled visit could have been used to document changes to the prescribed CS doses.

The average daily CS dose will be derived for each subject at each scheduled visit as follows based on the prescribed dose and the time interval taking into account any prescribed dose changes between routinely scheduled visits entered as either Unscheduled Visits or as Add Entry fields under the routinely scheduled visits:

- For each scheduled visit, define the time period for deriving the average daily CS dose at the current scheduled visit as follows: from the date of the last scheduled visit + 1 to the date of the current scheduled visit, inclusive. For example, for Week 39, the time period would be from the day after the date of visit for Week 36 to the date of visit for Week 39, inclusive. For the purpose of deriving the primary efficacy variable, Baseline and ET visits are also considered scheduled visits. Note a subject may have one or two Early Termination visits. The time periods for these visits are defined as follows:
    - Baseline Visit: from the day after the date of visit for Week -3 to the date of visit for Week 0, inclusive.
    - Early Termination Visit 1: from the day after the date of the last scheduled visit to the date of visit for the Early Termination Visit 1, inclusive.
    - Early Termination Visit 2 (if performed): from the day after the date of the Early Termination Visit 1 to the date of visit for the Early Termination Visit 2, inclusive.

- Calculate the total CS dose for each distinctive CS dose regimen in effect during this time period:
    - If the frequency is "total daily" for the CS dose regimen, then total CS dose = daily CS dose x number of days this CS dose regimen in effect
    - If the frequency is "every other day" for the CS dose regimen, then total CS dose = (every other day CS dose / 2) x number of days this CS dose regimen in effect
- Calculate the total CS dose for the time period as the sum of the total CS doses for all distinctive CS dose regimens in effect during this time period.
- Calculate the average daily CS dose: Average daily CS dose = Total CS dose / (date of current scheduled visit – date of last scheduled visit)

The calculated average daily CS dose at the scheduled visits will be used in all relevant efficacy analyses.

Note, as stated above, in general the average daily CS dose will only be derived at the scheduled visits, which include early termination visit(s). Unscheduled visits, if any, typically will fall between two scheduled visits and hence any prescribed CS dose data at unscheduled visits will automatically be taken into consideration in the algorithm above.

The only exception to this rule will be when a subject has an unscheduled visit AFTER the last scheduled visit and prescribed CS dose data were captured at this last unscheduled visit. For example, there may be rare occasions when a subject withdrew early from the study but did not return for any early termination visits; however, it was known that the subject's prescribed CS dose increased after the last scheduled visit and such dose increases were captured using an unscheduled visit. In this case the average daily CS dose will be additionally derived at the last unscheduled visit, and the time period for this visit will be: from the day after the last scheduled visit to the date of visit for the last unscheduled visit, inclusive.

The derived average daily CS dose at an unscheduled visit after the last scheduled visit will not be used directly in any summary tables that use scheduled visits but will be eligible for the LOCF/WOCF algorithm. This approach is deemed to be conservative should such an unscheduled visit capture an increase in CS dose.

Missing either the prescribed dose or the frequency of the dose for at least 1 CS dosing record at a visit will lead to missing derived average daily dose.

The percent change in daily CS (prednisone or equivalent) dose (%) will be calculated as:

- $$\frac{[\text{Average daily dose at a postbaseline visit} - \text{Average daily dose at baseline}]}{[\text{Average daily dose at baseline}]} \times 100$$

The percentage of subjects achieving a 50% or greater reduction in CS dose at Week 39 will be calculated for each treatment group.

16.1.2. Missing Data Methods for Primary Efficacy Variable

Subjects who discontinued the study early with adverse outcomes related to MG will be considered as not achieving a 50% or greater reduction. The missing dose reduction at Week 39 will be imputed using the WOCF method.

For subjects who do not have CS dose prescribed at Week 39 due to other reasons, the LOCF will be used to impute the prescribed CS dose at Week 39. The last non-missing post-baseline value (including scheduled, unscheduled, and early termination) prior to Week 39 will be carried forward to determine whether a subject achieves a 50% or greater reduction at Week 39. Subjects with no post-baseline CS dose 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 percent of subjects achieving a 50% or greater reduction in CS dose at Week 39 from Baseline in the IGIV-C group is equal to the percent in the Placebo group ($P_1=P_2$). The alternative hypothesis is that the percent of subjects achieving a 50% or greater CS dose reduction in the IGIV-C group is not equal to the percent in the Placebo group ($P_1 \neq P_2$).

The treatment comparison will be analyzed using Cochran-Mantel-Haenszel (CMH) test (Mantel, 1963), adjusted for baseline CS dose level (15-40 mg versus 41-60 mg). The p-value will be based on the general association statistic. The odds ratios for each baseline dose level, the common odds ratio and the Breslow-Day test for homogeneity of the odds ratios will be also summarized.

In the case of sparse events, where at least one of the frequencies is less than 5 in a given cell (i.e., a unique combination of baseline CS dose level, treatment, and the binary response), both unstratified and stratified analyses will be performed using exact methods. For the unstratified analysis, the Fisher's exact test (Agresti, 1992) will be used for treatment comparison. The odds ratio and the exact 95% confidence interval will also be calculated overall and separately for each stratified baseline CS dose level (15-40 mg/day versus 41-60 mg/day). For the stratified analysis, the Zelen's exact test will be used to test homogeneity of odds ratios. The CMH common odds ratio and its exact 95% confidence interval will also be calculated. Finally, an exact test will be used to test the hypothesis of the common odds ratio being 1.

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

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 daily CS dose at Week 39 will be performed. Subjects with missing daily dose at Week 39 will be excluded. This analysis will be performed on the mITT population using OC data only. The same analyses described in section 16.1.3 will be used.

16.2. SECONDARY EFFICACY

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Percent Reduction in Daily CS (Prednisone or Equivalent) Dose from Baseline to Week 39

Percent reduction in daily CS (prednisone or equivalent) dose is defined in Section 16.1.1.

16.2.1.2. Time to First Episode of MG Worsening from Baseline through Week 39

MG worsening is defined in Section 3.3.3 of the protocol as at least a 4-point increase in QMG total score from Baseline. Time to first episode of MG worsening from baseline through Week 39 is calculated as the date of the first QMG assessment meeting the MG worsening criterion – date of baseline visit + 1. Subjects who never experience MG worsening through Week 39 will be censored at the date of their last non-missing QMG total score assessment on or prior to the date of visit for Week 39.

16.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

16.2.2.1. Missing Data Method for Percent Reduction in Daily CS Dose at Week 39

For subjects who discontinued the study early with adverse outcomes related to MG, the missing percent reduction in CS dose at Week 39 will be imputed using the WOCF method. For subjects who have missing CS dose reduction at Week 39 due to other reasons, the missing CS dose will be imputed using the LOCF approach for continuous endpoints as detailed in Section 7.3.

Missing data will also be handled with the OC approach, where the analysis will be based on observed non-missing data only and subjects with missing data at Week 39 will be excluded from the analysis.

16.2.2.2. Missing Data Method for Time to First Episode of MG Worsening

Subjects with no post-baseline data will be censored at the date of Week 0 visit (i.e., 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 on or prior to the date of visit for Week 39, 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.

16.2.3. Analysis of Secondary Efficacy Variables

The secondary efficacy analyses will be performed for the mITT population.

16.2.3.1. Analysis of Percent Reduction in Daily CS Dose at Week 39

The percent daily CS dose reduction from baseline at Week 39 will be analyzed using analysis of covariance (ANCOVA; Dobson, 2002). The ANCOVA model will include the percent daily CS dose reduction as dependent variable, treatment as fixed effect, and baseline daily CS dose as a covariate.

16.2.3.2. Analysis of Time to First Episode of MG Worsening

For the endpoint of time to first episode of MG worsening, Kaplan-Meier estimates (Kaplan, 1958) will be provided for each treatment group. The probability of first episode of MG worsening at each scheduled visit will be calculated. The treatment comparison will be performed using a log-rank test adjusted for baseline CS dose level (15 to 40 mg versus 41 to 60 mg).

16.3. Exploratory Efficacy

16.3.1. Exploratory Efficacy Variables & Derivations

16.3.1.1. Percent of Subjects Achieving a 75% or Greater Reduction in CS Dose (Prednisone or Equivalent) at Week 39 from Baseline

This endpoint will be derived in the same way as the primary endpoint described in Section 16.1.1.

16.3.1.2. Percent of Subjects CS-free at Week 39

Subjects whose daily CS dose prescribed at Week 39 is 0 mg will be considered CS-free.

16.3.1.3. Percent of Subjects Achieving a Dose of CS of Less than or Equal to 7.5 mg per Day of Prednisone (or Equivalent) at Week 39

The percent of subjects whose daily CS dose prescribed at Week 39 is less or equal to 7.5 mg will be analyzed.

16.3.1.4. CFB in Fasting Serum Glucose (mg/dL) at Week 39

The CFB is calculated as indicated in section 6.7.

16.3.1.5. Percent of Subjects with Fasting Glucose Less than or Equal to 125 mg/dL at Week 39

The percent of subjects with fasting glucose less than or equal to 125mg/dL at Week 39 will be

calculated.

16.3.1.6. Percent of Subjects Experiencing MC or Episode of MG Worsening Requiring Inpatient Care from Baseline through Week 39

Subjects who experience MC or Episode of MG worsening requiring inpatient care from baseline to Week 39 will be those who had at least one adverse event (AE) that met ALL criteria below:

- The preferred term (PT) of the AE is either "Myasthenia gravis crisis" or "Myasthenia gravis"
- The AE is serious, with the reason for seriousness being "Required/Prolonged Hospitalization"
- The onset date/time of the AE is on or after the start date/time of the first infusion of study medication, i.e., the AE is treatment-emergent
- If the subject completed the Week 39 visit, the onset date of the AE is on or prior to the date of visit for Week 39

16.3.1.7. Percent of Subjects Experiencing MC or Episode of MG Worsening Requiring Inpatient Care from Week 39 to Week 45

This endpoint will be derived in the same way as the endpoint described in Section 16.3.1.6. Subjects who experience MC or Episode of MG worsening requiring inpatient care from Week 39 to Week 45 will be those who completed Week 39 visit and had at least one adverse event (AE) that met ALL criteria below:

- The preferred term (PT) of the AE is either "Myasthenia gravis crisis" or "Myasthenia gravis"
- The AE is serious, with the reason for seriousness being "Required/Prolonged Hospitalization"
- The onset date of the AE is after the date of visit for Week 39

16.3.1.8. Percent of Subjects with 0, 1, or 2 Episodes of MG Worsening from Baseline to Week 39

The number of episodes of MG worsening is defined as the number of QMG assessments where at least a 4-point increase in QMG total score from Baseline is observed. This includes assessments at scheduled, unscheduled or early termination visits on or prior to the subject reaching the Week 39 visit.

16.3.1.9. CFB in MG-QOL 15 at Week 39 and Week 45

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. CFB in MG-ADL at Week 39 and Week 45

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. 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.

16.3.1.11. CFB in QMG at Week 39, Week 42 and Week 45

The QMG consists of 13 individual items. The results of the QMG items are entered on the eCRF. The QMG is shown in Appendix 3.

The QMG total score is the sum of all 13 items (scored individually from 0-3) and ranges from 0 to 39. Higher item values represent greater severity of illness. 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 is calculated as indicated in section 6.7.

16.3.1.12. CFB in MG Composite at Week 39, Week 42 and Week 45

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.

The CFB is calculated as indicated in section 6.7.

16.3.1.13. CFB in Serum IgG Trough at Week 9, Week 24, and Week 39

The CFB is calculated as indicated in section 6.7. Results from this test may include unblinding information and will be available after database lock.

16.3.1.14. CFB in Binding, Blocking, and Modulating AChR Antibodies at Week 39

The CFB is calculated as indicated in section 6.7. Results from this test may include unblinding information and will be available after database lock.

16.3.1.15. CFB in HbA1c (%) at Week 39

The CFB is calculated as indicated in section 6.7.

16.3.1.16. CS-related Efficacy Variables at Week 39

The correlation between percent reduction in daily CS dose (%) at Week 39 and the following endpoints will be explored:

- CFB in systolic and diastolic blood pressure (mmHg) at Week 39
- CFB in fasting serum glucose (mg/dL) and HbA1c (%) values at Week 39
- CFB in Body weight (kg) at Week 39
- CS-related body habitus/cushingoid features at baseline and Week 39. See Section 17.4 for detailed description.
- CFB in total score of World Health Organization – Five (WHO-5) Well Being Index, which is the sum of all 5 items reported on the WHO-5 page of the eCRF, at Week 39. Each item is scored from 0 to 5 (higher scores mean better well-being). The total score, ranging from 0 to 25, are reported on the eCRF and will not be recalculated. If one or more individual scores are missing, the WHO-5 total score will be reported as missing. WHO-5 index is shown in Appendix 7.

16.3.2. Missing Data Methods for Exploratory Efficacy Variables

16.3.2.1. Missing Data Methods for Binary Endpoints

Missing values for binary endpoints will be handled using the approaches described in Section 7.3. First, the LOCF/WOCF algorithm will be used to impute the (continuous) missing values. The imputed values will then be used to derive the binary endpoints.

Note for binary endpoints related to CS dose, subjects who discontinued the study early with adverse outcomes related to MG will have their highest CS dose among all eligible visits, including the Baseline visit, carried forward to Week 39, and thus will automatically be considered as not achieving any of the following goals:

- A 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 from baseline
- CS-free at Week 39
- CS dose less than or equal to 7.5 mg per day (prednisone or equivalent) at Week 39

For subjects who have missing value due to other reasons, the missing value will be imputed using the LOCF approach as detailed in Section 7.3. The imputed LOCF values will be used to determine whether a subject achieves the goals above.

Missing data will also be handled with the OC approach, where the analysis will be based on observed

non-missing data only and subjects with missing data at Week 39 will be excluded from the analysis.

No imputation will apply to the summary of the endpoints related to MC or episodes of MG worsening. Only OC approach will be used.

16.3.2.2. Missing Data Methods for CFB Values

Missing CFB values will be handled using both the LOCF and the OC approaches described in Section 7.3. Subjects with no post-baseline values will be excluded from LOCF analysis.

Missing CFB values will also be handled using the mixed-effect model for repeated measures (MMRM) approach. The MMRM model will include CFB as the repeated dependent variable, with treatment, baseline CS dose level, protocol-specified visits, and treatment-by-visit interaction as fixed effects, with baseline 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 at scheduled post-baseline visits will be utilized, including visits during follow-up phase if the data are collected. Missing data will not be imputed for MMRM.

For AChR Antibody test results, missing data will not be imputed, as this test is only scheduled at baseline and Week 39. Only OC approach will be used.

16.3.2.3. Missing Data Methods for Correlation between CS Dose Reduction and Blood Pressure (Hypertension), Measures of Glycaemic Control, Weight, Body Habitus/Cushingoid Features, and Mood/Emotional Well-being

Missing values for correlation analysis will not be imputed and will be based on the OC approach.

16.3.3. Analysis of Exploratory Efficacy Variables

Exploratory efficacy analyses will be based on the mITT population. P-values presented for exploratory analyses are for information purposes only.

16.3.3.1. Analyses of Binary/Categorical Endpoints

The following exploratory endpoints will be analyzed with the same approach as the primary efficacy endpoint described in Section 16.1.3.

- Percent of subjects achieving a 75% or greater reduction in CS dose (prednisone or equivalent) at Week 39 from baseline
- Percent of subjects CS-free at Week 39
- Percent of subjects achieving a dose of CS of less than or equal to 7.5 mg per day of prednisone (or equivalent) at Week 39

- Percent of subjects with fasting glucose less than or equal to 125 mg/dL at Week 39
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from baseline through Week 39
- Percent of subjects experiencing MC or episode of MG worsening requiring inpatient care from Week 39 to Week 45
- Percent of subjects with 0, 1, or 2 episodes of MG worsening from baseline to Week 39

In the case of sparse events, where at least one of the frequencies is less than 5 in a given cell (i.e., a unique combination of baseline CS dose level, treatment, and the binary response), both unstratified and stratified analyses will be performed using exact methods. For the unstratified analysis, the Fisher's exact test (Agresti, 1992) will be used for treatment comparison. The odds ratio and the exact 95% confidence interval will also be calculated overall and separately for each stratified baseline CS dose level (15-40 mg/day versus 41-60 mg/day). For the stratified analysis, the Zelen's exact test will be used to test homogeneity of odds ratios. The CMH common odds ratio and its exact 95% confidence interval will also be calculated. Finally, an exact test will be used to test the hypothesis of the common odds ratio being 1.

16.3.3.2. Analysis of CFB Values

The following exploratory endpoints will be analyzed using ANCOVA model similar to the secondary endpoint in Section 16.2.3.1.

- CFB in fasting serum glucose (mg/dL) at Week 39
- CFB in MG-QOL 15 at Week 39 and Week 45
- CFB in MG-ADL at Week 39 and Week 45
- CFB in QMG Total Score at Week 39, Week 42 and Week 45
- CFB in MG Composite at Week 39, Week 42 and Week 45
- CFB in serum IgG Trough at Week 9, Week 24, and Week 39
- CFB in binding, blocking, and modulating AChR antibodies at Week 39
- CFB in HbA1c (%) at Week 39

The ANCOVA model will include CFB value as dependent variable, treatment and baseline daily CS dose level (categorical variable) as fixed factors, and baseline assessment value as covariates. Both the LOCF and OC approaches will be used to handle missing data. Treatment comparison will also be performed using the MMRM model described in Section 16.3.2.2.

16.3.3.3. Analysis of Correlation between CS Dose Reduction and Blood Pressure (Hypertension), Measures of Glycaemic Control, Weight, Body Habitus/Cushingoid Features, and Mood/Emotional Well-being at Week 39

The correlation between the percent reduction in daily CS dose (%) at Week 39 and each of the variables specified in Section 16.3.1.16 will be explored.

The Pearson correlation coefficient (Conover, 1998) will be calculated for continuous variables including CFB in blood pressure, fasting serum glucose, HbA1c, body weight, and the total score of WHO-5.

For body habitus/cushingoid features, the results will be mapped to the ordinal scale, as follows:

Absent = 0; mild = 1; moderate = 2; severe = 3

CFB will then be derived based on these mapped ordinal values, and the Pearson correlation coefficient between percent CS dose reduction and CFB in each body habitus/cushingoid feature will be calculated.

16.3.3.4. Subgroup Analysis of Primary Efficacy Variable

The primary efficacy variable of the percent of subjects achieving a 50% or greater reduction in CS dose (prednisone or equivalent) at Week 39 from Baseline will be summarized by treatment and by each of the subgroups defined in Section 7.5. Both the WOCF/LOCF and the OC approaches for handling missing data will be used. Only summary statistics will be presented without 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 from the study 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, and Hemolysis

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

Hemolysis labs 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.

Serum pregnancy test results will be listed.

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 (^{o}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.

There are 7 body habitus/cushingoid features related to CS side effects assessed on the CS-related Physical Assessment Findings page of the eCRF. Each feature will be graded as absent [0], mild [1], moderate [2] or severe [3]. The data will be summarized by treatment and visit as well as presented in a listing. Correlation between the body habitus/cushingoid features and CS dose reduction will be

explored in Section 16.3.3.3.

17.5. WHO-FIVE (WHO-5) WELL-BEING INDEX

The total score of WHO-5 Well Being Index (Appendix 7) is the sum of all 5 items reported on the WHO-5 page of the eCRF. Each item is scored from 0 to 5 (higher scores mean better well-being). The total score, ranging from 0 to 25, are reported on the eCRF and will not be recalculated. If one or more individual scores are missing, the WHO-5 total score will be reported as missing.

The total score will be summarized by treatment and visit. Both the total score and each individual score will also be presented in a listing. Correlation between the WHO-5 total score and CS dose reduction will be explored in Section 16.3.3.3.

18. REFERENCES

Agresti, A. (1992), "A Survey of Exact Inference for Contingency Tables," Statistical Science, 7(1), 131–177.

Conover, W. J. (1998), Practical Nonparametric Statistics, Third Edition, New York: John Wiley & Sons.

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

CCI

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 12 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 18	WK18
Week 21	WK21
Week 24	WK24
Week 27	WK27
Week 30	WK30
Week 33	WK33
Week 36	WK36
Week 39	WK39
Week 42	WK42
Week 45	WK45
Early Termination 1	ET1
Early Termination 2	ET2

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
- subject ID (which in this study includes the site ID as the first 3 digits),
- date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Any imputed AE start date/time will only be used to determine whether an AE is treatment emergent or not. The start and stop dates/times reported on the eCRF will 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

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

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

APPENDIX 4. MG COMPOSITE SCALE

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

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

APPENDIX 5. **MG-ADL PROFILE**

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

APPENDIX 6. **MG-QOL 15**

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

MG-QOL15
Muscle and Nerve 2008;38:957-963.
Muscle and Nerve;2010;41:219-226.
Muscle and Nerve;2011;43:14-18

Total MG-QOL15 score

APPENDIX 7. **WHO-5**

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

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

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

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

Scoring:

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

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

Interpretation:

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

Monitoring change:

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