Statistical Analysis Plan

Protocol Number: GTI1305

Protocol Title: "A multi-center, prospective, open-label, non-controlled clinical trial to assess the efficacy and safety of Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in patients with Myasthenia Gravis exacerbations"

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LIST OF ABBREVIATIONS

AChR	Acetylcholine receptor
ADR(s)	Adverse drug reaction(s)
AE	Adverse event
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CSR	Clinical study report
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
HR	Heart rate
ICU	Intensive care unit
IgG	Immunoglobulin G
IGIV	Intravenous immunoglobulin
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IP	Investigational product
IV	Intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis-activities of daily living
MGFA	Myasthenia Gravis Foundation of America
MuSK	Muscle specific kinase
QMG	Quantitative myasthenia gravis scale
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
T	Temperature
TE	Treatment emergent

TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 Purpose of the Analysis

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to support the completion of the clinical study report (CSR) for protocol GTI1305. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

2 Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction and is clinically manifested as variable and fluctuating muscle weakness. In most cases, the disorder is associated with the production of antibodies against acetylcholine receptors leading to the destruction of the postsynaptic motor end plate. Clinical symptoms of MG include muscle fatigue and weakness that can be localized, such as ocular, or generalized across multiple muscle groups (systemic).

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

Management for myasthenic exacerbations should be carried out in an intensive care unit (ICU) or general ward staffed with physicians who are experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. After stabilizing the patient and securing the airway, respiration, and haemodynamics, options for specific treatment include use of acetylcholinesterase inhibitors, plasma exchange, intravenous immunoglobulin (IGIV), and immunosuppressive drugs (such as corticosteroid).

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

This is a multicenter, prospective, open-label, non-controlled study to assess the efficacy and safety of IGIV-C in subjects with MG class IVb-V exacerbations according to the

MGFA. The primary measure of efficacy for this study is the change in the QMG score from Baseline to Day 14.

3 Study Objectives

3.1 Efficacy Objectives

3.1.1 Primary objective

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

3.1.2 Secondary objectives

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

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

3.1.3 Exploratory objectives

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

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

3.2 Safety Objective

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

4 Investigational Plan

4.1 Study Design and Plan

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

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

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

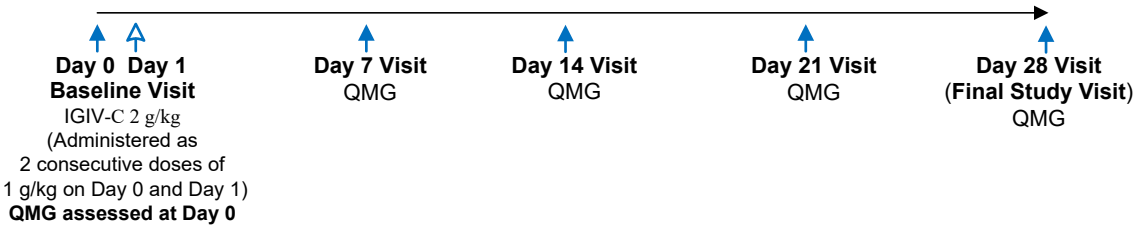

Figure 1: Overall Study Schema

4.2 Study Variables

4.2.1 Efficacy Study Variables

Primary Variable

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

Secondary Variables

Secondary efficacy variables assessed in this study are:

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

Exploratory Variables

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

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

4.2.2 Safety Study Variables

The following safety study variables will be assessed in this study:

- AEs, Suspected adverse drug reactions (Suspected ADRs), adverse reactions (ARs), Serious AEs (SAEs), and discontinuations due to AEs and SAEs.
- Vital Signs. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs. Clinically relevant changes as determined by the

Investigator in vital signs (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]) during infusions will be considered AEs temporally associated to the infusion.
- Physical Assessments. Physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria. Abnormal findings judged by the Investigator as clinically relevant will be considered AEs.
- Blood biochemistry and haematology. Laboratory results out of the normal range that are judged by the Investigator as clinically relevant will be considered AEs.
- Thromboembolic events risk.
- Hemolysis detection.

5 General Statistical Considerations

All analyses will be conducted using SAS Version 9.4 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. The statistical inferences on efficacy data analyses will be tested at 2-sided with α=0.05, if applicable. Additional details regarding the efficacy data analyses can be found in Section 10.

Unless otherwise noted, all data collected in the electronic case report forms or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and visit/time point.

For table summaries, the data will be presented at the scheduled visits according to protocol. Any data collected at the unscheduled visits will be listed.

5.1 Data Handling

Unless otherwise noted, if an observation is missing at a specific scheduled visit/time point, the value at that visit/time point will not be imputed and will be set to missing.

Baseline in general will be defined as the last non-missing measurement taken prior to the start of the study drug infusion.

5.2 Analysis Populations

Safety Population

The Safety population consists of all subjects who received any amount of investigational product (IP).

Evaluable Population

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

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in each of these two populations (safety and evaluable) will be assessed at a review meeting that will take place before finalizing the database. The review meeting will review the protocol deviation list, as well as data listings. If additional protocol deviations are identified which justify removing a subject from any population, then these decisions will be documented.

5.3 Sample Size

The data analysis from the single center study by Zinman et al indicated that the standard deviation for change from Baseline to Day 14 in QMG score is in the range of 2.74 – 3.48. To be conservative considering multi-national study, the standard deviation of 6.0 for QMG score change from Baseline to Day 14 is assumed, with 2-sided test, 33 subjects are needed to have 90% power to detect a clinically significant improvement of 3.5 in mean change in QMG. Fifty subjects are planned to be enrolled for the study.

6 Subject Disposition

Subject disposition will include the number and percentage of all subjects who signed an informed consent, dosed with IGIV-C (Safety population), and in Evaluable population. Subject disposition will also be summarized by study site.

The number and percentage of subjects who discontinue early from the study will be summarized for primary reason of discontinuation. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

7 Protocol Deviations

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (i.e., minor or major) will be summarized and listed.

8 Demographics and Medical History

Demographic (age, sex, race, and ethnicity) and baseline characteristics such as weight, height and MGFA classification at enrollment will be summarized using descriptive statistics for the Safety population.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history and history of MG including date of initial diagnosis, duration since initial diagnosis, MGFA classification at initial diagnosis, test performed to confirm the original MG diagnosis, date of last exacerbation, duration since last MG exacerbation, trigger for last MG exacerbation, and previous treatment for last MG exacerbation will also be summarized and/or listed.

9 Treatments and Medications

9.1 Prior and Concomitant Medications

Summaries of all medications taken during the course of the study will be presented in tabular form and coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug Dictionary (WHO-DD). All medications will be summarized and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 2 or 4 term is missing, the ATC level 1 or 3 term will be used respectively in the medication summary table and data listing.

The following convention will be used for missing or partial end date information in order to determine whether a medication is prior or concomitant:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of study treatment, then the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of study treatment, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications. Start/end dates reported in the electronic case report forms will be presented in the listings as is.

Prior medications are defined as any medication which ended before the start of study treatment. Concomitant medications are defined as any medication which is started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment. Prior medications and concomitant medications will be summarized separately.

For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once for each level of summary category.

All medications will be listed by subject.

9.2 Extent of Exposure

The duration of total infusion (hours), the total actual volume infused (mL), actual dose administered (mg/kg), rate of initial infusion (mL/kg/min), and rate of final infusion (mL/kg/min) by day and overall across the 2 consecutive days will be summarized. For each day, the duration of infusion will be calculated as stop time of infusion – start time of infusion. Actual dose infused (mg/kg) will be calculated as actual volume infused (mL) * 100 (mg/mL) / weight (kg). The percentage of subjects with infusion interruptions will also be summarized.

9.3 Treatment Compliance

Treatment compliance will be listed and summarized by day and overall across the 2 days. The number of subjects with compliance less than 80% will be summarized by day and overall across the 2 days. Treatment compliance will be calculated as total actual volume infused * 100% / total volume prepared by day and overall across the 2 consecutive days. The total volume prepared is collected on the electronic case report form and is calculated based on the subject's weight at baseline. The total volume prepared and dispensed by pharmacist is the intended dose volume a subject should be given based on the body weight.

10 Efficacy Analysis

Efficacy Analyses

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

Primary Efficacy Analyses

The primary efficacy variable is the change from Baseline in QMG score at Day 14. The primary efficacy variable will be summarized. A paired t-test (comparison between the pre and post) will be used to test for the treatment effect. The 95% confidence interval (CI) will be calculated. The hypothesis test is to test the null hypothesis: H_0: $\mu_d = 0$ versus alternative hypothesis Ha: $\mu_d \neq 0$ where μ_d is the mean change from Baseline to Day 14.

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

Secondary Efficacy Analyses

The following secondary efficacy variables will be descriptively summarized:

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

Exploratory Efficacy Analyses

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

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

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

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

In addition, the number and percentage of subjects who need ICU admission, length of ICU stay, need for intubation, and length of intubation will be collected and descriptively summarized.

11 Safety Analysis

The safety analysis will be based on safety population.

The safety analyses will be presented by listing and tabulation of AEs (includes suspected ADRs), vital signs, physical assessments and clinical laboratory tests. Data will be summarized using descriptive statistics.

Adverse events

Safety analysis will be primarily focused on a descriptive analysis of suspected ADRs. Safety assessment will be based on the prevalence of suspected ADRs that occurred during the clinical trial. When an AE is classified, assessing causal relationship by the Investigator, as definitive, probable, possible or doubtful/unlikely, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an AR. A separate summary of suspected ADRs based on the sponsor's assessment of causal relationship (if different from Investigator's assessment) will be provided.

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

For summary purpose, AEs will be classified as treatment emergent AEs (TEAEs) or non-TEAEs depending on the comparison of AE onset date/time with the start date/time of study treatment. A TEAE will be defined as an AE which occurs between the beginning of the first infusion of IGIV-C and the final visit of the clinical trial. A non-TEAE will be defined as an AE which occurs prior to the beginning of the first infusion of IGIV-C. Non-TEAEs and TEAEs will be summarized separately.

All AEs will be summarized for subject incidences and percentages by system organ class and preferred term.

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

AEs temporally associated to the infusion of the IP (i.e., infusional AEs, including infusional suspected ADRs), will be separately summarized. AEs occurring during the two-day infusion period (i.e., from the initiation of the IP infusion on the first day to the completion of the total dose of IP on the last day) and within 72 hours following the completion of the infusion of the total dose of IP on the last day, regardless of other factors that may impact a possible causal association with product administration, will be defined as infusional AEs (i.e., an AE temporally associated with an infusion of the IP). In addition, the infusion rate in effect at the time of onset of the AE, the time the AE is first reported and the time the AE changes materially in intensity and/or resolves will be also reported and listed.

Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed and presented in a narrative form. Subjects with TEAEs of special interest (thromboembolic events and hemolytic event) will be listed separately. The Wells score will be listed.

Vital signs

Vital signs (T, RR, HR, SBP and DBP) will be descriptively summarized and listed for each subject. Summaries will be presented for the original value and change from Baseline. Abnormal vital signs judged as clinically relevant by the Investigator will be considered AEs. In case a subject presents a clinically relevant abnormality of vital signs during an infusion, the event will be flagged and reported as an AE temporally associated to the infusion. For each subject and for each infusion, every vital sign will be considered. Clinical relevance will be based on the Investigator's criteria.

Physical Assessment

Physical Exam findings on Day 0 (normal and abnormal) and any change at final visit/early termination will be listed for each subject. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs. A summary table will also be provided by visit.

Blood biochemistry and hematology

All clinical laboratory data for renal, hepatic and hematological parameters will be listed for each subject. Laboratory results out of the normal range will be presented in shift tables. Laboratory results out of the normal range judged by the Investigator as clinically relevant will be considered AEs.

Lab test for thromboembolic events and hemolysis

The D-dimer for thromboembolic assessment and the laboratory tests for detecting hemolysis will be tested at local labs and listed, and out of normal range results will be flagged.

A listing of laboratory tests used for applicability of the algorithm for hemolysis event determination from Baseline to the end of study will be provided that includes all direct antiglobulin test (DAT) results, and all hemoglobin, absolute reticulocyte count, serum/plasma free hemoglobin, haptoglobin, LDH, and total direct and indirect bilirubin values at corresponding time points. Blood smear results (specifically whether there is presence of spherocytosis) and hemoglobinuria on urinalysis will also be included.

12 Interim Analysis

No interim analysis is planned.

13 Changes in Planned Analysis

A shift table will be provided for AChR antibodies (or MuSK antibodies) from Baseline (Day 0) to Day 14 and Day 28.