STATISTICAL ANALYSIS PLAN

ARGX-113-1602

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ARGX-113 IN PATIENTS WITH MYASTHENIA GRAVIS WHO HAVE GENERALIZED MUSCLE WEAKNESS

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VERSION NUMBER AND DATE: V1.0, 06 OCT 2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan v1.0 (Dated 06 Oct 2017) for Protocol ARGX-113-1602.

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OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates v1.0 (Dated 06 Oct 2017) for Protocol ARGX-113-1602.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	06 Oct 2017	PPD	Initial version after first draft review.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACh	Acetylcholine
AChR	Acetylcholine receptor
ADA	Anti-drug antibodies
AE	Adverse event
AUC_{tau}	Area under the concentration-time curve during the dosing interval
$AUC_{0\text{-infinity}}$	Area under the concentration time curve from time 0 extrapolated to infinity over the entire course of therapy
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence interval
Cmax	Maximum observed plasma concentration
CSH	Compound Symmetry Heterogeneous
Ctrough	Concentration observed at the end of the dosing interval
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early Discontinuation
EoS	End-of-Study
FAS	Full analysis set
Fc	Fragment, crystallized
FcRn	Neonatal Fc receptor
FU	Follow-Up
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
Gmean	Geometric mean
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IV	Intravenous
LLOQ	Lower limit of quantification
LS	Least Squares
MedDRA	Medical dictionary for regulatory authorities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis activities of daily living
MGC	Myasthenia Gravis composite score
MGFA	Myasthenia Gravis Foundation of America
MGQoL15r	15-item Quality of life scale for Myasthenia Gravis [revised version]
MMRM	Mixed Model Repeated Measures
PD	Pharmacodynamics
PK	Pharmacokinetics

Abbreviation	Definition
PR interval	Duration from the start of the T wave to the start of the QRS complex, representing the time taken for electrical activation (of the cardiac conduction system) to pass from the sinus node to the atrium, the atrioventricular node and the His-Purkinje system to the ventricle
PT	Preferred term
QMG	Quantitative Myasthenia Gravis score
QRS interval	Pertains to depolarization of ventricles
QT interval	Duration from the start of QRS interval to the end of the T wave, representing the time taken for depolarization and repolarization of the ventricular myocardium
QTcF	QT interval with Fridericia's correction
Rac	Accumulation ratio
Rsq	Coefficient of determination
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SoC	Standard of care
SOC	System Organ Class
SOP	Standard operating procedures
t1/2,λz	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Events
tmax	The time of occurrence of C_{max}
UN	Unstructured
WHO-DD	World Health Organization drug dictionary

1. INTRODUCTION

This document describes the statistical analyses to be performed and data presentations to be produced for this Randomized, Double-blind, and Placebo-Controlled Phase II Study to evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in subjects with Myasthenia Gravis who have Generalized Muscle Weakness.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of double-blinded data prior to database lock. This SAP was developed based on the International Council for Harmonisation (ICH) E3 and E9 Guidelines and in reference to the Protocol ARGX-113-1602 v2 dated 28NOV2016.

Any deviations during the analysis and reporting process from the current SAP will be described and justified in the final report. Analysis issues that suggest changes to the principal features stated in the protocol will be documented in a protocol amendment. Otherwise, the statistical analysis plan will be updated through an amendment with the changes in the analysis documented in the amendment.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is

- To evaluate the safety and tolerability of ARGX-113.

2.2. SECONDARY OBJECTIVES

The secondary objectives are

- To evaluate the clinical effect of ARGX-113 using:
  - Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.
  - Quantitative-Myasthenia Gravis score (QMG).
  - Myasthenia Gravis Composite score (MGC).
- To evaluate the impact of ARGX-113 on quality of life using the 15-item quality of life scale for Myasthenia Gravis (MGQoL15r [revised version]).
- To investigate the pharmacokinetics (PK) of ARGX-113.
- To assess the pharmacodynamic (PD) markers (e.g., total immunoglobulin G (IgG) and subtypes, anti-acetylcholine receptor [AChR] antibodies).
- To evaluate the immunogenicity of ARGX-113.

3. STUDY DESIGN

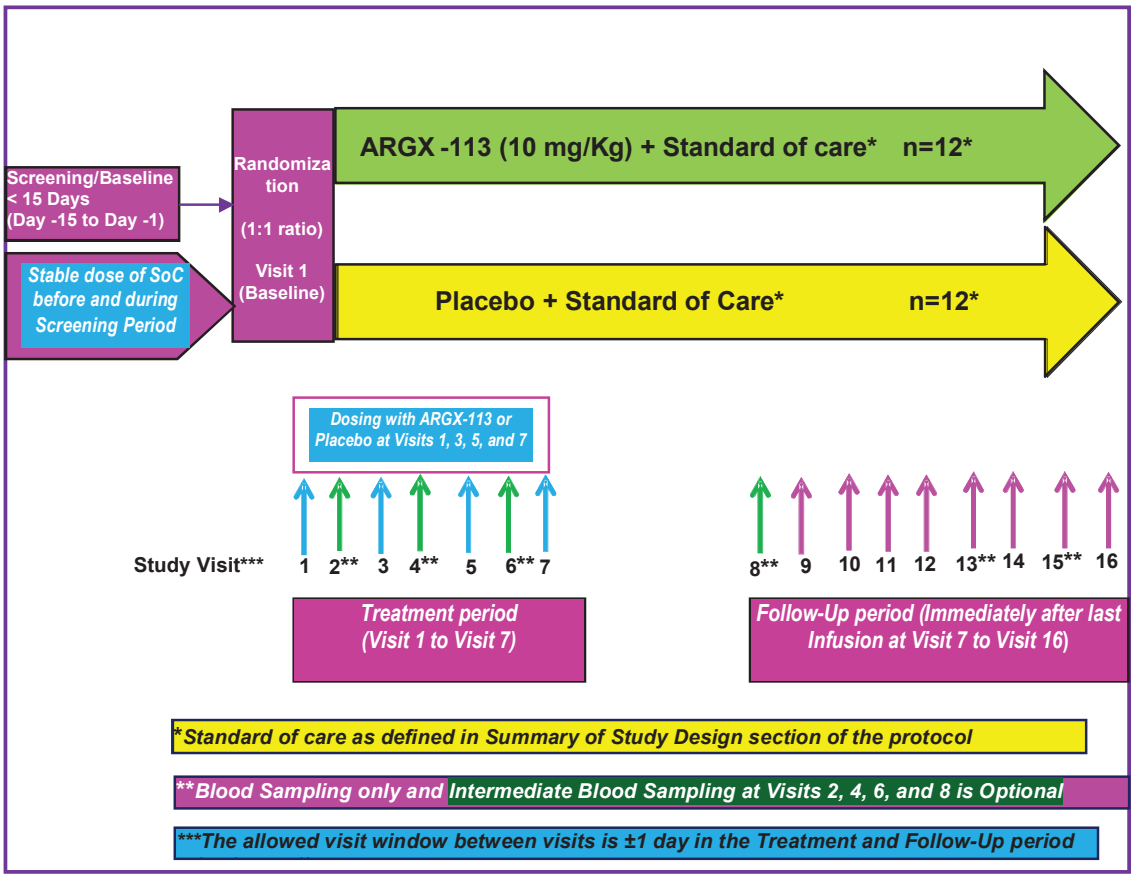
3.1. GENERAL DESCRIPTION

This is a randomized, double-blind, placebo-controlled, multicenter Phase II study to evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics and immunogenicity of ARGX-113 for the treatment of autoimmune Myasthenia Gravis (MG) with generalized muscle weakness.

Approximately 24 subjects will be randomized in a 1:1 ratio to receive either ARGX-113 (10 mg/kg) or matching placebo via intravenous (IV) infusion in addition to Standard of Care (SoC) over a period of 2 hours during the treatment period, i.e. on Days 1 (Visit 1), 8±1 (Visit 3), 15±1 (Visit 5), and 22±1 (Visit 7). The Treatment period consists of 7 visits (of which the 3 visits between the weekly dosing visits are optional).

A schematic of the study design is included as Figure 1.

Figure 1: Schematic of Study Design



The study will include a screening period of at most 15 days, a treatment period of 3 weeks (4 infusions administered one week apart) from Visit 1 to Visit 7 and a follow-up (FU) period of 8 weeks starting after completion of Visit 7 to Visit 16.

Although the FU period is from Visit 8 to Visit 16, the FU in fact starts immediately after the last Investigational Medicinal Product (IMP) infusion at Visit 7.

The total dose per IMP infusion is capped at 1200 mg for subjects with body weight ≥ 120 kg

3.2. SCHEDULE OF EVENTS

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

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

As per the protocol, the analysis of change from baseline in the efficacy rating scales is to be performed using Mixed Model Repeated Measures (MMRM) with fixed treatment, baseline score and subject as a random effect. This has been updated in Section 16 of the SAP to use MMRM model including treatment, visit and treatment x visit interaction terms as fixed effects, with baseline and baseline x visit terms as covariates and subject as random effect.

4. PLANNED ANALYSES

This Statistical Analysis Plan describes the methodology for final analysis and reporting.

4.1. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Separate SAP and Mock shells are provided for the IDMC.

4.2. INTERIM ANALYSIS

No interim Analysis is planned for this study.

4.3. FINAL ANALYSIS

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

5. Analysis Sets And Presentation of Data

The analysis of data will be based on different analysis sets according to the purpose of the analysis in question. Data summaries will be presented by treatment and overall as appropriate. Listings will be presented for all the subjects available in the data transfer received from data management.

The following analysis sets will be used.

All Subjects

Subjects who have signed the informed consent form and have been screened.

Randomized Analysis Set

Subjects who have been allocated to a randomized treatment arm, regardless of whether they received the planned treatment or not.

Full Analysis Set (FAS)

FAS is defined as all randomized subjects with at least one of the MG-ADL, QMG, MGC, and MGQoL15r scales available for one of the post-baseline assessments up to Visit 16 along with the corresponding baseline value.

Safety Analysis Set

The safety analysis set used for all safety analyses will comprise all subjects in the randomized population who received at least one dose or part of a dose. The safety analysis will be based on the actual treatment received.

Pharmacokinetic (PK) Analysis Set

The PK analysis set considered for PK analysis will comprise all subjects in the randomized population who have at least one plasma concentration data value available for ARGX-113 without major protocol deviations thought to impact PK. Subjects who did not receive IMP will not be included in the PK Analysis Set.

Pharmacodynamic (PD) Analysis Set

The PD analysis set considered for all PD analyses will comprise all subjects in the randomized population who have at least one non-missing post dose PD measurement available without major protocol deviations thought to impact PD.

A listing will be presented to report the number of subjects in each Analysis set under each treatment arm.

6. General Considerations

The following descriptive statistics will be presented in summary tables:

- Continuous variables: number (valid cases), mean, median, standard deviation (SD), minimum, and maximum
- Categorical variables: summarized by treatment group using frequency tables (frequencies and percentages). Percentages are routinely based on the total within the group count excluding the

missing category if not otherwise mentioned. Missing category with zero count will not be presented.

In general, the number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.
- SD: 2 more than the number of decimal places allotted in the raw data.
- Minimum and maximum: equal to the number of decimal places allotted in the raw data.
- Percentages: All percentages between 0% and 100% will be rounded to one decimal unless there is a need to report more than one decimal for percentages.
- Ranges will be reported to the same number of decimal places displayed by the laboratory.

6.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears. If Reference Start Date < Date of randomization, it will be considered as protocol deviation and detailed accordingly in the PD Log.

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

- If the date of the event is on or after the reference date then:
  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. PRECISION

Safety variables (i.e. clinical laboratory values, vital signs, and ECG intervals), including derivations thereof will be reported to the same precision as the source data.

All PK and PD concentrations will be reported and analysed with the same precision as the source data provided by the bio-analytical laboratory or clinical laboratory regardless of how many significant figures or decimals the data carry. Time variables for PK/PD will have units of hour and have two decimal places, for source data used for calculation of PK/PD parameters, and for reporting in listings. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The rounded derived PK parameter values in listings will be considered the source data for the calculation of descriptive statistics. For most derived PK/PD parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g. C_{max}) will be reported and analysed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data, normally 2 decimal places.

For the reporting of descriptive statistics, the mean will be presented to one digit more precision than the source data. Standard deviation will be presented to two digits more precision than the source data. The minimum, median, and maximum, will be presented to the same precision as the source data. Coefficient of variation and percentages will always be reported to 1 decimal place.

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to the reference start date and/or time. If the last non-missing measurement is recorded on the day of IP administration and is specified to be done pre-dose as per the protocol then it will be considered baseline. For Adverse Events/Concomitant Medications if start date and/or time of measurement and IP administration coincide, that measurement will be considered as post-baseline.

6.4. UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit (including optional visits) will be presented. Unscheduled measurements will not be included in by-visit summaries and efficacy analyses.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early termination data.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

The default significance level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.8. SOFTWARE VERSION

For tables, listings and graphs SAS ® version 9.4 will be used.

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 6.4 or higher (Certera, Princeton, New Jersey).

Figures may be prepared using SAS®, Phoenix® WinNonlin®, or SigmaPlot 12.5 or higher (Systat Software, Inc., San Jose, California, United States).

7. STATISTICAL CONSIDERATIONS

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

Baseline will be used as covariate in all analyses of change from baseline MG data. Wherever appropriate baseline x visit term will be included in the analysis. In case of non-convergence, baseline*visit term will be excluded from the model and/or an appropriate covariance matrix will be used.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple sites. However, because of the small sample size (12 subjects planned per treatment group) analysis models will not include the factor center.

7.3. MISSING DATA

Missing safety and efficacy data will not be imputed. For efficacy data the missing data handling approach will be based on MMRM.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment is made for multiplicity since this is an exploratory study and no confirmatory hypothesis testing is performed.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

The Mock Shells provided with this SAP describe the format, layout and content of the summary tables, figures and listings to be provided by QuintilesIMS Biostatistics. This document will be a working document and updates will be documented in its modification history.

All visit assessments will be presented according to the nominal visit name. Study populations will be summarized and listed as well.

9. DISPOSITION AND WITHDRAWALS

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

Data collected on Early Termination (ET) and End of Study (EOS) in the electronic Case Report Form (eCRF) will be used to present disposition and withdrawal results. Frequency tables will be provided for:

- number of subjects who provided informed consent
- number of subjects randomized
- number of subjects treated with at least one dose of study medication
- number of subjects who completed the treatment period with minimum of 2 weeks FU
- number of subjects who completed the study
- number of subjects still ongoing in the study
- number of subjects who discontinued the study
- primary reason for discontinuation of the study
- number of subjects who discontinued the treatment
- primary reason for treatment discontinuation

A listing will be presented of dates of Screening, randomization, screen failure with reason, completion or early discontinuation/withdrawal and the reason for early discontinuation, if applicable, for each subject.

10. PROTOCOL DEVIATION

All protocol deviations/violations observed during study conduct will be captured in Clinical Trial Management System (CTMS).

QuintilesIMS and sponsor will review the protocol deviation records from CTMS and provide confirmation of the categorization of deviations as minor, major or critical.

A frequency table for major protocol deviations will be provided. The listing of all protocol deviations will be presented.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The Summary statistics will be provided for:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Frequency tables will be provided for:

- Sex
- Ethnicity
- Race

A listing for subject demographic data and other baseline characteristics; including Weight, Height and BMI will be presented.

12. MEDICAL HISTORY

Medical History will be presented for the Safety population and coded using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 19.1. Medical History conditions are defined as those conditions which stop prior to or at Screening.

Frequency tables (presented by System Organ Class (SOC) and Preferred Term (PT) and Listings will be provided for the Safety Population. Myasthenia Gravis History including information about MGFA classification, anti-ACHr antibodies testing, neuromuscular transmission test, edrophonium chloride test and improvement on MG signs on oral cholinesterase will be listed and summarized for the Safety Population.

13. CONCOMITANT MEDICATIONS

Prior and concomitant medications will be presented for the Safety Analysis Set. A frequency table will be provided for all medications by Anatomic, therapeutic and chemical classification (ATC) Level 1 and 3. A separate frequency table will be provided for Myasthenia Gravis therapy medications. All medications will be coded by the WHO Drug Dictionary version Dec 2016.

See Appendix 1 for handling of partial dates for medications. If it is not possible to define a medication as either 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 of first dose of study medication or were ongoing at the end of the study.

Listings of medications and of MG therapy given to subjects with all details will be presented.

14. STUDY MEDICATION EXPOSURE

Study medication exposure will be presented for the Safety Analysis Set. A listing of exposure to study medication in days will be presented along with details of start and end time of infusion, interruptions, total volume administered, prematurely stopped and whether subject remained at the site for 2 hours after end of infusion. A summary of exposure to report the number of completed infusions and a separate listing to show any overdoses will be presented.

15. EFFICACY OUTCOMES

All efficacy analysis will be performed using FAS. The following summaries and corresponding listings will be provided for the efficacy results:

- Summary of scores and change from baseline by visit, at each post baseline visit for
  - Myasthenia Gravis-Activities of Daily Living (MG-ADL) score
  - Quantitative-Myasthenia Gravis score (QMG)
  - Myasthenia Gravis Composite score (MGC)
  - Quality of life using 15-item quality of life scale for Myasthenia Gravis (MGQoL15r [revised version])
- Maximum reduction in score from baseline across visit days for MG-ADL, QMG, MGC, and MGQoL15r score.

The analyses of data derived from the various scales (MG-ADL, QMG, MGC, and MGQoL15r) will be based on the FAS. Actual score, change from Baseline and maximum reduction from Baseline will be summarized descriptively.

Analyses of change from baseline by visit will be performed using a mixed-model repeated measures (MMRM) analysis from Visit 1 to Visit 16. The model will include treatment, visit and treatment x visit interaction terms as fixed effects, with baseline and baseline x visit terms as covariates. If the baseline x visit term is found to be not significant then it can be excluded from the model. An unstructured (UN) covariance matrix for the repeated measures within subject will be specified for the analysis* and the following statistics will be presented for each visit:

- Least Square (LS) Means per treatment group
- Standard error of LS Means
- 95% confidence interval (CI)
- LS Mean Difference (ARGX-113 – Placebo)
- Standard error of LS Mean Difference

- 95% confidence interval (CI) for LS Mean Difference
- p-value for testing differences between treatment groups

*If the model does not converge upon using UN, a simpler covariance matrix like CSH (not restrictive) will be used instead.

A box plot for change from baseline of ARGX and Placebo will be presented across visits. A box plot also presented for maximum reduction from baseline score.

Analysis of maximum reduction in scores will be performed using ANCOVA with baseline score as a covariate and treatment as fixed factor.

16. SAFETY OUTCOMES

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

There will be no statistical tests performed for differences between the treatment groups with regards to safety data.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.1.

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of the IMP. Any AEs started after the informed consent form has been signed and before the first administration of the IMP will be considered as Non-TEAEs.

The relationship to study drug will be summarized as related and unrelated. AEs that are recorded as ‘related’, ’possibly’ or ‘probable’ in the eCRF are categorized as ‘related’ whereas the AEs that are recorded as ‘unrelated’ and ‘unlikely’ are categorized as ‘unrelated’. Missing relationship/missing severity would be considered by the worst case as "Related" and "Grade 5" respectively.

Listings will include TEAEs and Non-TEAEs. Separate listing will be provided for AEs leading to discontinuation, serious adverse events (SAEs) and deaths.

For each treatment group, TEAEs, non-TEAEs, drug related AEs, relationship to study drug, AEs leading to discontinuation and SAEs will be summarized by primary SOC and PT. Also, summary of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03) will be presented by primary SOC and PT. AE tables include number and percentage of subjects and number of events.

An overall summary of adverse events will be produced including frequency counts of:

- number of subjects with at least one TEAE
- number of subjects with at least one non-TEAE
- number of subjects with at least one serious TEAE
- number of subjects withdrawn from treatment with at least one serious TEAE

- number of subjects with at least one related serious TEAE
- number of subjects who discontinue from the study due to a TEAE
- number of subjects with at least one TEAE with CTCAE severity grade >=3
- number of subjects with at least one related TEAE
- number of deaths

16.2. SUICIDALITY ASSESSMENT

A separate listing for suicidality assessment will also be presented.

16.3. LABORATORY EVALUATIONS

Results from both the central and local laboratory will be included in the reporting. Central laboratory results will be reported for hematology, clinical chemistry and urinalysis. A list of laboratory assessments to be included in the outputs is given in the protocol.

A summary will be provided for the incidence of abnormal values according to normal range criteria for the laboratory data. A listing of subjects with values outside the normal range in question will be presented. Urinalysis quantitative results will be summarized with descriptive statistics and qualitative results will be presented with frequency and percentages. All the results will be listed as well.

All parameters will be summarized descriptively and shift tables will be presented for categorical data. Hematology, Clinical Chemistry, Urinalysis and other tests with numeric data will be presented graphically.

16.4. ECG EVALUATIONS

The following ECG parameters will be summarized descriptively:

- Heart Rate (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)

The overall assessment of the ECG (Investigator's judgment) will be summarized with frequency and percentage for the following categories:

- Normal
- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

Absolute values for QT and QTcF intervals will be classified as:

- >=450 msec
- >=480 msec
- >=500 msec

Change from Baseline for QT and QTcF intervals will be classified as:

- >30 msec
- >60 msec

A listing for all ECG parameters will also be presented.

16.5. VITAL SIGNS

The following Vital Signs measurements will be summarized descriptively:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Oral Body Temperature (^{0}C)
- Weight (kg)

Listings will be provided for above vital signs parameters.

16.6. PHYSICAL EXAMINATION

The frequency (percentage) table for physical examinations along with a shift table of clinically significant findings will be summarized by body system. All the collected data will be listed as well.

17. PHARMACOKINETIC ANALYSIS

All PK analysis will be performed using PK Analysis Set.

17.1. PHARMACOKINETIC CONCENTRATIONS

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

A subject listing of all concentration-time data will be presented. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

Plasma concentrations of ARGX-113 will be summarized by nominal time point using the following statistics:

- Number of observations (n)
- Number of observations ≥ lower limit of quantification (LLOQ)
- Arithmetic mean
- SD
- Geometric mean
- Geometric SD
- Minimum
- Median
- Maximum

If warranted by the data, concentrations may be further summarized by ADA presence. Concentrations of ARGX-113 that are below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLOQ) for the computation of descriptive statistics. A figure of geometric mean concentration-time (in days) data (±SD, as appropriate; from the start of the first infusion) will be presented on linear and semi-logarithmic scales.

17.2. PHARMACOKINETIC PARAMETERS

For PK parameter calculations, Visit 1 pre-dose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at pre-dose on Visit 1 will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed if the pre-dose anomalous concentration is not greater than 5% of the observed maximum concentration (C_{max}). If a pre-dose concentration value on Visit 1 is greater than 5% of C_{max} in the profile, PK parameters for the profile shall not be included in the summaries but will be calculated and listed. Additionally, these anomalous pre-dose concentrations will be flagged in the concentration listings, with different symbols for those greater than or less than 5% of C_{max}.

Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters for Visit 7. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve on Visit 7, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters will be estimated for ARGX-113 by non-compartmental methods using actual elapsed time from start of dosing after Visits 1, 3, 5 and 7:

C_{max}	maximum observed plasma concentration. If the end of infusion sample is collected more than one hour post infusion, C_{max} will be listed only and not included in summaries.
t_{max}	the time of occurrence of C_{max}

C_{trough}	plasma concentration observed at the end of the dosing interval at Visits 3, 5 7, and 9. These concentrations will be included in summaries regardless of sampling time deviation.
$t_{1/2,\lambda z}$	the apparent terminal half-life, calculated from (ln 2)/λ_z (Visit 7 only)
R_{ac}	accumulation ratio, calculated as Visit 7 C_{max} /Visit 1 C_{max}
AUC_{tau}	area under the concentration-time curve during the dosing interval. This parameter will be determined for each active subject and dose if there are two quantifiable postdose concentrations available. If the end of infusion sample is collected more than one hour post infusion, AUC_{tau} will be listed only and not included in summaries.
$AUC_{0\text{-infinity}}$	area under the concentration-time curve from time 0 (pre-infusion on Day 1 Visit 1) extrapolated to infinity over the entire course of therapy using time elapsed from the start of the first infusion. If the extrapolated area is greater than 20% of $AUC_{0\text{-infinity}}$, then $AUC_{0\text{-infinity}}$ will be listed but not summarized.

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

The following summary statistics will be presented for all the PK parameters except for t_{max} :

- Geometric Mean
- Geometric Coefficient of Variation (GCV) % (calculated as GCV = 100 * sqrt { exp(s^2) – 1 }, where 's' is the SD of the data on a log scale.
- Arithmetic mean
- SD
- Minimum
- Median
- Maximum
- Number of observations

For t_{max} the following summary statistics will be presented:

- Number of observations
- Median
- Minimum
- Maximum

If warranted by the data, PK parameters may be further summarized by ADA presence.

The following PK parameters will be calculated for Visit 7 for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z.
Rsq	Coefficient of determination for calculation of λ_z (Regression coefficient). If Rsq < 0.800, then λ_z and related parameters will be listed but not included in summary statistics.

18. PHARMACODYNAMIC OUTCOMES

Pharmacodynamic analysis will be performed using the PD Analysis Set (unless specified differently underneath). Pharmacodynamic endpoints include observed, change from baseline (post baseline value – baseline value), and percent change from baseline ((change from baseline/baseline) *100%) total IgG, IgG subtypes (IgG 1, IgG 2, IgG 3 and IgG 4), and binding and blocking anti-AChR antibodies. See Section 6.3 for baseline definition.

Observed, change from baseline, and percent change from baseline values for all PD endpoints will be listed and summarized with descriptive statistics including geometric mean. Frequency table for percentage drop in IgG for ARGX-113 below cut-off per visit will be presented. Same table will be presented for subjects with QMG and MG-ADL clinical significant improvement. QMG clinical significant improvement means a drop of at least 3 points as compared to baseline and MG-ADL clinical significant improvement means a drop of at least 2 points as compared to baseline. For these mentioned frequency tables, FAS will be used.

Plots of geometric mean (±SD) percent change from baseline by treatment will be presented for each PD marker. Plot of evolution of percentage drop in IgG from baseline (mean +/- stderr) and delta QMG (mean +/- stderr) in function of visit will also presented. Same plot will also be made for evolution of drop in IgG from baseline and delta MG-ADL, delta MGC and MGQoL15r in function of visit. For these evolution plots, FAS will be used. Plots will be made for ARGX-113 and for Placebo separately.

19. ADDITIONAL ASSESSMENT OF IMMUNOGLOBULINS

The observed, change from baseline, and percent change from baseline of IgA, IgM, IgE and IgD will be listed and summarized with descriptive statistics, using PD Analysis Set.

See Section 6.3 for baseline definition.

20. ANTI-DRUG ANTIBODIES (ADA) ANALYSES

ADA will be summarized by frequency and percentages of response, using PD Analysis Set. The following statistics will be presented for ADA response for each treatment

- Proportion
- 95% Confidence Interval of Proportion (using Clopper-Pearson exact method)
- Difference in proportions (ARGX-113 – Placebo)
- 95% CI of Difference
- p-value (using Fisher's Exact Test)

21. PHARMACOGENETIC OUTCOMES

For subjects who signed a separate Pharmacogenetic ICF, FcRn polymorphisms will be examined as a part of exploratory assessments. Assessment of FcRn polymorphism will be done to examine the gene sequence, gene expression, transcription and polymorphism. No genetic testing or genetic profiling will be done.

Descriptive statistics will be used to study the genetic makeup of these subjects. Any categorical variables (if available) will be summarized by frequency (percentage) under each category. A listing of all Pharmacogenetic outcomes will be presented.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date and time < study med start date and time, then not TEAE If start date and time >= study med start date and time, then TEAE
	Partial	If start date and time < study med start date and time, then not TEAE If start date and time >= study med start date and time, then TEAE
	Missing	If start date and time < study med start date and time, then not TEAE If start date and time >= study med start date and time, then TEAE
Partial, but known components show that it cannot be on or after study med start date and time	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date and time	Known	If stop date and time < study med start date and time, then not TEAE If stop date and time >= study med start date and time, then TEAE
	Partial	Impute stop date and time as latest possible date and time (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date and time < study med start date and time,

START DATE	STOP DATE	ACTION
		then not TEAE If stop date and time >= study med start date and time, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date and time < study med start date and time, then not TEAE If stop date and time >= study med start date and time, then TEAE
	Partial	Impute stop date and time as latest possible date and time (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date and time < study med start date and time, then not TEAE If stop date and time >= study med start date and time, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	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), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication hence assign as concomitant.
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and 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), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication hence assign as concomitant.
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	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), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant