HORIZON THERAPEUTICS IRELAND DAC

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STATISTICAL ANALYSIS PLAN

Investigational Product: **Inebilizumab**

Protocol Number: **VIB0551.P3.S1(20230049)**

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED PHASE 3 STUDY WITH OPEN-LABEL PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF INEBILIZUMAB IN ADULTS WITH MYASTHENIA GRAVIS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AChR-Ab+	Acetylcholine receptor antibody positive
ADA	Anti-drug antibody(ies)
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-AChR	anti-acetylcholine receptor antibody
anti-MuSK	anti-muscle-specific kinase antibody
AST	Aspartate aminotransferase
CI	Confidence interval
CRF	Case report form
eCDF	Empirical cumulative distribution function
ECG	Electrocardiogram
eCRF	Electronic case report form
[redacted]	
FAS	Full Analysis Set
Ig	Immunoglobulin
IP	Investigational product
IST	Immunosuppressive therapy(ies)
ITT	Intent-to-treat
IV	Intravenous(ly)
IVIg	Intravenous immunoglobulin
IXRS	Interactive voice/web response system
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MGQOL-15r	Myasthenia Gravis Quality of Life-15, revised
MI	Multiple imputation
MMRM	Mixed-effects model for repeated measures
MuSK-Ab+	Muscle-specific kinase antibody positive
[redacted]	
OLP	Open-label period
PAS	Per-protocol analysis set
[redacted]	
PK	Pharmacokinetic(s)
PLEX	Plasma exchange

PRO	Patient-reported outcome
PT	Preferred term
QMG	Quantitative Myasthenia Gravis
QOL	Quality of life
RCP	Randomized controlled period
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SFP	Safety Follow up Period
SOC	System organ class
SPP	Statistical programming plan
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal

1. Introduction

This document describes the statistical analysis plan for protocol VIB0551.P3.S1(20230049), a Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study with Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults with Myasthenia Gravis (MG).

2. Study Overview

2.1 Study Objectives and Endpoints

The objectives and corresponding endpoints are listed in Table 1 below:

Table 1 Study Objectives and Endpoints

Primary objective	**Endpoints/variables**
• To assess whether inebilizumab can reduce MG-related disability	• Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at Week 26 in the overall study population, i.e., the Acetylcholine receptor antibody positive (AChR-Ab+) and Muscle-specific kinase antibody positive (MuSK-Ab+) populations.
Secondary objectives	**Endpoints/variables**
• To evaluate whether inebilizumab can reduce the frequency of MG exacerbations • To evaluate whether inebilizumab can improve MG-related quality of life (QOL) • To evaluate the effect of inebilizumab on corticosteroid usage	**Key secondary endpoints:** • Change from baseline in Quantitative Myasthenia Gravis (QMG) score at Week 26 in the overall study population. • Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population. • Change from baseline in QMG score at Week 26 in the AChR-Ab+ population. • Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population. • Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population. **Other secondary endpoints:** • Proportion of subjects with both (1) ≥ 3-point improvement in MG-ADL score at Week 26 and (2) no use of rescue therapy between Day 28 and Week 26 in the overall study population, AChR+ and MuSK-Ab+, and at Week 52 and no use of rescue therapy between Day 28 and Week 52 in AChR-Ab+ population. • Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population. • Change from baseline in QMG score at Week 52 in the AChR-Ab+ population. • Change from baseline in Myasthenia Gravis Composite (MGC) score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 in AChR-Ab+ population.

	• Change from baseline in Myasthenia Gravis Quality of Life-15, revised (MGQOL-15r) score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 in AChR-Ab+ population. • Patient Global Impression of Change (PGIC) score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 in AChR-Ab+ population. • Time to first exacerbation by Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and by Week 52 for AChR-Ab+ populations. • The proportion of subjects with steroid tapered to ≤ 5 mg/day steroid at Week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 for AChR-Ab+ population. • The proportion of subjects in whom steroid dose was reduced by ≥ 50% from baseline by Week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and by Week 52 for AChR-Ab+ population. • Proportion of subjects achieving minimal symptom expression, defined as MG-ADL= 0 or 1, at Week 26.
• To evaluate the safety and tolerability of inebilizumab in MG	• The safety and tolerability of inebilizumab as measured by the incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and treatment-emergent serious adverse events (TESAEs). • Clinical Laboratory. • Vital signs. • Electrocardiogram (ECG).
• To characterize the pharmacokinetic (PK) profile and immunogenicity of inebilizumab in subjects with MG	• Serum concentration of inebilizumab. • Anti-drug antibody (ADA) status and titer.
Exploratory objectives	**Endpoints/variables**
[redacted]	

[redacted]

Baseline is defined as the last non-missing valid observation prior to the 1st Investigational product (IP) administration during RCP. In cases where measurements are taken on the same day as the first administration of IP and no time is reported, it will be assumed that these measurements are taken prior to the first administration of IP.

2.2 Study Design Overview

This study is a phase 3, randomized, double-blind, placebo-controlled study, to be conducted at approximately 100 study sites. Approximately 230 subjects (188 AChR-Ab+ and 42 MuSK-Ab+) will be enrolled. The study includes 4 periods, a screening period, a randomized controlled period (RCP, 52 weeks for AChR-Ab+ population and 26 weeks for MuSk-Ab+ population), an optional open-label period (OLP, up to 3 years), and an optional safety follow up period (SFP, up to 2 years after the last IP dose administration).

Subjects who do not have anti-AChR or anti-MuSK antibodies are not eligible and will not be enrolled. Subjects with MGFA classification II, III, or IV disease, MG-ADL score between 6 and 10 with > 50% of this score attributed to non-ocular items or a MG-ADL score ≥ 11, and QMG score ≥ 11 are eligible for this study. These criteria define a population of subjects with generalized MG and inadequate symptom control.

Within each population, subjects will be stratified by region first (non-Japan vs Japan). In the non-Japan population, subjects will be further stratified according to baseline disease severity ('Baseline QMG score = 11-15' vs 'Baseline QMG score ≥ 16') and baseline corticosteroid use ('prednisone > 5 mg/day' vs 'prednisone ≤ 5 mg/day'), and randomized 1:1 to receive either IV inebilizumab 300 mg or placebo) (Figure 1and Figure 2). In the Japan population, no further stratification will be applied due to the small sample size expected, and subjects will be randomized 1:1 to receive either IV inebilizumab or placebo.

The duration of the RCP is 52 weeks for the AChR-Ab+ population (Figure 1) and 26 weeks for the MuSK-Ab+ population (Figure 2). The primary endpoint of the study is change from baseline in MG-ADL score at Week 26 in the overall study population (AChR-Ab+ and MuSK-Ab+ populations).

Subjects who enter the study on prednisone > 5 mg/day (or equivalent dose of another corticosteroid) will have their corticosteroid dose tapered per protocol, starting at Week 4 of the RCP. Steroid tapering will continue until the subject is on a dose of prednisone 5 mg/day; the dose of prednisone 5 mg/day will then be continued until the end of the RCP. Corticosteroid treatment will not be initiated if the subject is not being treated with those at the time of randomization.

The dose of azathioprine, mycophenolate mofetil, mycophenolic acid, and Acetylcholinesterase inhibitors must remain stable throughout the RCP. Tacrolimus is allowed in Japan only.

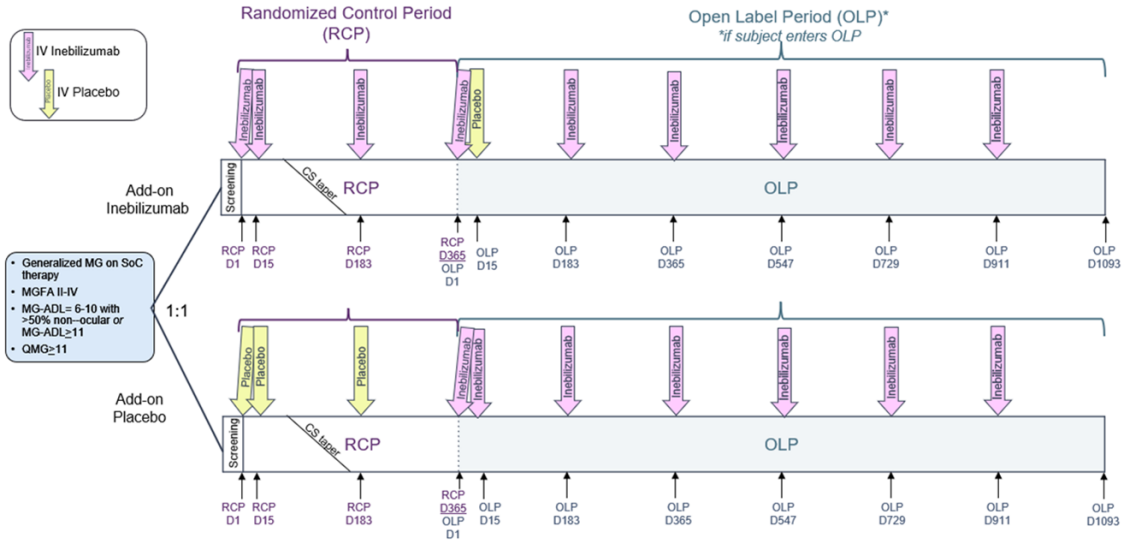
All subjects who complete the RCP will have the option to enroll in a 3-year OLP. In the OLP, further tapering of corticosteroids is at the discretion of the investigator. Tapering of non-steroidal immunosuppressive therapies (ISTs, e.g., azathioprine, mycophenolate mofetil, or mycophenolic acid) is recommended per standard of care.

Subjects who discontinued treatment during RCP or OLP will have the option to roll over into a 2-year safety follow up period (SFP).

- If a subject discontinues treatment during the RCP, this subject should be followed per the RCP schedules listed in the protocol. After the end of the RCP, subjects will be followed every 6 months until 2 years after the last dosing date.
- If a subject discontinues treatment during the OLP, this subject will be followed every 6 months until 2 years after the last dosing date.

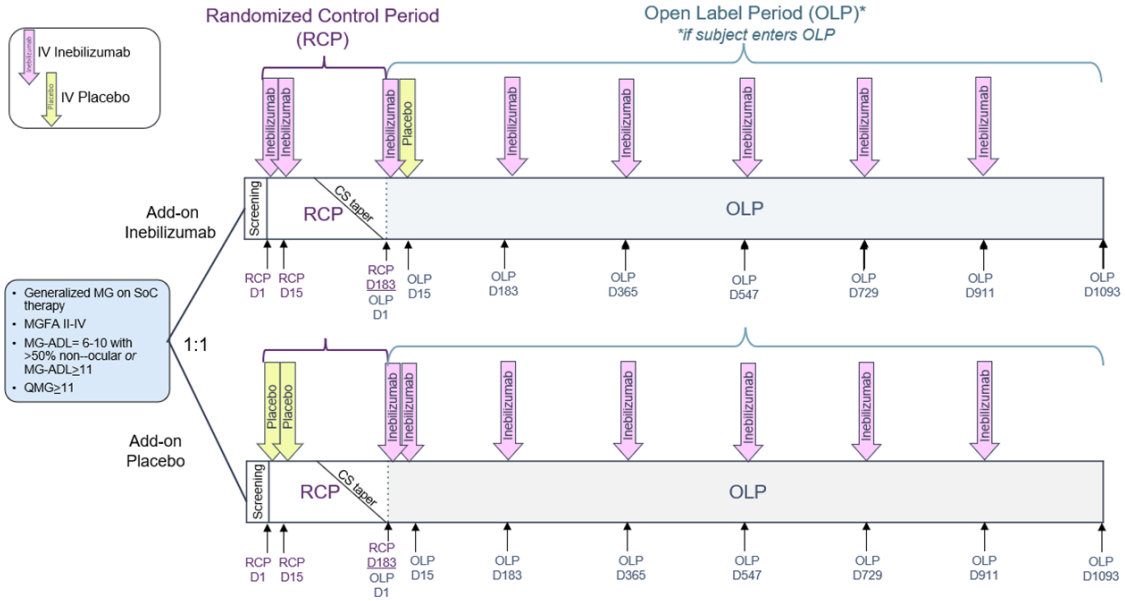
The basic study flow diagram is presented in Figure 3.

Figure 1 Randomization Scheme for AChR-Ab+ Population



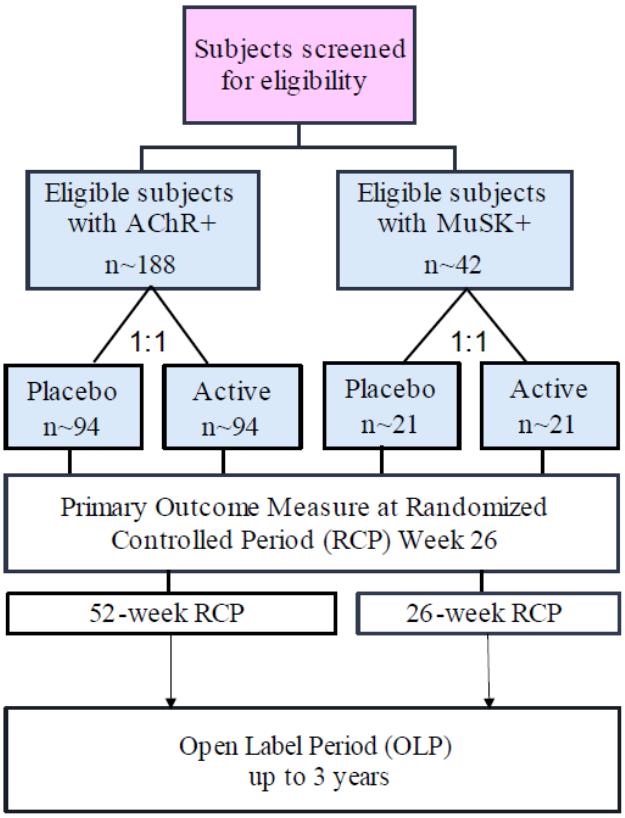
CS = corticosteroid; D = Day; IV = intravenous(ly); MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activity of Daily Living score; MGFA = Myasthenia Gravis Foundation of America; OLP = Open-Label Period; QMG = Quantitative Myasthenia Gravis scale; RCP = Randomized Controlled Period; SoC = Standard of Care.

Figure 2 Randomization Scheme for MuSK-Ab+ Population



CS = corticosteroid; D = Day; IV = intravenous(ly); MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activity of Daily Living score; MGFA = Myasthenia Gravis Foundation of America classification; MuSK-Ab+ = the population of subjects who are antibody positive for muscle-specific kinase; OLP = Open-Label Period; QMG = Quantitative Myasthenia Gravis scale; RCP = Randomized Controlled Period; SoC = standard of care.

Figure 3 Study Flow Diagram



~ = projected; AChR+ Ab = positive for antibodies against the acetylcholine receptor; **IP** = investigational product; **MuSK+ Ab** = positive for antibodies against muscle-specific kinase; **n** = number of subjects represent upper estimated limit and may be reduced based on enrollment of subjects in Japan; **OLP** = open label period; **RCP** = randomized controlled period.

* Safety follow-up period for up to 2 years after the last IP dose will be offered to those subjects who have:
a) Discontinued IP during the RCP and completed all the RCP assessments, but have not entered the OLP.
b) Discontinued IP during the OLP and completed Early Discontinuation Visit in the OLP.

2.3 Sample Size

The primary endpoint is the change from baseline in MG-ADL score at Week 26 in the overall study population (i.e., the AChR-Ab+ and MuSK-Ab+ populations). Sample size was estimated using a 2-sided t-test. Approximately 230 subjects (188 subjects with AChR-Ab+ MG and 42 with MuSK-Ab+ MG) will be randomized at a 1:1 ratio to either receive inebilizumab or placebo. This sample size will provide more than 95% power to detect a true mean (population) treatment difference of 2 points in the MG-ADL score in the overall study population with a two- sided 0.05 alpha level assuming the common standard deviation is 4 using two-sided t-test.

The sample size of AChR-Ab+ subjects was also estimated using a 2-sided t-test, which will provide at least 90% power to detect a true mean (population) treatment difference of 2 points in change from baseline of MG-ADL with a 2-sided 0.05 alpha level. The sample size of MuSK-Ab+ population was estimated based on the feasibility of enrollment. Assuming the

common standard deviation is 4 and a two- sided 0.05 alpha level, the minimum detectable treatment difference in MuSK-Ab+ population is 2.5.

3. Statistical Methods

3.1 General Considerations

All efficacy analyses described below apply to the RCP unless stated otherwise. The efficacy endpoints will be summarized at scheduled visits during RCP and OLP in the overall study population, AChR+-Ab+ population, and MuSK+-Ab + population, respectively. For subjects in the OLP, the efficacy may also be summarized over the combined RCP and OLP to characterize the durability of the treatment effect, if applicable.

The safety endpoints will be summarized for the RCP, OLP and combined study periods, respectively in the overall study population, AChR+-Ab+ population, and MuSK+-Ab + population, respectively.

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. [redacted]

All hypothesis testing will be reported using 2-sided tests. Unless otherwise stated, nominal p-values will be reported. P-values will be rounded to 4 decimal places. The 95% confidence interval (CI) will be reported as appropriate.

The absolute change from baseline is computed as (visit value – baseline value). Percent change from baseline is computed as (visit value – baseline value) / baseline value x x100%. If either a visit value or the baseline value is missing, the absolute change from baseline and the percent change from baseline will also be set to missing.

All statistical calculations will be primarily performed using SAS® System Version 9.4 or higher.

[redacted]

3.1.2 Analysis Sets

Full Analysis Set: The 'Full Analysis Set' (FAS) includes all subjects randomized who received at least one dose of IP in the study, and have a baseline MG-ADL assessment, and at least one post-baseline observations of MG-ADL assessment. Subjects will be analyzed

according to the treatment randomized. The efficacy analysis for RCP will be based on the FAS.

Safety Analysis Set (Randomized-controlled Period): The 'Safety Analysis Set' includes all subjects who received any dose of IP **during the RCP**. Subjects will be analyzed according to the treatments that they actually received. The safety, **PD,** and ADA analysis for RCP will be based on the Safety Analysis Set. A subject who received any dose of inebilizumab during the RCP will be included in the inebilizumab treatment group. A subject who received placebo only during the RCP will be included in the placebo treatment group.

Open-label Analysis Set: The 'Open-label Analysis Set' will include all subjects who receive any dose of inebilizumab during the OLP. The efficacy and safety for OLP will be summarized based on Open-label Analysis Set.

Any inebilizumab Analysis Set: The 'Any inebilizumab Analysis Set' will include all subjects who receive any dose of inebilizumab during the study. The efficacy and safety for the combined RCP and OLP will be based on the Any inebilizumab Analysis Set unless otherwise specified.

Safety Follow up Analysis Set: The 'safety Follow up Analysis Set' will include all subjects who entered the SFP.

Pharmacokinetic Analysis Set: The 'PK Analysis Set' includes all subjects who receive any dose of inebilizumab during the RCP and have at least one quantifiable serum PK observation post first dose. The PK analysis will be based on the PK Analysis Set. **Subjects will be analyzed according to the treatment that they actually received.**

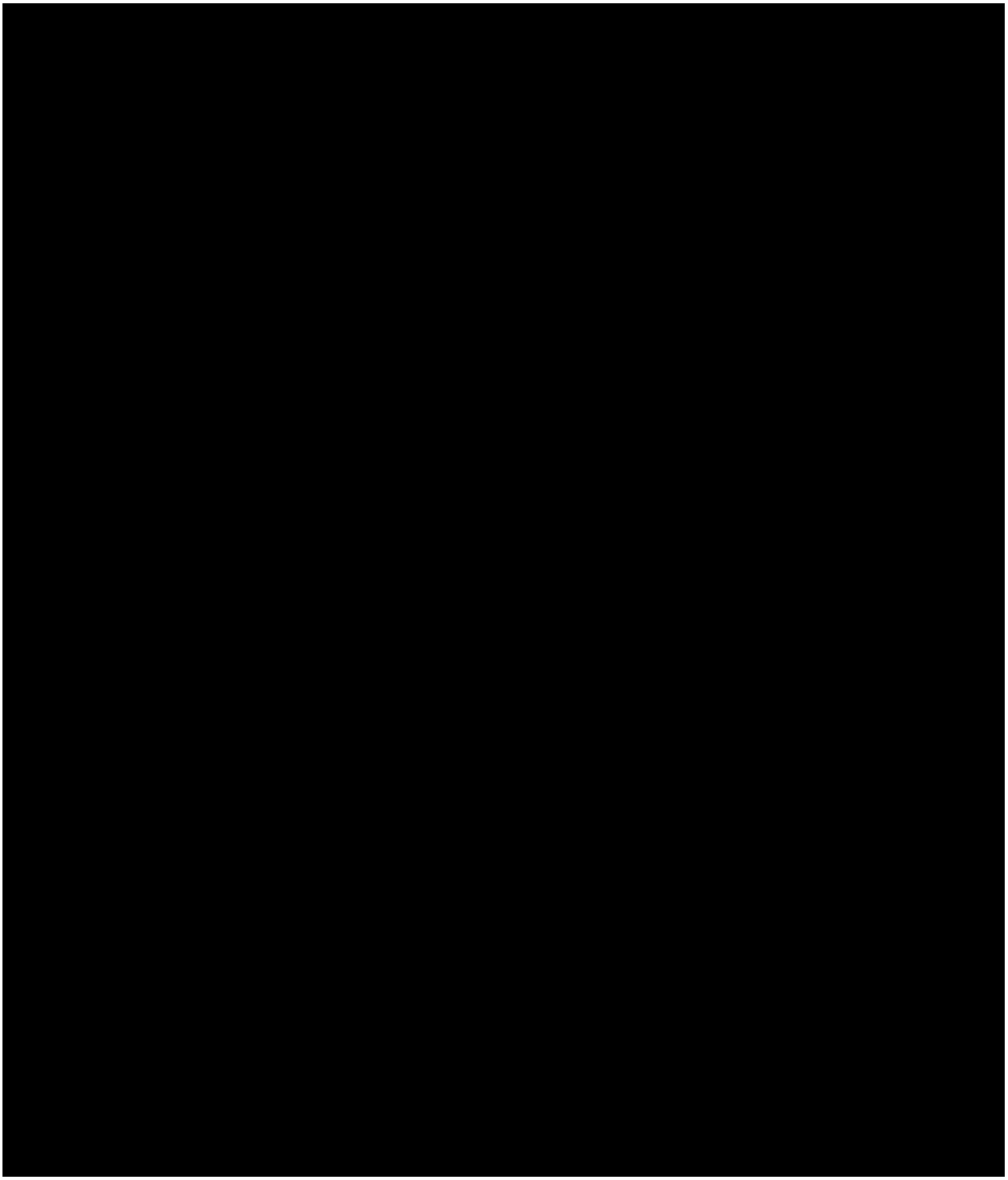
Per-protocol Analysis Set (PAS): The PAS includes all subjects in the FAS who are sufficiently compliant with the protocol. Major reasons to exclude subjects from the PAS analysis set are listed below:

[redacted]

The complete list of reasons for excluding the subjects from the PAS will be identified and documented before study unblinding. The efficacy analysis for RCP based on the PAS will be conducted for primary and key secondary endpoints as a sensitivity analysis.

3.1.3 Definition of Study Day and Baseline

In general, baseline will be defined as the last non-missing valid observation prior to the first administration of IP in the corresponding study period. In cases where baseline measurements are taken on the same day as first administration of IP and no times are reported, it will be assumed that these measurements are taken prior to first administration of IP. The definition of baseline in each study period is listed in the [redacted] below.



3.1.4 Analysis Windows

Unless otherwise specified, analysis visit windows will be used for all visit-based assessments to map longitudinal observations to scheduled visits, since not all assessments are performed on the scheduled day. The analysis visit windows will be defined by bisecting the interval between adjacent scheduled visit days unless otherwise specified. Detailed specifications will be included in the statistical programming plan (SPP) within each study period (RCP, OLP, and SFP).

Assessments will be mapped to analysis windows using study days and the following rules will be used to select the assessment to be included in analyses:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- **If more than one non-missing assessment falls on the same day, the later one will be used in the analysis.**
- If two non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.

However, an unscheduled visit with the assessments listed per protocol should be performed to evaluate worsening of MG symptoms if rescue therapy is being considered per protocol. If an unscheduled visit occurred on or before the rescue therapy use in a derived visit window, the observations collected during this unscheduled visit will be selected as the observation for this visit window. For example, the derived visit window for the scheduled Day 85 is from Day 72 to Day 105, assuming 3 records (Day 83, Day 95 and Day 100) collected in this derived visit window for this scheduled Day 85 visit, and the Day 95 visit is for RT evaluation (i.e., rescue therapy starts on or right after Day 95 visit), then the observation collected on Day 95 will be used for this scheduled Day 85 visit.

3.1.5 Missing data

Missing data will not be imputed except for the following:

QMG and MGC are allowed to have partially completed assessments per the system setup. If ≤ 50% of the individual items in the questionnaire are missing at a visit, the missing items will be imputed using last observation carried forward (LOCF) before the calculation of the total scores. If > 50% of the individual items are missing, the total score at that visit will be considered as missing and no imputation will be applied.
For the other questionnaires, the individual items in the questionnaire will be either all available or all missing per the system setup. No imputation will be applied to these missing records.

3.2 Protocol Deviations

All protocol deviations **(PD)** will be reviewed, documented, **and classified as critical PDs, major PDs, or minor PDs** prior to the database lock **according to the PD guidelines.** [redacted] **All critical and major PDs will be summarized**.

3.3 Study Subjects

3.3.1 Subject Disposition

Subject disposition will be summarized using all the subjects enrolled into the study. The total number of subjects will be summarized for those who were enrolled, who were screen failed, and who were randomized. The numbers and the percentages of the subjects will be summarized for the following groups in the overall study, AChR-Ab+ and MuSK-Ab+ population, respectively.

- Subjects who are randomized

- Subjects who discontinued treatment during the RCP
- Subjects who early discontinued **participation** from the RCP
- Subjects who completed RCP
- Subjects who entered OLP
- Subjects who discontinued treatment during the OLP
- Subjects who early discontinued from the OLP
- Subjects who entered SFP

3.3.2 Demographics, Baseline Characteristics, and Medical History

Demographic data and key baseline characteristics will be summarized using descriptive statistics on FAS. The demographic data and key baseline characteristics will include but are not limited to the following variables.

- Demographic: age, gender, race, ethnicity, height, weight, and body mass index.
- Baseline Characteristics: baseline antibody status, MG-ADL score, QMG score, MGFA class, MGC Score, PGIC, MGQOL-15r score, Steroid use, non-steroid IST use and CD20+ B-cell count etc.

Significant medical history findings will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

3.3.3 Study Drug Exposure

The total number of doses received, total amount of inebilizumab received, total duration of the inebilizumab exposure, and treatment compliance will be summarized within RCP, OLP, and Combined RCP and OLP, respectively.

- Total duration of the inebilizumab exposure (days) = last inebilizumab dose date in a specific study period – first inebilizumab dose date within that study period [redacted]
- The amount of inebilizumab exposure at each visit: if a subject received partial dose at a dosing visit, then the amount of inebilizumab at that dosing visit will be estimated based on the actual volume administered. and the dose administered = intended dose (300 mg) x x actual volume received/planned volume. If a subject received placebo at a dosing visit, then the amount of inebilizumab at that visit is 0 mg.
- Treatment compliance for an individual subject = [Total number of IP doses received during a specific study period] / [Total number of IP doses planned per protocol within that study period] x x100%.

3.3.4 Concomitant Medications

Number (%) of subjects who received concomitant medications (coded according to WHO Drug dictionary) will be summarized within RCP and OLP, respectively, as appropriate. At each level of summarization, a subject is counted once if the subject reported one or more medications at that level. The concomitant medications are defined as below. In addition, separate analyses of steroid usage for MG disease control and analyses of the rescue therapy usage for MG crisis will be conducted.

- Concomitant medications for RCP are defined as:
  1) Medications started between the first RCP IP dose date and the end of the RCP (inclusive), or
  2) Medications stopped between the first RCP IP dose date and the end of the RCP (inclusive), or
  3) Medications started before the first RCP IP dose date, and ongoing before the end of the RCP.
- Concomitant medications for OLP are defined as:
  1) Medications started on or after the first OLP IP dose, or
  2) Medications stopped on or after the first OLP IP dose, or
  3) Medications started before the first OLP IP dose and did not stop during OLP.

Missing start/stop dates will be imputed as appropriate, and the details of the imputation will be included in the SPP.

3.4 Analyses Methods

3.4.1 Intercurrent events and Strategies

Potential intercurrent events such as discontinuing from the treatment, early discontinuing from the study, death, or initiating rescue therapy, which includes intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), may occur during the study. Subjects who discontinue from the treatment and/or receive rescue therapy will be encouraged to stay in the study after those intercurrent events and data will be collected through planned study completion. These intercurrent events will be addressed using different strategies in the efficacy and safety analyses as appropriate. The following analyses strategies will be used and detailed components of each strategy are included in the sub-sections under Section 3.4 and Section 3.5.

[redacted]

Treatment-policy strategy: The analyses will include all data captured in each study period, defined as the period after randomization to the conclusion of the last scheduled visit in the corresponding study period regardless of the rescue therapy use.

While on-treatment strategy: The analyses will include all data captured while subjects are on treatment during the RCP, [redacted]

All efficacy analyses described below apply to the RCP unless stated otherwise. The efficacy endpoints will be analyzed in the overall study population, AChR-Ab+ population, and MuSK-Ab + population, respectively, [redacted] as suitable. Supplementary analyses using treatment-policy strategy will be conducted for primary endpoint and key secondary endpoints to assess the robustness of the conclusions. For subjects in the OLP, the efficacy may also be summarized based on OLP and the combined RCP and OLP using treatment-policy strategy, if applicable.

The safety endpoints will be summarized for the RCP, OLP, **and combined RCP and OLP** separately and analyzed using treatment-policy strategy. Summary of AEs/ SAEs/ AESIs, CD20+ B-cell count, and Serum Immunoglobulins would be provided for subjects based on combined RCP and OLP, and based on SFP if applicable.. [redacted] **may** be conducted using while on-treatment strategy for TEAE/TESAE/AESI as needed.

3.4.2 Primary Efficacy Endpoint and Analyses

3.4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in MG-ADL score at Week 26 in the overall study population (AChR-Ab+ and MuSK-Ab+). The primary analysis will be conducted after all subjects complete the Week 26 visit or end of study visit if the subject discontinues from the study before the Week 26 visit.

3.4.2.2 Analyses for Primary Efficacy Endpoint

For the primary analysis, the primary estimand is defined as follows:

1. Population: Subjects in the FAS.
2. Variable (endpoint): change from baseline in MG-ADL score at Week 26.
3. Intercurrent events:

[redacted]

4. Population-level summary: Mean difference between inebilizumab and placebo.

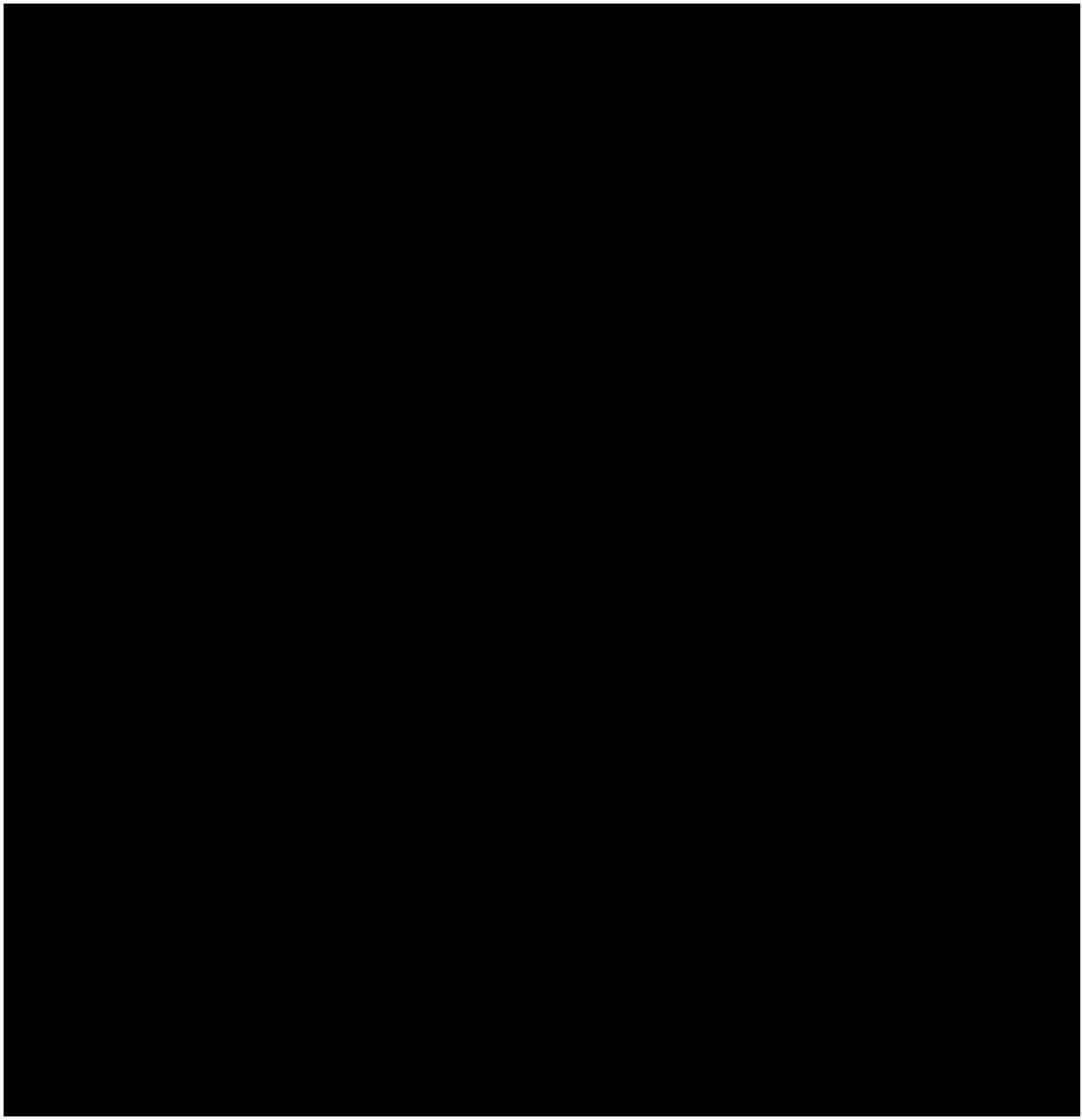
Rationale for estimand: The occurrence of the intercurrent event of rescue therapy is informative about the effect of treatment. If a subject is administered rescue therapy after Day 28, it may be considered that the allocated treatment was not effective, and the subject was not successfully treated. Taking rescue therapy will confound treatment effect.

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM) analysis [redacted] The estimate of the treatment effect estimator will be based on a contrast from this MMRM model. The variance-covariance

matrix will be assumed to be unstructured. If the procedure doesn't converge, then a compound symmetric variance-covariance matrix will be applied.

Supplementary analysis will be performed for the primary efficacy endpoint using a treatment-policy strategy to address both intercurrent events of rescue therapy and treatment discontinuation (i.e., including data collected after rescue therapy and treatment discontinuation in the analysis).

The primary analysis will be conducted using the MMRM, which is valid under the missing at random (MAR) assumption. To examine the sensitivity of the results of the primary analysis to departures from the underlying MAR assumptions, additional analyses using Partial Dropout Reason-based Multiple Imputation (Partial-DRMI) and Dropout Reason-based Multiple Imputation (DRMI) will be performed as mentioned in Section 3.4.2.3.



[redacted]

3.4.3 Key Secondary Efficacy Endpoints and Analyses

3.4.3.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Change from baseline in QMG scores at Week 26 in the overall study population.
- Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.
- Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
- Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.
- Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

3.4.3.2 Key Secondary Efficacy Analyses

Change from baseline in QMG scores at Week 26 in the overall study population

The primary estimand of the changes from baseline in QMG score in the overall study population at Week 26 is defined as follows:

- Population: Subjects in the FAS.
- Variable (endpoint): Change from baseline at Week 26.
- Intercurrent event:

[redacted]

- Population-level summary: Mean difference between inebilizumab and placebo.

[redacted]

The estimate of the treatment effect estimator will be based on a contrast from a MMRM model [redacted]

[redacted]

[redacted]

Changes from baseline in MG-ADL at Week 26 in the AChR-Ab+ population and Changes from baseline in MG-ADL at Week 26 in the MuSK-Ab+ population

The definitions of primary estimand of the changes from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population and in the MuSK-Ab+ population are similar to the definition of the primary endpoint except the population is based on the subjects in the FAS with the corresponding baseline antibody status only.

Similar to the primary endpoint as mentioned in Section 3.4.2.2, a supplementary analysis will be performed using a treatment-policy strategy to address both intercurrent events of rescue therapy and treatment discontinuation (i.e., including data collected after rescue therapy use and/or treatment discontinuation in the analysis).

The estimate of the treatment effect estimator will be based on a contrast from a MMRM model [redacted]

Changes from baseline in QMG at Week 26 in the AChR-Ab+ population and Changes from baseline in QMG at Week 26 in the MuSK-Ab+ population

The definitions of primary estimand of the changes from baseline in QMG at Week 26 in the AChR-Ab+ population and in the MuSK-Ab+ population are similar to the definition of the primary endpoint except the population is based on the subjects in the FAS with the corresponding baseline antibody status only.

[redacted]

The estimate of the treatment effect estimator will be based on a contrast from a MMRM model [redacted]

3.4.5 Other Secondary Efficacy Endpoints and Analyses

3.4.5.1 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints include:

- Proportion of subjects with both (1) ≥ 3-point improvement in MG-ADL score at Week 26 and (2) no use of rescue therapy between Day 28 and Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+; and at Week 52 and no use of rescue therapy between Day 28 and Week 52 in AChR-Ab+ population.
- Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population.
- Change from baseline in QMG score at Weeks 52 in the AChR-Ab+ population.
- Change from baseline in MGC score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 for AChR-Ab+ population.
- Change from baseline in revised MGQOL-15r score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 in AChR-Ab+ population.
- Patient Global Impression of Change score at Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and at Week 52 for AChR-Ab+ population.
- Time to first MG exacerbation by Week 26 in the overall study population, AChR-Ab+ and MuSK-Ab+ and by Week 52 in AChR-Ab+ populations
- The proportion of subjects with steroid tapered to ≤ 5 mg/day steroid at Week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and by Week 52 for AChR-Ab+ population.
- The proportion of subjects in whom steroid dose was reduced by ≥ 50% from baseline by Week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and by Week 52 for AChR-Ab+ population.
- Proportion of subjects achieving minimal symptom expression, defined as MG-ADL= 0 or 1, at Week 26.

3.4.5.2 Other Secondary Efficacy Analyses

Analyses for the proportions

The primary estimand of the proportions of subjects is defined as follows:

- Population: Subjects in the FAS.
- Variable (endpoint): responder at Week 26 or at Week 52, where a responder is defined as a subject who meets all the criteria listed in the corresponding endpoint. For example, a subject will be considered as a responder of 3-point improvement in MGADL score at Week 26 if this subject achieved (1) ≥ 3-point improvement in MG-ADL score at Week 26 and (2) no use of rescue therapy between Day 28 and Week 26.
- Intercurrent event:

[redacted]

- Population-level summary: difference of the inebilizumab vs placebo groups in the proportion of the responders regardless of treatment discontinuation.

Subjects will be considered as non-responders if they discontinue from the study before the timepoint of interest (Week 26 or Week 52).

The estimate of the treatment effect estimator will be evaluated using [redacted] logistic regression [redacted]

Analyses for the changes from baseline

The primary estimand of the change from baseline is the same as the one defined for the key secondary endpoints as mentioned in Section 3.4.3.2. The estimate of the treatment effect estimator will also be based on a contrast from an MMRM approach [redacted]

Analyses for the time to first exacerbation

An exacerbation is defined as one of the following:

[redacted]

[redacted]

The time to first exacerbation will be analyzed utilizing treatment- policy strategy. The primary estimand of the time to first exacerbation is defined by the following:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 to the date of the first exacerbation by the timepoint of interest (Week 26 or Week 52).
- Intercurrent event: All data captured from Day 1 to the timepoint of interest will be used for analysis. Subjects who do not complete the timepoint of interest and who don't have an exacerbation between Day 1 and the timepoint of interest will be censored at the time of discontinuation from the study or at the timepoint of interest, whichever is earlier.
- Population-level summary: Hazard ratio (HR) between inebilizumab versus placebo.

The hazard rate in the inebilizumab group will be compared to that in the placebo group using a Cox proportional hazard model [redacted]

[redacted]

3.4.6 Exploratory endpoints and Analyses

3.4.6.1 Exploratory Endpoints

[redacted]

3.4.6.2 Exploratory Endpoint Analyses

[redacted]

[redacted]

3.4.7 Subgroup Analyses

To explore the consistency of treatment effect, subgroup analyses will be performed on the FAS for the primary and the key secondary endpoints in the following subgroups as appropriate. [redacted]

[redacted]

These analyses are to be considered as exploratory and will be performed on the FAS. Interaction tests would be conducted to evaluate the consistency of the treatment effect among the different categories of each subgroup variable.

[redacted]

3.5 Safety Analysis

The safety endpoints will be summarized for the RCP, OLP, combined RCP and OLP, and SFP, separately, and analyzed using treatment-policy strategy. [redacted].

During the RCP, the safety analysis will be based on the safety analysis set. For the treatment-policy strategy, the analyses will include all data captured after Day 1 in RCP to the last scheduled visit in the RCP regardless of the rescue therapy use. [redacted]

For the combined RCP and OLP, the safety analysis will be based on the any inebilizumab analysis set using treatment-policy strategy. The analyses will include all data captured after the first IP or first inebilizumab administration date to the last scheduled visit in the OLP regardless of the rescue therapy use.

For the SFP, safety analysis will be summarized using treatment-policy strategy**.** The summary will include all data captured between Day 1 of SFP and the last scheduled visit in the SFP regardless of the rescue therapy use.

3.5.1 Adverse Events

In general, if an adverse event (AE) onset is on or after the first dose of IP administration during a specific study period, the AE will be considered as a treatment-emergent adverse event (TEAE) in that study period. Otherwise, the AE will be considered as a non-TEAE in that study period. The detailed definitions are included in [redacted]

[redacted]

3.5.1.1 Adverse event of special interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the IP. AESIs reported per protocol include:

- Anaphylaxis and serious hypersensitivity reactions

- Infusion-related reaction (IRR)
- Immune complex disease
- Cytopenia
- Serious and/or opportunistic infections, including Progressive multifocal leukoencephalopathy.

[redacted]

3.5.1.2 Analyses for Adverse Events

AEs will be coded using the most recent version of MedDRA **and reported for the overall population, AChR-Ab+ population, and MuSK-ab+ population, separately**. The number and percentage of subjects reporting TEAEs, TESAEs and AESIs will be summarized by SOC and PT, severity, and relationship to the IP. If a subject reports multiple occurrences of the same AE, the highest recorded severity will be taken as the severity in the summary. [redacted]

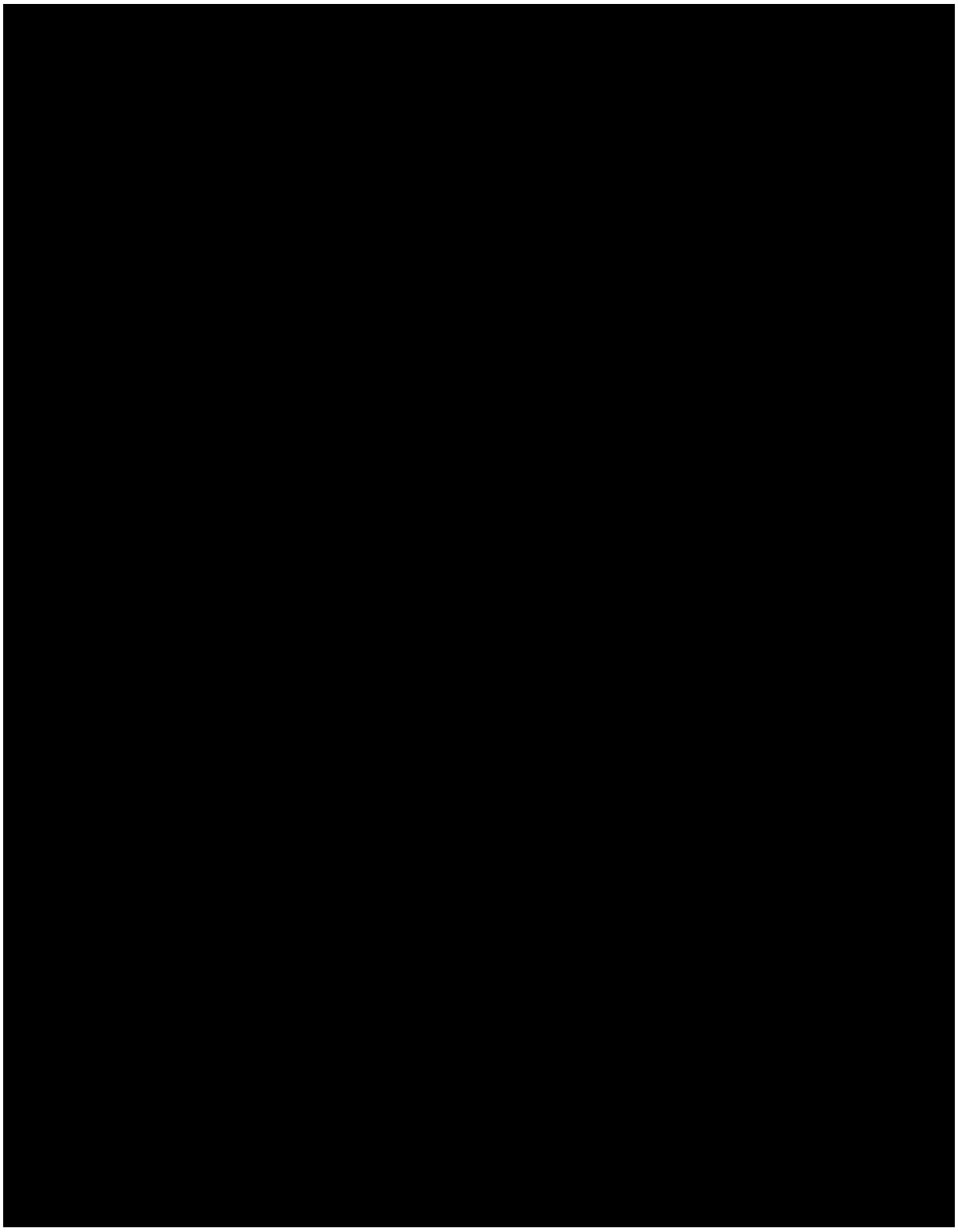
An overall summary table will be produced showing the number and percentage of subjects with at least 1 TEAE in any of the following categories: TEAEs, TESAEs, Death, TEAEs leading to discontinuation of IP, Grade 3 or higher TEAEs considered related to the investigational product etc. A summary of the most common (frequency of ≥ 5%) TEAEs will also be presented by PT.

The TEAEs per 100 Person-years for a specific reporting period will be summarized, where TEAEs per 100 Person-years = 100 x x Total number TEAEs for a specific study period / Total person-years for the specific study period. The person-year definition is included in [redacted]

A list of TEAEs, AESIs and TESAEs described in [redacted] will be summarized in RCP, OLP, combined RCP and OLP and SFP as appropriate.

In addition, the overall summary of TEAEs and summary of TEAEs by SOC and PT for treatment policy will be investigated when appropriate by age, sex, region, racial/ethnic subgroups as needed for national/regional regulatory submissions, and by ADA status at any time during RCP including baseline if data allows.

[redacted]



3.5.2 Clinical Laboratory Evaluation

The lab data will be summarized for RCP, OLP, combined RCP and OLP, and SFP, respectively. The analyses for the laboratory results are listed in Table 7. The toxicity will be

summarized using NCI-CTCAE version 5 for the tests with objective criteria and NCI-CTCAE version 4 was used for the tests with subjective criteria. The international system of units will used for all the lab data.

Table 7 Laboratory Results Analysis

Laboratory dataset	Planned Analysis
Hematology and Chemistry	• Summary of worst post-baseline toxicity grade • Summary of at least 2-grade shift from the baseline to the worst post-baseline toxicity grade • Summary of shift from the baseline relative to the normal range • Summary of observed values, change from baseline and percent changes from baseline •
Immunoglobulins	• Summary of observed values and changes from the baseline

To evaluate the association between reduced Ig levels and infections/serious infections /opportunistic infections, **proportions of subjects with these AEs** will be summarized by the worst Ig Level during the combined RCP and OLP by the categories listed in [redacted] **Additionally, TEAEs by SOC and PT during the combined RCP and OLP will be summarized by the categories listed in [redacted] as well**.

[redacted]

3.5.3 Other Safety Evaluations

3.5.3.1 Columbia Suicide Severity Rating Scale

Two versions of the Columbia Suicide Severity Rating Scale (C-SSRS) (C-SSRS Baseline/Screening version and C-SSRS since last visit version) are collected during the study. The outcomes listed in Table 9 are C-SSRS categories and have binary responses (yes/no).

Table 9 C-SSRS Categories for Reporting

Category #	Category
1	Wish to be Dead
2	Non-specific Active Suicidal Thoughts
3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5	Active Suicidal Ideation with Specific Plan and Intent
6	Preparatory Acts or Behavior
7	Aborted Attempt
8	Interrupted Attempt
9	Actual Attempt (non-fatal)
10	Completed Suicide
11	Self-injurious behavior without suicidal intent (not suicide-related)

Composite endpoints, defined as in Table 10 based on the categories in Table 9, will be summarized in the overall study population, AChR-Ab+ population, and MuSK-Ab + population, respectively, for baseline, post-baseline by week 26 in RCP, post-baseline in OLP, and post-baseline in SFP. For the AChR-Ab+ population, the composite endpoints during week 26 and week 52 in RCP will also be summarized.

Table 10 Composite Endpoints Based on C-SSRS

Endpoint	Description
Suicidal ideation	A "yes" answer at any time during **the given period** to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
Suicidal behavior	A "yes" answer at any time during **the given period** to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
Suicidal ideation or behavior	A "yes" answer at any time during **the given period** to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Analysis of C-SSRS will be restricted to subjects who have at least one response at both baseline and post-baseline visits.

3.5.3.2 Vital Signs

The observed values, along with the changes from baseline, will be summarized for systolic blood pressure, diastolic blood pressure, body temperature, pulse rate, and respiratory rate. In

addition, a summary of subjects with clinically significant vital signs values (as defined below) within 24 hours after each dosing will also be provided.

- Systolic blood pressure: < 90 mmHg, > 140 mmHg, > 160 mmHg
- Diastolic blood pressure: < 50 mmHg, > 90 mmHg, > 100 mmHg
- Heart rate: < 60 beats/min, > 100 beats/min
- Respiratory rate: < 12 breaths/min, > 20 breaths/min
- Temperature: < 36°C, >38°C
- Body weight: decrease of ≥ 7% from baseline and increase of ≥ 7% from baseline.

3.5.3.3 Electrocardiogram

The observed values, along with the changes from baseline, will be summarized for ventricular heart rate, PR interval, QRS duration, QT interval, and the corrected QT (QTc) interval by Fridericia (QTcF) approach and by Bazette approach (QTcB). The number (%) of subjects meeting the following criteria will be summarized:

- QTc > 450 msec
- QTc > 480 msec
- QTc > 500 msec
- QTc increases from baseline > 30 msec
- QTc increases from baseline > 60 msec

In addition, the overall clinical evaluation of electrocardiogram results (normal, abnormal, not clinically significant, abnormal potentially clinically significant, not evaluable) will also be summarized.

3.5.3.4 Physical Examination and Weight

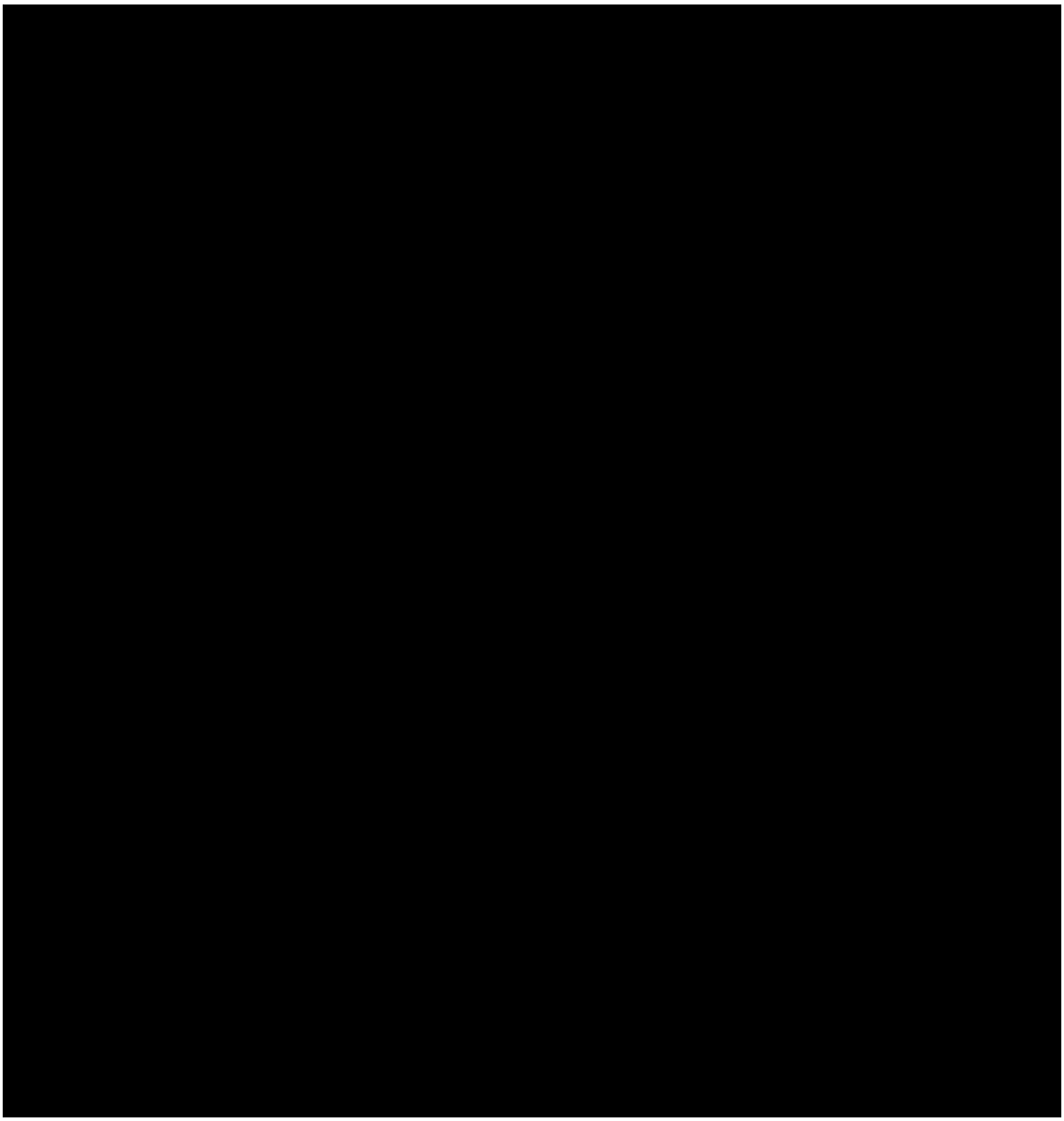
The clinically important abnormal findings from the physical examinations will be recorded as AEs. The observed values and the changes from baseline in the weight will be summarized.

3.6 Pharmacokinetics

The PK components of the clinical study report (CSR) will be generated and presented in a separate report by PK group. The PK analyses will be based on the PK Analysis Set.

3.7 Immunogenicity

The ADA status in [redacted] will be summarized and the ADA titer may be summarized for ADA positive subjects. The impact of ADA on PK, [redacted], safety, and efficacy will be evaluated if data allows. The ADA incidence will also be summarized for the subjects who discontinue IP, who do not enter the OLP, and who complete OLP, respectively, as needed.



3.8 Multiplicity Adjustment

The type I error will be controlled across the primary and the key secondary endpoints at 0.05 (2-sided). A hierarchical approach will be used to control for multiplicity and the testing strategy is proposed as follows:

- Step 1: Test the primary endpoint at a significance level (2-sided) of 0.05; if the p-value is less than 0.05, then proceed to Step 2. Otherwise, no null hypothesis is rejected in the overall population.
- Step 2: Test the key secondary endpoints at a significance level (2-sided) of 0.05 sequentially following the order below:
    - Change from baseline in QMG score at Week 26 in the overall study population.

- Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.
- Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
- Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.
- Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

4. Planned Analysis

4.1 Primary Efficacy Analysis

The primary analysis will be conducted when all subjects have completed Week 26 in the RCP or if subject discontinues early from the study before Week 26. **All** efficacy and safety data collected **during the RCP and** prior to the data cut-off for the primary analysis will be analyzed. **In addition, the safety data collected during the OLP and prior to the data cut-off will also be analyzed**. The AChR-Ab+ subjects who have not completed the RCP will complete the remaining visits during the RCP per protocol. To ensure the blinding of each subject's treatment assignment during the study, the study site personnel, the sponsor personnel who are directly associated with the conduct of the study, and the subjects will remain blinded to the treatment assignment until the last subject completion of the study or, if a subject discontinues early from the study.

4.2 Final Analysis

The final analysis will be performed when all subjects have completed the study.

5. Reference

Firth, D. 1993. "Bias reduction of maximum likelihood estimates." Biometrika, 80: 27-38.

Heinze, G. and Schemper, M. 2002. "A solution to the problem of separation in logistic regression." Statistics in Medicine, 21: 2409-2419.

6. Revision History

Version #	Description of Change
Version 1.0	Initial version
Version 2.0	Updated per protocol version 7, dated 13SEP2023 • Change the analysis to pooled analysis • Change the primary timepoint to Week 26 • Change the endpoints per protocol

Version #	Description of Change
	• Change the primary analysis: use worst observation carried forward for subjects used rescue therapy after Day 28 in RCP instead of censoring the data after initiation rescue therapy during the RCP • Rewording the estimand definition • Add the AE summary by FMQ • Add the AESI definition per sponsor
Version 3.0	[redacted] • Simplified the PAS definition • Added 3.1.5 Missing data for clarity • Removed language around protocol deviations that is not in the scope of the SAP • Remove definition for Prior Medications • [redacted] • Changed exact logistic regression to Firth logistic regression • Edited [redacted] • Updated 3.5.3.1 Columbia Suicide Severity Rating Scale • Reduced the scope of Primary Efficacy Analysis to RCP only