STATISTICAL ANALYSIS PLAN

AMENDMENT 3

Study: MG0003

Product: Rozanolixizumab

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING EFFICACY AND SAFETY OF ROZANOLIXIZUMAB IN ADULT PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

SAP/Amendment Number	Date
Final SAP	31 March 2020
SAP Amendment 1	7 October 2020
SAP Amendment 2	29 March 2021
SAP Amendment 3	10 November 2021

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LIST OF ABBREVIATIONS

AChR	Acetylcholine Receptor
ADA	Anti-Drug Antibody
AE	Adverse Event
AEOF	Adverse Event of Focus
AESI	Adverse Event of Special Interest
AESM	Adverse Event of Special Monitoring
ALP	Alkaline Phosphatase
ALQ	Above the Limit of Quantification
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CfB	Change from Baseline
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DEM	Data Evaluation Meeting
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EQ VAS	EQ Visual Analogue Scale
EQ-5D-5L	Euro-Quality of Life 5-Dimensions, 5 Levels
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
geoCV	Geometric Coefficient of Variation
geoMean	Geometric Mean

GGT	Gamma Glutamyltransferase
HbA1c	Glycosylated Hemoglobin
hCG	Human Chorionic Gonadotropin
HLGT	High Level Group Term
HLT	High Level Term
IA	Interim Analysis
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
ICE	Intercurrent Event
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
IVIg	Intravenous Immunoglobulin G
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LLT	Lower Level Term
LSMD	Least Squares Mean Difference
MA	Markedly Abnormal
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis -Activities of Daily Living
MG-C	Myasthenia Gravis- Composite
MGFA	Myasthenia Gravis Foundation of America
MGII	Myasthenia Gravis Impairment Index
MG-QOL15r	Myasthenia Gravis MG Quality of Life 15 Item Scale Revised
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures

MNAR	Missing not at Random
MSE	Minimum Symptom Expression
MSR	Minimum Significant Ratio
MuSK	Muscle Specific Kinase
n	Number of Participants
NAb	Neutralizing Antibody
NRI	Nonresponse Imputation
OLE	Open-Label Extension
PD	Pharmacodynamic
pDILI	Potential Drug Induced Liver Injury
PEOT	Premature End of Treatment
PEX	Plasma Exchange
PGI-C	Patient Global Impressions of Change
PGI-S	Patient Global Impressions of Severity
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PLS	Population-Level Summary
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient-Reported Outcome
PT	Preferred Term
PTT	Partial Thromboplastin Time
QMG	Quantitative Myasthenia Gravis
RBC	Red Blood Cell Count
RLZ	Rozanolixizumab
RPACT	R Package for Adaptive Clinical Trials
RS	Randomized Set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SS	Safety Set

TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the statistical analyses of study MG0003, including interim and final analyses. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity with, the following documents:

- Protocol Amendment 4: 23 February 2021
- IDMC Charter: 19 January 2021

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP may be amended accordingly. Changes to the analysis from the protocol are documented in Section 3.9. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To demonstrate the clinical efficacy of rozanolixizumab in patients with generalized myasthenia gravis (MG).

2.1.2 Secondary objective

To assess safety and tolerability of rozanolixizumab in MG patients.

2.1.3 Other objectives

- To assess pharmacokinetic (PK) characteristics of rozanolixizumab
- To assess the pharmacodynamics (PD) effects of rozanolixizumab on IgG, disease-specific autoantibodies
- To evaluate the emergence and incidence of anti-drug antibody (ADA) and impact on PK and PD
- To evaluate the effects of rozanolixizumab on the concentration of total protein, IgM, IgA, and IgE, serum and plasma complement levels and serum cytokines
- To assess the effect of rozanolixizumab on tetanus IgG antibodies
- To assess the effect of rozanolixizumab on exploratory biomarkers and protein expression, and explore the relationship between protein, and metabolite biomarkers and cause, progression, and appropriate treatment of MG

2.2 Study endpoints

2.2.1 Efficacy endpoints

2.2.1.1 Primary efficacy endpoint

- Change from Baseline to Day 43 (Visit 10) in MG-activities of daily living (ADL) score

2.2.1.2 Secondary efficacy endpoints

- MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)
- Change from Baseline to Day 43 (Visit 10) in MG-Composite (MG-C) score
- Change from Baseline to Day 43 (Visit 10) in quantitative myasthenia gravis (QMG) score
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms patient-reported outcome (PRO) 'Muscle Weakness Fatigability' score
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score

2.2.1.3 Other efficacy endpoints

- Use of rescue therapy due to worsening (IVIg, PEX)
- Time to first rescue therapy
- Time to MG-ADL response (≥2.0 points improvement from Baseline)
- Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods
- QMG responder (≥3.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in MG-C score at each scheduled assessment during Treatment and Observation Periods
- MG-C responder (≥3.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- MG-ADL responder (≥2.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in the MG Symptoms PRO 'Muscle Weakness Fatigability' score at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in the MG Symptoms PRO 'Physical Fatigue' score at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in the MG Symptoms PRO 'Bulbar Symptoms' score at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in the MG Symptoms PRO 'Respiratory Symptoms' score at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in the MG Symptoms PRO 'Ocular Symptoms' score at each scheduled assessment during Treatment and Observation Periods
- Patient Global Impressions of Severity (PGI-S) at each scheduled assessment during the Treatment and Observation Periods

- Patient Global Impressions of Change (PGI-C) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in MG-ADL (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in QMG (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in MG-C score (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline to Day 43 in MG Quality of Life 15 Item scale revised (MG-QOL15r)
- Change from Baseline to Day 43 in Euro-Quality of Life 5-Dimensions, 5 levels (EQ-5D-5L)
- Minimal Symptom Expression (MG-ADL score of 0 or 1) at any time up to and including Day 43 (Visit 10)
- Change from Baseline in MG Impairment Index (MGII) scores at each scheduled assessment during Treatment Period
- Change from Baseline in MGII ocular sub-scores at each scheduled assessment during Treatment Period
- Change from Baseline in MGII generalized domain sub-scores at each scheduled assessment during Treatment Period

2.2.2 Pharmacokinetic/pharmacodynamic endpoints

2.2.2.1 Pharmacokinetic endpoint

- Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment and Observation Periods.

2.2.2.2 Pharmacodynamic endpoints

- Change (absolute and percentage) from Baseline in MG-specific autoantibodies at each scheduled assessment during the Treatment and Observation Periods
- Change (absolute and percentage) from Baseline in serum total IgG and IgG subclasses concentrations at each scheduled assessment during the Treatment and Observation Periods

2.2.3 Safety endpoints

2.2.3.1 Secondary safety endpoints

- Occurrence of treatment-emergent adverse events (TEAEs)
- TEAEs leading to withdrawal of investigational medicinal product (IMP)

2.2.3.2 Other safety endpoints

- Occurrence of adverse events of special monitoring (AESM)
- Vital sign changes from Baseline (systolic and diastolic blood pressure (BP) and pulse rate at each scheduled assessment during the Treatment and Observation Periods)

- 12-lead electrocardiogram (ECG) change from Baseline at each scheduled assessment during the Treatment and Observation Periods
- Laboratory change from Baseline at each scheduled assessment during the Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis)
- Suicidality as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

2.2.4 Anti-drug antibody endpoints

- ADA status at each scheduled assessment during the Treatment and Observation Periods

2.2.5 Immunological endpoints

- Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during the Treatment and Observation Periods
- Change from Baseline in serum cytokines at each scheduled assessment during the Treatment Period
- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) at each scheduled assessment during the Treatment and Observation Periods
- Change from Baseline in anti-tetanus toxoid serum titers at each scheduled assessment during Treatment and Observation Period

2.2.6 Other and exploratory endpoints

- Exploratory biomarkers may be measured to evaluate the effect of rozanolixizumab
- Proteins, and metabolites changes that may be measured to understand the cause, progression, and appropriate treatment of MG

A specific SAP will be written to describe the analysis methods for those endpoints, as the results will not be summarized in the CSR. The nature and format of these analyses will be detailed in this SAP.

2.3 Study design and conduct

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm, repeat dose study evaluating the efficacy and safety of two doses of rozanolixizumab and matching placebo in patients with generalized MG who experience moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA II-IVa]) and are being considered for additional treatment such as IVIg or PEX.

Fixed unit doses across body weight tiers and study arms will be employed:

Treatment Arm 1 (rozanolixizumab) – equivalent to approximately [redacted]

- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]
- Bodyweight ≥100kg; dose to be administered [redacted]

Treatment Arm 2 (rozanolixizumab) – equivalent to approximately [redacted]

- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]
- Bodyweight ≥100kg; dose to be administered [redacted]

The placebo arm will be 0.9% sodium chloride aqueous solution (physiological saline, preservative free) for subcutaneous (sc) administration.

Approximately up to 388 study participants will be screened at about 135 sites from North America, Europe and Asia to achieve the minimum targeted number of 150 to a maximum of 240 evaluable study participants.

Participants have the opportunity to rollover into an open-label extension (OLE) study, as described below. The OLE study, MG0004 ([redacted] chronic treatment) will be replaced by MG0007, which consists of [redacted] based on MG worsening. Upon study site approval of MG0007, as well as fulfilment of regulatory requirements, study participants will have the opportunity to rollover directly into MG0007. In the event a study participant has already started MG0004, a minimum treatment duration of 6 visits (if IMP treatment is held for low IgG, study participants missed dose(s) can be counted as part of the total 6 visits for completion of MG0004 and meet eligibility requirements for MG0007) must be completed prior to moving into MG0007. Once the site is active for MG0007, no further participants will enroll in MG0004 and the study will be closed at the site once all eligible study participants have discontinued MG0004 and had the opportunity to rollover into MG0007.

The maximum duration of MG0003 study per study participants will be up to 18 weeks, consisting of a Screening Period (1 to 28 days to account for central laboratory turn-around time), a Treatment Period (6 weeks), and a blinded Observation Period (8 weeks).

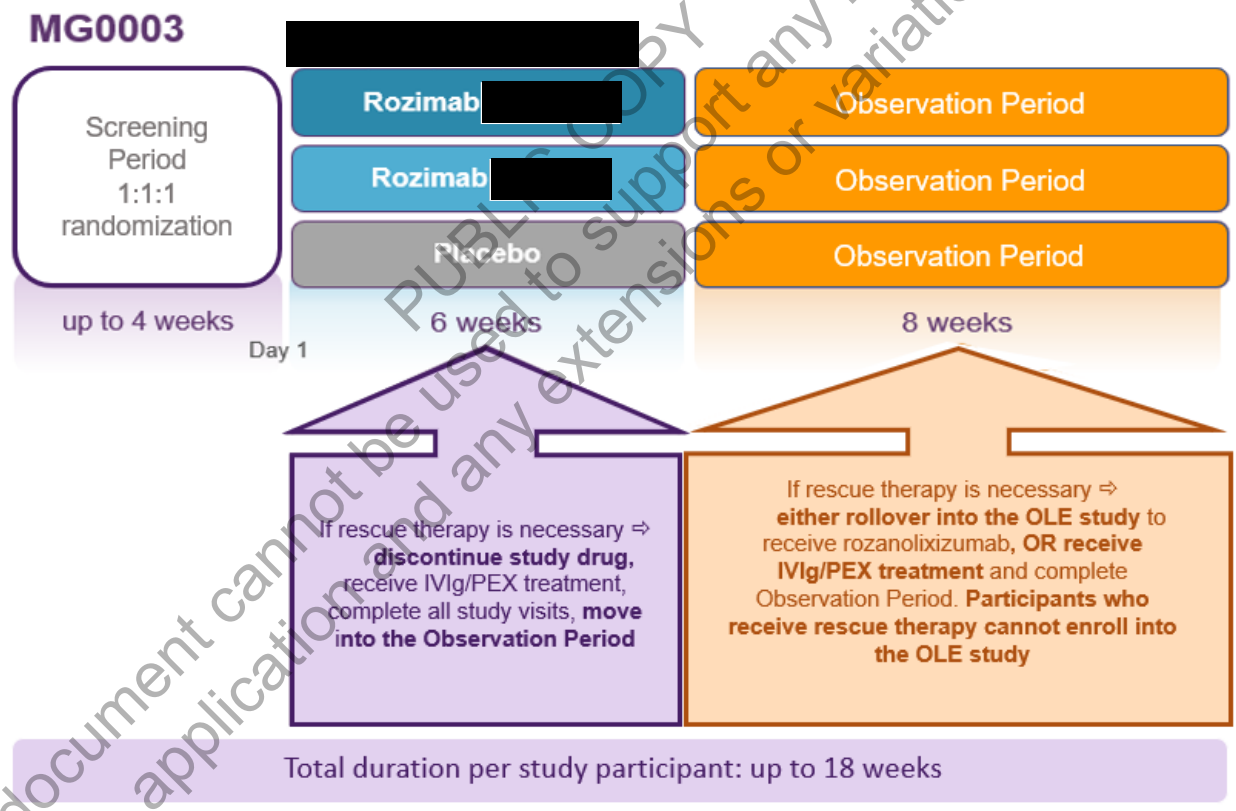
1. All study participants who complete the 6-week Treatment Period may roll over into an 8-week Observation Period.
2. All eligible study participants who complete the Observation Period will be invited to be re-randomized into an OLE study to either active dose arm 1 or 2.
3. Study participants who experience disease worsening during the 6-week Treatment Period (e.g., an increase of 2 points on the MG-ADL or 3 points on the QMG scale between two consecutive visits) may be considered for rescue therapy (IVIg or PEX) at the discretion of the Investigator.
4. Study participants who need rescue therapy during the 6-week Treatment Period will receive IVIg or PEX and complete any subsequent visit(s). No further infusions of rozanolixizumab will be administered after initiation of rescue therapy. Once the participant completes Visit 10, he or she will move into the 8-week Observation Period.
5. Study participants who complete the Treatment Period and require initiation of rescue therapy after they start the 8-week Observation Period, may either opt to receive IVIg or PEX or complete the EOS visit and immediately roll over into an OLE study where the participant

will receive rozanolixizumab. Participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study.

6. Study participants who did not complete the 6-week Treatment Period because they needed rescue therapy and require initiation of a second course of rescue therapy while in the 8-week Observation Period can roll over to an OLE study if a minimum of 2 weeks have lapsed since completion of the last IVIg or PEX session. The EOS visit must be completed before enrolling into an OLE study. Alternatively, they can be treated with IVIg or PEX. Study participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study.
7. Study participants who discontinue study medication for any reason other than requiring rescue therapy will not be eligible for enrollment into an OLE study.

A schematic diagram of the study is provided in Figure 2-1.

FIGURE 2-1: STUDY SCHEMATIC



IVIg=intravenous immunoglobulin G; PEX=plasma exchange; Rozimab=rozanolixizumab

2.4 Determination of sample size

As detailed in Section 4.4, this study will consist of 2 stages, with a formal interim analysis at the end of Stage 1.

Based on historical data, the mean difference in adjusted changes from Baseline of MG-ADL at Day 43, between rozanolixizumab and placebo, is assumed to be 1.5 to 2.0 and the standard deviation is assumed to be 3.5 to 4. A difference of >1.5 could be judged to be clinically meaningful.

It is proposed that the interim analysis will be conducted when approximately 90 eligible study participants have been treated and are evaluable for the primary endpoint, i.e., approximately 30 study participants per dose group in Stage 1. If the study is not stopped for futility after Stage 1, the sample size will be increased, subject to a maximum cap, to provide an overall conditional power target of 90% based on the observed effect size in Stage 1. For each dose that is not futile, the comparison-wise conditional power will be calculated which is the probability of, given the observed data, to achieve a significant result for the completed trial if only the considered treatment is selected. If two doses are selected, then the conditional power associated with the higher treatment effect will be used to determine the stage 2 sample size. Conditional power will be calculated as described in formula 7.2 of Wassmer and Brannath (2016). Similarly, the stage 2 sample size required to achieve a target conditional power of 90% will be calculated using a formula derived from formula 7.4 of Wassmer and Brannath (2016) as follows:

Second stage sample size per arm = $2*SD^2*[\ \phi^{-1}(TP)+ \phi^{-1}(1\text{-}CRP)]^2 / Delta^2$
Where,

SD = pooled standard deviation from the stage 1 statistical model using all dose groups
TP = target conditional power = 0.9
CRP = Conditional rejection probability at stage 1 for the dose group being considered
Delta = assumed true treatment effect for second stage data

If two doses are considered for stage 2 then the above formula will be applied with the conditional error divided by two, to account for multiplicity. Depending upon the selection of one, or two, of the doses after Stage 1, a further 60 to up to a maximum of 150 eligible study participants will be randomized in Stage 2 of the study. Thus, the total sample size of the study could range between 150 and 240 study participants if the study is not futile at Stage 1.

The power of the study using the above adaptive design and expected sample sizes with a sample size cap of 80 per arm and various scenarios of true treatment effect and standard deviation were determined from a stimulation study using the statistical software ADDPLAN MC, the results of which are summarized in Table 2-1.

The simulation results also indicate that across the various scenarios the average sample size for the study ranges between 169 and 203 study participants. The power for scenarios 5 to 7 and 12 to 14, that is, when the high dose has an effect compared to placebo of 2 points, are at least 80%, indicating that the sample size re-assessment process helps maintain reasonable power when only one dose has a clinically meaningful effect of 2 and the data variability is greater than anticipated (standard deviation[SD]=4).

The chances of stopping the study for futility i.e. both doses individually futile, when at least one dose has a clinically meaningful true effect of 2 or more versus placebo, is less than 3%.

These results support the strategy of entering 30 eligible study participants per dose group in Stage 1 and between 30 to 50 study participants per dose group in Stage 2. Note that ADDPLAN MC implements the sample size increase rule ‘per arm’ rather than ‘per stage’, so that if only one dose is selected for Stage 2, then the maximum sample size for this stage is 100, whereas if two

doses are selected than the maximum Stage 2 sample size is 150. Therefore, if an overall study sample size cap of 240 (i.e., 150 in Stage 2) were implemented, irrespective of whether one or two doses are selected, then we would expect power for each scenario to be slightly increased compared to those contained in Table 2-1.

Table 2-1: Simulation results from ADDPLAN MC (x100,000 simulations per scenario) with a capped maximum sample size of 80 per arm using a Bonferroni intersection test

Scenario	Treatment Effect		Standard Deviation	Power	Interim			Average Sample Size
	Dose 1	Dose 2			Proportion Futility	Proportion Selecting Low Dose	Proportion Selecting High Dose	
1	0.0	0.0	3.5	0.020	0.335	0.474	0.474	169.0
2	1.0	1.0		0.400	0.049	0.781	0.782	203.3
3	1.0	1.5		0.632	0.023	0.657	0.914	199.1
4	1.5	1.5		0.750	0.011	0.838	0.841	199.8
5	1.0	2.0		0.864	0.008	0.474	0.975	186.4
6	1.5	2.0		0.892	0.004	0.697	0.942	191.7
7	2.0	2.0		0.943	0.002	0.859	0.860	189.9
8	0.0	0.0	4.0	0.020	0.335	0.467	0.463	168.1
9	1.0	1.0		0.315	0.066	0.734	0733	199.9
10	1.0	1.5		0.515	0.037	0.621	0.875	198.2
11	1.5	1.5		0.632	0.021	0.795	0.797	199.4
12	1.0	2.0		0.755	0.016	0.468	0.953	189.5
13	1.5	2.0		0.792	0.010	0.663	0.912	193.7
14	2.0	2.0		0.871	0.005	0.823	0.822	192.3

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, participant data listings, and statistical output will be performed using SAS® Version 9.3 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For continuous variables, descriptive statistics will include number of participants with available measurements (n), mean, SD, median, minimum, and maximum.

For categorical variables, the number and percentage of participants in each category will be presented. Unless otherwise noted, the denominator for percentages will be based on the number of participants included in the respective analysis set. Participants with missing data can generally be accounted for using the following approaches:

- For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the analysis set and include a "Missing" category (corresponding to participants with missing data for the variable being summarized) as the last row in the list of categories being summarized.
- For summaries of efficacy and safety variables, unless otherwise specified: summarize percentages based only on those participants with observed data for the variable being summarized. As the denominator may be different from the number of participants in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)."

Unless otherwise noted, all percentages will be displayed to one decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

For the purpose of the tabulations the lower and upper confidence limits for the percentages will be truncated at 0 and 100% respectively.

Statistical tests of efficacy variables will be presented as p-values rounded to three decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999". Statistical comparisons will be two-sided and will be performed at the 0.05 level of significance unless specified otherwise. The significance levels used as part of the multiple testing procedure are detailed in Section 4.6.

For PK concentrations, summary statistics will include geometric mean, geometric coefficient of variation (geoCV), 95% confidence intervals (CIs) for geometric mean, arithmetic mean, SD, median, minimum, and maximum. All summaries of PK variables will be based on the observed values. No imputation will be used.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer;
- Mean, SD, and median will use one additional decimal place compared to the original data;
- CV [%] will be presented with one decimal place;
- Minimum and maximum will have the same number of decimal places as the original value.

If no participants have data at a given time point, for example, then only n=0 will be presented. However, if n<3, present the n, minimum and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank.

Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied, then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics.

3.2 General study level definitions

3.2.1 Analysis time points

All data will be analyzed based on the visits identified per the Schedule of Activities in protocol. Mapping to analysis visit windows is not applied, except for premature end of treatment (PEOT) visits (specified in Section 3.2.3).

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first sc infusion of IMP as reference.

Relative days for an event of measurement occurring before the date of first sc infusion will be prefixed with '-' and are calculated as follows:

Relative Day = [(Event Date – Date of First Infusion)]

The relative day for an event or measurement occurring on or after the reference date to the date of the last infusion is calculated as follows:

Relative Day = [(Event Date - Date of First Infusion) + 1]

For events or measurements occurring after the date of the last sc infusion, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = + [(Event Date – Date of Last Infusion)]

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a participant data listing. In such cases, relative day should be presented as '- -' in the participant data listings.

3.2.2 Study periods

The maximum duration of the study per participant will be approximately 18 weeks, consisting of the following 3 periods:

- Screening Period: 1 to 28 days
- Treatment Period: 6 weeks
- Observation Period: 8 weeks

The end of the study is defined as the date of the last visit of the last participant in the study.

The following definitions for starting and entering the study periods will be applied:

- **Treatment Period** starts with the first day of IMP and ends after Day 43/PEOT assessments. All participants in the Safety Set will be considered to have started the Treatment Period. A participant is considered to have completed the Treatment Period if assessments from Treatment Period Day 43 are completed.
- **Observation Period** starts one day after the end of the Treatment Period and ends after the final assessments on the last visit. Participants with assessment on any Observation Period day are considered to have started the Observation Period. Participants who have a completed status in the study termination case report form are considered to have completed the Treatment and Observation Periods.

3.2.3 Mapping of assessments performed at Premature End of Treatment Visit

PEOT assessments will be assigned to the next scheduled site visit (following the last scheduled visit that the study participant completed prior to PEOT) where each assessment is evaluated as

per protocol. This approach means that there is a chance that PEOT data will be mapped to different visits according to the schedule of assessments.

3.3 Definition of Baseline values

Baseline will be the last available value prior to or on the same date (and time if time is collected for the individual assessment) of the first infusion of IMP in the Treatment Period, or if missing, the Screening value. Scheduled or unscheduled measurements can be used as the Baseline value. If a Baseline measurement is not available but an unscheduled measurement occurs after the planned baseline measurement time point but before dosing, then the unscheduled measurement will be used. MG-specific autoantibodies MuSK and AChR Baseline is detailed in Section 9.2.1, and ADA Baseline is detailed in Section 9.3.1.

3.4 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual study participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All IPDs will be identified and documented prior to unblinding and will be utilized to decide, which data will exclude study participants from the Pharmacokinetic Per-Protocol Set (PK-PPS).

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all study participants who have signed the informed consent.

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all study participants who were randomized, using the treatment assigned instead of the actual treatment received.

3.5.3 Safety Set

The Safety Set (SS) will consist of all randomized study participants who received at least one dose of IMP and analyzed according to the actual treatment the participants received.

3.5.4 Pharmacokinetic Per-Protocol Set

The PK-PPS will consist of a subset of the SS, consisting of those study participants who received at least 1 dose of rozanolixizumab, had at least 1quanifiable concentration of rozanolixizumab, and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock. Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PK-PPS but may lead to exclusion of specific data.

3.5.5 Full Analysis Set

The Full Analysis Set (FAS) will consist of all study participants in the RS, who have a Baseline and least 1 post-Baseline MG-ADL measurement.

3.6 Treatment assignment and treatment groups

If after unblinding it is determined that study participants at any time receive incorrect treatment from their randomized assignment, then for safety and PK/PD analyses these study participants will be reallocated to the appropriate treatment group. For example, if study participants randomized to placebo received rozanolixizumab, then for the safety and PK/PD analyses, these study participants will be reallocated to rozanolixizumab. If a study participant received both doses of rozanolixizumab at different time points, then the study participant will be allocated to the higher dose (i.e. [redacted]) group in the safety and PK/PD analysis. Study participants randomized to rozanolixizumab will only be reallocated to the placebo treatment group if they never received rozanolixizumab.

Efficacy data will be summarized by randomized treatment group as shown below:

- Placebo
- Rozanolixizumab [redacted] equivalent, displayed as RLZ [redacted]
- Rozanolixizumab [redacted] equivalent, displayed as RLZ [redacted]

3.7 Center pooling strategy

It is planned to recruit study participants in North America, Europe, and Asia in this study, with possible extension to other regions and countries. The data from all sites will be pooled for analyses. Geographic regions and countries are categorized as following,

- Asia (excluding Japan): Taiwan
- Europe: Belgium, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, Georgia, Hungary, Italy, Poland, Russian Federation, Serbia
- North America: Canada, United States
- Japan: Japan

3.8 Coding dictionaries

Adverse events (AEs) and medical histories will be coded using version 24.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA®).

Medications will be coded according to B3 version Mar 2021 or later of the World Health Organization Drug Dictionary (WHODD).

3.9 Changes to protocol-defined analyses

- Mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) is specified as the model used for the analysis of primary endpoint. In the SAP, MMRM is used as the model only.
- ADDPLAN MC is specified in the protocol for making determinations from the interim analysis. However, SAS or the R package for Adaptive Clinical Trials (RPACT) will be used instead. For the purposes of this analysis, these packages will provide the same functions as ADDPLAN MC.

- The treatment group by week interaction term is specified to be used in the model of analysis of primary efficacy endpoint. In the SAP, treatment group by day interaction will be used instead.
- The Full Analysis Set (FAS) will consist of all study participants in the RS, who have a baseline and at least one post-Baseline MG-ADL measurement. The protocol incorrectly states this as SS.
- Stratification factors used in statistical modeling, such as muscle specific kinase [MuSK(+/-)] and acetylcholine receptor [AChR(+/-)] are defined in the SAP as two binary variables, instead of one binary variable [MuSK(+) or AChR(+)] – this is to account for study participants who may be double-positive.
- Estimands and Intercurrent event handling strategies have been updated based on regulatory feedback.
- Minimal Symptom Expression (MG-ADL score of 0 or 1) at any time up to and include both treatment and observation phase, where the protocol only states to include up to Day 43 (Visit10).
- Potential Hy's Law has been updated to Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 3x Upper Limit of Normal (ULN) and total Bilirubin (TBL) > 2x ULN, and Alkaline Phosphatase (ALP) < 2x ULN.
- Calculation of Low-density lipoprotein (LDL) will follow Friedewald equation, where LDL in mmol/L= TC - HDL - TRIG/2.22; LDL in mg/dL= LDL=TC-HDL-TRIG/5 (if all values are in mg/dL). This formula is applicable only if Triglycerides is less than or equal to 400 mg/dL (4.52 mmol/L).
- MG-C responders are defined as at least a 3-point improvement (decrease) from Baseline instead of 5-point improvement.
- Patient Global Impressions of Severity (PGI-S) at each scheduled assessment during the Treatment and Observation Periods instead of change from Baseline of PGI-S.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The efficacy analyses will be adjusted for the following covariates:

- Baseline MG-ADL score,
- Region (North America, Europe, and Asia [excluding Japan], Japan),
- Stratification factors – MG-specific autoantibodies, including muscle specific kinase [MuSK(+/-)] and acetylcholine receptor [AChR(+/-)], both as binary variables.

In statistical modeling, the stratification factors MuSK(+/-) and AChR(+/-) will be based on the values from MG-specific autoantibody assessment at Baseline. In case Baseline MG-specific autoantibody result is missing (and not resolved after data queries), a post-Baseline measurement may be used. If this is not available, then the historical result will be used in the model; if the historical result is missing as well, the stratification factor from IWRS randomization file will be used to determine values used in the model (i.e., if the stratification is MuSK in IWRS, then

MuSK(+/-) will be imputed as positive, otherwise negative; similarly, if stratification factor is AChR in IWRS, then AChR(+/-) will be imputed as positive, otherwise negative).

4.2 Handling of dropouts or missing data

4.2.1 Efficacy data

The rules for handling missing data of individual items in the calculation of the QMG, MG-C, MG-ADL, MG Symptom PRO, MGII, and MG-QOL15r scores at a certain visit are described in Section 13.1, Section 13.2, Section 13.3, Section 13.4, Section 13.5 and Section 13.6, respectively.

Imputation methods for missing overall scores (including missing data due to intercurrent events Section 8.1) for the analyses of primary and secondary endpoints are listed as below. The estimand corresponding to these analyses are described in Section 8.

Efficacy Endpoints	Statistical Analysis Type	Statistical Analysis Methods	Imputation Methods
Primary	Primary	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 1	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 2	MMRM	Imputation: J2R
	Sensitivity 3	MMRM	Imputation: maximum likelihood estimation
	Sensitivity 4	MMRM	Imputation: maximum likelihood estimation
	Supplemental 1	Trimmed Mean using ANCOVA	Imputation: worst score
	Supplemental 2	MMRM	Imputation: maximum likelihood estimation
Secondary (continuous)	Secondary	MMRM	Imputation: maximum likelihood estimation
	Sensitivity	MMRM	Imputation: J2R
	Supplemental	Trimmed Mean using ANCOVA	Imputation: worst score
Secondary (binary)	Secondary	Logistic model	Imputation: NRI

MMRM=mixed model for repeated measures; ANCOVA= analysis of covariance; J2R=Jump to reference; NRI= nonresponse imputation

For other binary efficacy endpoints (e.g. QMG responder), missing data will be imputed using nonresponse imputation (NRI). That is, study participants with missing data at the timepoint of interest, and all timepoints after use of rescue medication will be treated as non-responders.

For ordinal endpoints (EQ-5D-5L, PGI-S, PGI-C), the observed case method will be applied. No further imputation is used.

4.2.2 Dates and times

Partially or completely missing dates may be imputed for the following reasons:

- Classification of AEs as TEAEs;
- Classification of medications as past, prior, or concomitant medications;
- Durations of AEs;

Imputed dates will not be shown in listings. All dates will be displayed as reported in the database.

The following rules will be applied for partially or completely missing start dates:

- If year, month and day are all missing then assign the date of first dose of IMP. If an imputed start date is after the specified end date, then assign January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).
- If month and day are missing, and year is:
  - the same as the year of the first dose of IMP then assign the month-day of first dose of IMP. If the imputed start date is after the specified end date, then assign January 01, or the month-day of screening date if this is later (if the latter imputation results in an end date that is earlier than the start date, then assign January 01);
  - not the same as the year of the first dose of IMP then assign January 01.
- If only day is missing, and month-year is:
  - the same as the month-year of the first dose of IMP then assign the day of first dose of IMP. If the imputed start date is after the specified end date, then assign first day of the month, or the day of screening date if this is later (if the latter imputation results in an end date that is earlier than the start date, then assign first day of the month);
  - not the same as the month-year of the first dose of IMP then assign the first day of the month.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, then use discharge date or data cut-off date.

Note: Discharge date refers to the date of the end of study visit for completed study participants or the date of discontinuation for study participants that were withdrawn. For any AEs with known start date after the date of discontinuation, the date of last contact will be used as the discharge date. For study participants still ongoing in the study at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

Any medication with a start date on the first dosing date and time unknown, will be assumed to be concomitant.

Imputed AE dates will be used for the calculation of duration of AEs as described in Table 4–1.

Table 4–1: Calculation rules for duration of AEs

Data availability	Onset date	Outcome date	Calculation rules
Complete data	D1	D2	Duration = D2 – D1 + 1 day
Start date partially or completely missing	--	D2	Duration ≤ D2 – D0 + 1 day Notes: D0 is imputed start date per above rules.
End date partially or completely missing	D1	--	For ongoing AE: Duration ≥ D3 – D1 day For resolved AE: Duration ≤ D3 – D1 day Notes: D3 is imputed end date per above rules.
Start and end date partially or completely missing	--	--	For ongoing AE: Duration ≥ D3 – D0 day For resolved AE: Duration ≤ D3 – D0 day Notes: D0 is imputed start date and D3 is imputed end date per above rules.

4.2.3 Missing data due to COVID-19

Missing data is expected to be one of the major implications of the COVID-19 pandemic. The following approaches/strategies will be applied to assess the impact of COVID-19 pandemic in this study.

- Added an eCRF page “COVID-19 Impact”, including impacted visits, impact categories and relationship to COVID-19 pandemic.
- Additional fields were added in protocol deviation specification documents to record protocol deviations relationship to COVID-19 pandemic.
- Included additional summary analyses based on the timing of COVID-19 impact (pre/during/post COVID-19 pandemic).

- Additional intercurrent events related to COVID-19 pandemic were included in the estimands for the evaluation of the primary and secondary efficacy endpoints.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated or unscheduled measurements obtained prior to the first dose of IMP the latest reliable value (scheduled or unscheduled) will be used in the calculation of descriptive statistics (i.e., Screening and/or Baseline);
- For repeated or unscheduled measurements obtained at the designated Baseline visit and prior to the first dose of IMP, the latest reliable value (scheduled or unscheduled) will be defined as the Baseline;
- For repeated or unscheduled measurements obtained at any time point after the first dose of IMP, the scheduled values (if non-missing) will always be used in the calculation of changes from Baseline and for the descriptive statistics (i.e., in summaries by time point). If repeated scheduled values are obtained at any time point, the latest non-missing will be used.

See Section 10.3 for the rules applied to repeated lab results.

See Section 10.4.2 for the rules applied to ECG triplicate measurements.

4.4 Interim analyses and data monitoring

4.4.1 Timing of and basis for periodic data reviews and interim analysis

An independent Data Monitoring Committee (IDMC) will be formed to monitor the ongoing safety and efficacy of the study.

Approximately 3 periodic data reviews are planned to oversee the safety of the study:

- The first periodic data review will be performed when approximately 15 study participants have completed the 6-week Treatment Period;
- The second periodic data review will be conducted after approximately 60 study participants have completed the 6-week Treatment Period (ad hoc as needed);
- Third review dependent on the outcome of the interim analysis (see details below) will be conducted after approximately 150-180 study participants have completed the 6-week Treatment Period.

The timing of any further data reviews will be decided by the IDMC in conjunction with sponsor. Further details of the IDMC will be provided in an IDMC charter.

In addition to the periodic data reviews mentioned above, a formal interim analysis (IA) is planned for this study at the end of Stage 1, once approximately 90 (see Section 2.4 for sample size details) enrolled study participants (30 per arm) are evaluable for the primary endpoint (having completed up to Day 43). The IA is based on an a 2-stage adaptive design and powered on the primary efficacy endpoint: change from Baseline to Day 43 in MG-ADL.

For the periodic data reviews, all data available at the time of the data cut-off will be included. For the formal interim analysis, only data for the 90 study participants at Stage 1 that have

completed the primary endpoint will be included in the analysis. Listings and descriptive statistics for both the periodic data reviews and the interim analysis may include data beyond the specified cut-off visit for study participants who were enrolled earlier. This will also include data for screen failures.

The database will not be locked for each periodic data review or for the interim analysis. Study enrollment will not be halted during the periodic data reviews or interim analysis. A snapshot of the data will be taken at the required cut-off timepoint.

The data should be as clean as possible for the periodic data reviews and interim analysis, but it is not required to have resolved all queries prior to each database snapshot.

Protocol deviations will be considered for the interim analysis; thus, it will be required to schedule a data evaluation meeting (DEM) prior to the interim analysis. Protocol deviations will not be considered for the periodic data reviews.

At IA, stage 1 data will be presented to and reviewed by the IDMC and the following decisions will be made:

1. Early stopping for futility: if there is no evidence of either dose of rozanolixizumab being effective compared to placebo.

   Notes: the non-binding futility stopping rule will require that the nominal Stage 1 p-value of each dose to be greater than 0.5 (1-sided). This corresponds to both estimated treatment effects being in the wrong direction, i.e., inferiority.

2. Move to the next stage:

   Before moving to the next stage, the following will be considered:

   2.1 Dose Selection: If the study is not stopped for futility (not established), then the "best dose" of rozanolixizumab (and the other active dose if the mean response is not worse than 1 point than the selected "best dose") will be selected for Stage 2 of the study.

   This approach allows selection of the dose with the largest effect defined in terms of the observed mean responses and any doses with a mean response no worse than the best dose by 1 point providing that they are not dropped due to futility, i.e., to be retained nominal 1-sided p-value must be less than 0.5. However, this may not be the sole criterion for selecting the dose, since, additionally, the IDMC will take account other factors, including safety, for the assessment of overall benefit-risk, which will be detailed in the IDMC charter.

   2.2 Sample size re-estimation: it will be conducted during the IA, as mentioned in Section 2.4.

Note: Early Stopping for Efficacy will not be considered during the IA hence no alpha spending function will be implemented.

4.4.2 Data required for periodic data reviews and interim analyses

The analyses and data required for review are described in this SAP and include all data specified in the IDMC Charter.

4.4.2.1 Data required for periodic data reviews

Required safety and efficacy data to be used to support the periodic data review will include the following:

- Adverse events
- ECGs
- Vital signs
- Medical and procedure history
- Prior and concomitant medications
- Demographics
- Safety labs (hematology, chemistry, urinalysis)
- Total IgG
- Pregnancy
- C-SSRS
- MG-ADL observed results and change from Baseline
- MG-ADL responder (≥2.0 points improvement from Baseline) rates
- MG-C score observed results and change from Baseline
- QMG score observed results and change from Baseline

These data will be summarized using descriptive statistics. Data will also be provided in listings.

4.4.2.2 Data required for Interim analysis

Descriptive summaries to be used to support the interim analysis for futility will include the following:

- Demographics
- Baseline characteristics
- ECGs
- Vital signs
- Important PDs
- Analysis of MG-ADL change from Baseline at Day 43
- MG-ADL observed results and change from Baseline
- MG-ADL responder (≥2.0 points improvement from Baseline) rates
- MG-C score observed results and change from Baseline
- QMG score observed results and change from Baseline
- Adverse events

- Safety labs (MA values in hematology, chemistry)
- Total IgG

Any changes to this list will be documented in IDMC meeting minutes.

These data will be summarized using descriptive statistics. Data will also be provided in listings. For the futility analysis, dose selection, and sample size re-estimation for Stage 2, a treatment comparison will be conducted using the primary endpoint (MG-ADL) as described in Section 8.2.2.

4.5 Multicenter studies

Individual center results will not be displayed.

4.6 Multiple comparisons/multiplicity

The statistical analysis of the primary efficacy and selected secondary efficacy endpoints will account for multiplicity and control the familywise type I error rate at a 2-sided alpha level of 0.05 by using a parallel gatekeeping testing procedure with a truncated Hochberg test for each of the 6 type I error families (corresponding to the primary endpoint and the five secondary endpoints).

The hypotheses are mapped into 2 sets so that hypotheses within each set correspond to the same rozanolixizumab dose.

Serial restrictions are applied so that the endpoints can only be tested for each dose, if all previous endpoints for that dose are significant.

For family 1, (the primary endpoint hypotheses corresponding to the pairwise comparisons of each dose versus placebo) the Hochberg truncation parameter is set to 0 which is equivalent to using the Bonferroni approach, where the type I error will be split equally between dose level rozanolixizumab [redacted] so that each dose level will be tested at a 2-sided alpha level of 0.025. Whereas, for families 2-5 the Hochberg truncation parameter is set to 0.2, and for the final family the truncation parameter is 1, so that the standard Hochberg test is used.

The scenarios for the sequential procedure are described below and begins with the evaluation of the primary efficacy endpoint.

Scenario 1: One of the two doses of rozanolixizumab is statistically significant for the primary endpoint:

1. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG-C score at a 2-sided alpha level of 0.025. If significant in favor of rozanolixizumab, then proceed to step 2. Otherwise, the testing procedure is concluded.
2. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in QMG score at a 2-sided alpha level of 0.025. If significant in favor of rozanolixizumab, then proceed to step 3. Otherwise, the testing procedure is concluded.
3. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Muscle Weakness Fatigability' score at a 2-sided alpha level of 0.025. If significant in favor of rozanolixizumab, then proceed to step 4. Otherwise, the testing procedure is concluded.

4. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Physical Fatigue' score at a 2-sided alpha level of 0.025. If significant in favor of rozanolixizumab, then proceed to step 5. Otherwise, the testing procedure is concluded.
5. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Bulbar Symptoms' score at a 2-sided alpha level of 0.025.

Scenario 2: Both doses of rozanolixizumab are statistically significant for the primary endpoint:

1. Perform a truncated Hochberg test of rozanolixizumab vs placebo for change from Baseline to Day 43 in MG-C score at a 2-sided alpha level of 0.05:
   a) Both doses are significant if the larger of the 2-sided p-values is less than or equal to 0.5(1+0.2)*0.05=0.03. Then 2-sided alpha=0.05 is transferred to the next pairwise comparison (family).
   b) If the previous step does not hold, then one dose is significant if the smaller 2-sided p-value <0.025. In which case, 2-sided alpha=0.5(1-0.2)*0.05=0.02 is transferred to the next family.
   c) Otherwise, the testing procedure is concluded.
2. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in QMG score:
   a) If both doses are significant in the previous family, then perform a truncated Hochberg test at 2-sided alpha=0.05 as described in 1.
   b) If only 1 dose is significant in the previous family, then perform a 2-sided test alpha=0.02 for the single dose which was significant in the previous family. If this dose is significant then transfer alpha=0.02 to the next family.
   c) If no significant tests result from scenarios a or b above, then the testing procedure is concluded.
3. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Muscle Weakness Fatigability' score:
   a) If both doses are significant in the previous family, then perform a truncated Hochberg test at 2-sided alpha=0.05 as described in 1.
   b) If only 1 dose is significant in the previous family, then perform a 2-sided test at alpha=0.02 for the single dose which was significant in the previous family.
   c) If no significant tests result from scenarios a or b above, then the testing procedure is concluded.
4. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Physical Fatigue' score:
   a) If both doses are significant in the previous family, then perform a truncated Hochberg test at 2-sided alpha=0.05 as described in 1.
   b) If only 1 dose is significant in the previous family, then perform a 2-sided test at alpha=0.02 for the single dose which was significant in the previous family

c) If no significant tests result from scenarios a or b above, then the testing procedure is concluded

5. Test rozanolixizumab vs placebo for change from Baseline to Day 43 in MG Symptoms PRO 'Bulbar Symptoms' score:

   a) If both doses are significant in the previous family, then perform a standard Hochberg test at 2-sided alpha=0.05. Both doses are significant if the larger of the 2-sided p-values less than 0.5(1+1)*0.05=0.05. If not, then one dose is significant if the smaller p-value less than 0.025.

   b) If only 1 dose is significant in the previous family, then perform a 2-sided test at alpha=0.02 for the single dose which was significant in the previous family

   c) The testing procedure is concluded following steps 5a and 5b.

Note: all p-values used in the above procedure will be based upon the inverse-normal combination approach as described for the primary endpoint.

4.7 Use of an efficacy subset of study participants

A sensitivity analysis of the primary endpoint will be performed based on the FAS.

4.8 Active-control studies intended to show equivalence

Not applicable.

4.9 Examination of subgroups

4.9.1 General subgroups

The primary and continuous secondary efficacy endpoints will be evaluated for subgroups of interest including:

- Age (18 - <65 years, ≥65 years)
- Age (18 - <65, 65 - <85, ≥85 years)
- Sex (male, female)
- Region (North America, Europe, and Asia [excluding Japan], Japan)
- Stratification factors – MG-specific autoantibodies, MuSK(+/-) and AChR(+/-)

  Note: The stratification factors MuSK(+/-) and AChR(+/-) in the subgroup analysis will be based on the values from MG-specific autoantibody assessment taken at Baseline, using the same algorithm for missing values as specified in Section 4.1. Historical MuSK (+/non +) and historical AChR(+/non +) will also be examined in the subgroup analysis, in this case, Baseline MuSK(+/-) and Baseline AChR(+/-) will replaced by Historical MuSK (+/non +) and historical AChR (+/non +).

The MG-ADL scores and change from Baseline will be summarized in the five subgroups as above and additional subgroups as follow:

– Duration of disease at Baseline (<median, ≥ median)

- MGFA disease class at Baseline
- Thymectomy at Baseline (yes, no)
- Baseline MG-ADL category (<5, ≥5).

The following subgroups of MG baseline medications will be derived in the analysis datasets and used for ad-hoc reporting purposes. See Section 6.4.3 for definition of MG baseline medications.

- Baseline Oral steroid (yes, no)
- Baseline Immunosuppressants other than oral steroid (yes, no)
- Baseline Cholinesterase inhibitor (yes, no)

All subgroup analyses will be descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out. No subgroup analysis is planned for safety variables.

Forest plots will be provided to summarize subgroup analysis.

Subgroup analyses will only be performed for subgroups where there are at least 5 study participants in each subgroup level, otherwise it will not be performed.

4.9.2 Examination of COVID-19 subgroups

Summary tables will be produced for study participant disposition, demographics and other Baseline characteristics to account for the amount of data captured pre-, during and post- the COVID-19 pandemic. The cut-off dates for the subgroup levels will be defined prior to database lock. Details of the analyses will be specified in the following sections.

4.9.3 Examination of weight subgroups and administered doses

To support the goal of a fixed dosing strategy for Rozanolixizumab, additional subgroup analyses will be performed by administered dose group for each weight subgroup below:

- Weight (< 50kg, 50 - <70 kg, 70 - <100kg, ≥100kg, total)
- Administered dose (Placebo, RLZ [redacted], RLZ [redacted], RLZ [redacted], RLZ [redacted], RLZ [redacted], RLZ Total)

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

The following outputs will be created.

Summaries:

- **Reasons for screen failures** (as collected on the Study Termination Screen Failure Case Report Form [CRF] page) will be summarized using the ES for overall. Additionally, the reasons for screen failures will be summarized by pre-, during and post- the COVID-19 pandemic based on the screen failure date relative to the pandemic cut-off date.
- **Disposition of study participants screened** will be summarized using the ES for overall, by region and by site. In this summary, the site number, principal investigator name, first

participant in date, last participant out date, will be captured by randomized treatment and by each analysis set (RS, SS, FAS and PK-PPS).

- **Disposition of analysis sets** will be summarized by treatment groups, RLZ total and by analysis sets (RS, SS, FAS and PK-PPS) using the RS.
- **Disposition and discontinuation reasons** using the RS will contain the number and percentage of study participants who started, completed and permanently discontinued Treatment Period / Observation Period overall and by pre-, during and post- the COVID-19 pandemic based on the start, completed and discontinuation date relative to the pandemic cut-off date. The discontinuation reason in each period will also be summarized. Discontinuation due to COVID-19 pandemic and mandatory withdrawal due to need for rescue therapy and roll over to extension study will be listed as sub-category under "Other" reason.
- **Discontinuation due to AEs** using the RS will summarize the total number of study participants who discontinued the study due to AEs by treatment group, RLZ total and the categories: AE serious fatal, AE non-fatal and other AE non-serious fatal.
- **Count of participants by visit** using RS will summarize the number of participants at each visit by treatment group.
- **Impact of COVID-19 for any reason** using the RS will summarize number and percentage of study participants in each impact category by visit.

Listings of study participant disposition, study discontinuation and study participants who did not meet study eligibility criteria will be provided.

5.2 Protocol deviations

A summary of number and percentage of study participants with an important protocol deviation by relationship to COVID-19 pandemic and treatment group will be provided for the RS. Additionally, the summary will be repeated by pre-, during and post- the COVID-19 pandemic based on the deviations start date relative to the pandemic cut-off date.

A listing of important protocol deviations will be provided based on the RS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographic variables will be summarized on the RS, by categories mentioned below using descriptive statistics by treatment group, RLZ total and overall. The same summary will also be presented by stages.

Categories for continuous variables (including n, mean, SD, Median, Min and Max):

- Age at the time of study entry (years) as captured on Demographics CRF

  Notes: Missing age will be calculated as year of informed consent signed – year of birth
- Height (cm)
- Weight (kg)

- Body Mass Index (BMI) (kg/m^2) calculated as: $BMI = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$

Categorical variables (using frequency counts and percentages):

- Age (18 to <65, 65 to <85, ≥ 85 years)
- Age (≤18, 19 to <65, ≥65 years)
- BMI (<30 kg/m^2, ≥30 kg/m^2)
- Bodyweight (<50kg, 50kg to <70 kg, 70kg to <100kg, ≥100kg)
- Bodyweight (<50kg, ≥50kg)
- Bodyweight (<70kg, ≥70kg)
- Sex (Male, Female)
- Race (American Indian or Alaska native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (North America, Europe, Asia [excluding Japan], Japan)
- Country

Additional subgroup summary of above variables will be presented by pre-, during and post- the COVID-19 pandemic based on the enrolled date relative to the pandemic cut-off date.

For subgroup summary by weight subgroups and total for the administered dose and RLZ total, following variables will be analyzed:

- Age at the time of study entry (years) as captured on Demographics CRF
- Sex (Male, Female)
- Weight (kg)
- Region (North America, Europe, Asia [excluding Japan], Japan)

A by-participant listing of demographics will be provided using the RS. Childbearing potential and lifestyle will be listed using the ES separately.

6.2 Other Baseline characteristics

The following variables will be summarized by treatment group, RLZ total and overall for the RS. The same summary will also be presented by stages :

- MGFA disease class at Baseline
- MG medication as captured on Prior and Concomitant Medications CRF where indication is MG, details in Section 6.4.3
- Myasthenic crisis (yes/no) as captured on History of MG CRF
- Thymectomy (yes, no) as captured on Medical History CRF and Procedure History CRF.
- MG-specific autoantibody (MuSK+ / AChR+) as recorded into the IWRS at randomization

- Historical MuSK antibody status (positive, negative, unknown) as captured on Confirmatory (Historical) Diagnostic Tests for Primary Condition CRF
- Historical AChR antibody status (positive, negative, unknown) as captured on Confirmatory (Historical) Diagnostic Tests for Primary Condition CRF
- Baseline MuSK antibody status (positive, negative, unknown) as evaluated at Baseline visit
- Baseline AChR antibody status (positive, negative, unknown) as evaluated at Baseline visit
- Comparison between historical and Baseline MG-specific autoantibody (MuSK+ / AChR+)
- Baseline MG-ADL score
- Baseline MG-ADL category (<5, ≥5)
- Baseline QMG score
- Baseline total IgG value
- Duration of disease (years)

  Duration of disease (years) will be calculated as:

  $$\text{Disease Duration} = \frac{(\text{Date of randomization} - \text{Date of Initial MG Diagnosis}^{1} + 1)}{365.25}.$$

  [1]If the date of initial MG diagnosis is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or the last day of the year if day and month are missing). Note that if the date of randomization is missing then the duration of disease will be derived using the date of screening.

- Age at initial MG diagnosis (years)

  Age at initial MG diagnosis will be calculated as:

  $$\text{Age at initial MG diagnosis} = \frac{(\text{Date of Initial MG Diagnosis}^{2} - \text{Date of Birth} + 1)}{365.25}$$

  [2]If the date of initial MG diagnosis is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or the last day of the year if day and month are missing).

The summary will be repeated by pre-, during and post- the COVID-19 pandemic based on the enrolled date relative to the pandemic cut-off date.

Additionally, summary by weight subgroup and total for administered dose and RLZ total will be provided for above variables.

A by-participant listing of Baseline characteristics will be provided.

6.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by treatment group, RLZ total and overall, system organ class (SOC), high level term (HLT) and preferred term (PT). Medical procedures are not coded.

Medical history will be listed for the RS. Besides, history of headaches, procedure history and family medical history for drug-induced liver injury (DILI) will be provided in separate by-participant listings using the RS.

6.4 Prior and concomitant medications

The number and percentage of study participants taking Past, Prior, Baseline, Concomitant or Concomitant Only medications will be summarized using the RS by Anatomical Therapeutic Chemical (ATC) class, presenting as Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), PT, treatment group and overall.

Additionally, all rescue medications mentioned in Protocol section 6.5.4 and identified if Rescue Medication is ticked as yes on CRF will be summarized using the RS.

Medications classified as past, prior, Baseline concomitant or concomitant only will be listed using the RS. A by-participant listing of concomitant procedures will also be listed using the RS. Originally reported dates will be used for listings.

6.4.1 Categories of prior and concomitant medications

Medications will be classified as follow based on imputed start and stop dates & times as outlined in Section 4.2.2.

- **Past** medications will include any medications that started and stopped before the first administration of IMP.
- **Prior** medications will include any medications that started before the first administration of IMP.
- **Baseline** medications will include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).
- **Concomitant** medications will include any medications that have been taken at least once after the first administration of IMP during the Treatment and/or Observation Period.
- **Concomitant Only** medications will include any medication that started after the first administration of IMP and continues during the Treatment and/or Observation Period.

Table 6–1: Concomitant Medications Classification

Medication Started	Medication finished	Classification
Before 1st Dose IMP	Before 1st Dose IMP	Past
Before 1st Dose IMP	Any time	Prior
Before 1st Dose IMP	After 1st Dose IMP	Baseline (= prior and concomitant)
Any time	After 1st Dose IMP	Concomitant
After 1st Dose IMP	After 1st Dose IMP	Concomitant Only

6.4.2 Assignment of medications to study period

The following rules will be used to assign a concomitant medication to a study period:

- **Treatment Period:** a medication will be assigned to the Treatment Period if it has been taken at least once between the first administration of IMP on Day 1, up to the minimum of Day 43 and 7 days after the last dose of IMP. This includes medications that started prior to the Treatment Period and those that continued into the Observation Period.
- **Observation Period:** a medication will be assigned to the Observation Period if it has been taken at least once from the day after Treatment Period to the EOS visit. This includes medications that started prior to the Observation Period.

Thus, a medication taken from the time of the first drug administration in the Treatment Period to the end of the study will be assigned to the Treatment Period and the Observation Period.

6.4.3 Baseline MG medication definition

MG Baseline medication is defined as an indication related to MG and includes one of the following ATC codes:

- [redacted] (Corticosteroids)
- [redacted] (Immunosuppressants)
- [redacted] (Parasympathomimetics)

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable. The number of infusions will be recorded as detailed in Section 10.1.

8 EFFICACY ANALYSES

All efficacy analyses will be performed using the RS unless specified otherwise, including for the interim analysis.

8.1 Handling of intercurrent events

The main intercurrent events (ICEs) of interest are:

- ICE1 – The use of rescue therapy prior to Day 43 (Visit 10)
- ICE2 – Permanent treatment discontinuation (or withdrawal from study) due to TEAEs

Two additional types of ICEs will be included to account for data affected by the COVID-19 pandemic as follows:

- ICE3 – Treatment discontinuation due to suspected/confirmed COVID-19 infection ("Confirmed COVID-19" or "Suspected COVID-19" as the relationship to COVID-19 in the COVID-19 Impact eCRF)
- ICE4 – Treatment discontinuation due to non-COVID-19 infection related issues ("General circumstances around COVID-19 pandemic without infection" or "other" as the relationship to COVID-19 in the COVID-19 Impact eCRF)

The number and percentage of study participants with each intercurrent event will be summarized by treatment group and RLZ total.

The strategies to handle ICEs are summarized as below:

Strategies	Description
Hypothetical & treatment policy strategy	If study participants experience ICE1, data at and after the point of the ICE for the purpose of analysis will be treated as missing and imputed under proposed method per Section 4.2.1. For participants experiencing ICE2-4, data in the Treatment Period from Baseline to Day 43 will be used regardless of whether any ICEs occurred, missing data will be imputed per Section 4.2.1. For participants who permanently discontinue treatment or withdraw from the study during Treatment Period and who continue into the Observation Period, the observation phase data (collected bi-weekly) will be mapped to the nearest visit for primary analysis where treatment windows will be utilized for the mapping.
Treatment policy strategy	The data in the Treatment Period from Baseline to Day 43 will be used regardless of whether any intercurrent events occurred.
Composite strategy	The occurrence of any intercurrent events above will be handled by evaluating the corresponding study participants as treatment failures and imputed with a worst score (continuous) or non-responder (binary).
COVID-19 Hypothetical strategy	If participant experience ICE1 and/or ICE2, then data at and after the point of the intercurrent event for the purpose of analysis will be treated as missing. Additionally, participant experience ICE3, ICE4 or those that have visits in treatment period affected (e.g. visit performed by video call) will be completely removed from analysis.

8.2 Statistical analysis of the primary efficacy endpoint

The primary efficacy endpoint is the change from Baseline in MG-ADL score to Day 43 (Visit 10) and will be evaluated under the 'hypothetical & treatment policy' estimand based on RS using Hypothetical & Treatment Policy strategy.

Missing data in the primary analysis will be handled under a missing at random (MAR) assumption.

To check the assumptions around the estimand in the (primary) analysis of the primary endpoint, the following sensitivity and supplemental analyses will be performed:

- A sensitivity analysis using:
  - Hypothetical & treatment policy strategy on FAS;
  - Hypothetical & treatment policy strategy with a J2R approach on missing data will be used to verify the robustness of the MAR approach;
  - Hypothetical & treatment policy strategy based on the subgroup of the RS who received all [redacted] doses.
  - Hypothetical & treatment policy strategy based on the subgroup of the FAS excluding confirmed COVID-19 cases.
- A supplemental analysis using:
  - Composite strategy to handle the occurrence of an intercurrent event as treatment failures. A trimmed mean approach will be implemented to impute missing data;
  - Treatment policy strategy to allow intercurrent events to be included in the treatment paradigm.

An additional analysis will be performed using COVID-19 Hypothetical strategy on RS.

The methods to handle the missing data caused by occurrence of ICEs in each analysis are detailed in Section 4.2.1.

Please see below for details about the estimands attributes for the evaluation of the primary endpoint (primary, sensitivity and supplemental analyses).

1. **Treatment Conditions**: please see table below.

Table 8-1: Treatment Conditions:

Study Treatment Name:	**Rozanolixizumab (Treatment Arm 1)**	**Rozanolixizumab (Treatment Arm 2)**	**Placebo (Treatment Arm 3)**
Dosage formulation:	Solution for infusion	Solution for infusion	Aqueous solution
Unit dose strength(s)/Dosage level(s):	[redacted]		0.9% sodium chloride aqueous solution (physiological saline, preservative free)
Route of Administration	Subcutaneous (sc)		
Dosing instructions:	[redacted] doses of rozanolixizumab at [redacted] (equivalent to approximately [redacted]): Bodyweight <50kg: dose to be administered [redacted] Bodyweight ≥50kg and <70kg: dose to be administered [redacted] Bodyweight ≥70kg and <100kg: dose to be administered [redacted] Bodyweight ≥100kg: dose to be administered [redacted]	[redacted] doses of rozanolixizumab at [redacted] (equivalent to approximately [redacted]): Bodyweight <50kg: dose to be administered [redacted] Bodyweight ≥50kg and <70kg: dose to be administered [redacted] Bodyweight ≥70kg and <100kg: dose to be administered [redacted] Bodyweight ≥100kg: dose to be administered [redacted]	[redacted] doses of placebo at [redacted]
Packaging and Labeling	Rozanolixizumab and matching placebo are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.		

2. **Population**: study participants with generalized MG who comply with the inclusion/exclusion criteria specified in Section 5 in the study protocol
3. **Endpoint**: please refer to Section 2.2.1.1 for details.
4. **Intercurrent Events (ICEs)**: See Section 4.2.1.
5. **Population Level Summary (PLS)**: See table below.

Table 8-2: Intercurrent Events and Population Level Summary by Statistical Category

Statistical Category	Intercurrent Event Strategy	Population Level Summary
Primary	The ICEs are detailed in Section 8.1. A **hypothetical & treatment policy strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving rozanolixizumab versus placebo, using the RS.
Sensitivity	**Hypothetical & treatment policy strategy**, same as for the primary analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving rozanolixizumab versus placebo, using the FAS.
Sensitivity	**Hypothetical & treatment policy strategy**, same as for the primary analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving rozanolixizumab versus placebo, using the RS. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
Sensitivity	**Hypothetical & treatment policy strategy**, same as for the primary analysis.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving all [redacted] doses of rozanolixizumab versus placebo.
Sensitivity	**Hypothetical & treatment policy strategy**, same as for the primary analysis.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score on the subgroup of the FAS excluding confirmed COVID-19 cases.

Statistical Category	Intercurrent Event Strategy	Population Level Summary
Supplemental	The ICEs are detailed in Section 8.1. A **composite strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score of its respected questionnaire. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.
Supplemental	The ICEs are detailed in Section 8.1. A **treatment policy strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the MG-ADL score for study participants receiving rozanolixizumab versus placebo.

Note: CfB=Change from Baseline; LSMD=Least Squares Mean Difference; MMRM=mixed model for repeated measures; ANCOVA= analysis of covariance; MAR=Missing at Random

8.2.1 Derivation of primary efficacy endpoint

The complete list of MG-ADL items and scores are provided in Table 13–3. The total score will be calculated according to the rules set down in Section 13.3. The total score calculated after single item imputation will be used to calculate change from Baseline, in summaries and for efficacy analyses.

8.2.2 Primary analysis of the primary efficacy endpoint

The primary analysis is based on the RS under the hypothetical & treatment policy strategy (see details in Section 8.1). Any missing MG-ADL scores (including missing data after the intercurrent events) will be handled based on maximum likelihood estimation method under MAR assumption.

A stage-wise MMRM with treatment group, Baseline MG-ADL score, region, stratification factor(s) including MuSK(+/-) and /or AChR(+/-), and treatment group by day (interaction term) as fixed factors and study participant as a random effect. The MMRM will include Days 8, 15, 22, 29, 36 and 43.

The model will utilize an unstructured covariance pattern for the repeated measures. If the model does not converge using the unstructured pattern, then an autoregressive covariance structure

will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

For each stage, the least squares means (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between each dose group and placebo will be reported for Day 43 (Visit 10), along with the corresponding 2-sided 97.5% Cis and p-values.

The study follows a 2-stage group sequential adaptive design using combination test (Lehmacher and Wassmer, 1999) based on the inverse-normal method of combining independent stagewise p-values (Hedges and Olkin, 1985)

The analysis takes into account that the study is a 2-stage group sequential adaptive design assuming equal weighting of each stage, with weights = 1/√2:

- Stage 1 – Cohort up to the formal IA
- Stage 2 – Cohort post-IA

The following sequential test statistic will be used to test the global null hypothesis at the end of stage 2:

$$T = \sum_{i=1}^{2} w_i \, \Phi^{-1}(1 - p_i)$$

Where subscript $i = 1, 2$ represents the stage, p_i represents the appropriate multiplicity adjusted p-value at stage i (for example at stage 1, p_1= min(2*p_{min},1) where p_{min} is the minimum of the two nominal p-values), the weights w_{ki}= 1/√2 satisfy $\sum_{i=1}^{2} w_{ki}^2 = 1$ and Φ^{-1} is the inverse cumulative standard normal distribution function. The test statistic T and $z = \Phi^{-1}(1 - p_i)$ have a standard normal distribution, (Lehmacher and Wassmer, 1999).

The combined p-value (2-sided) for the 2 stages, which tests the global null hypothesis, can be calculated by:

$$p = 2 * \{1 - \Phi[\frac{1}{\sqrt{2}} \{\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2)\}]\}$$

At the IA one p-value will be computed for each pairwise comparison. Assuming that the trial is not stopped for futility at IA, at the end of the trial the t-test statistics computed at each stage will be used following the p-value combination test method to derive the combined p-value for evaluation of primary efficacy endpoint. Overall statistical significance will be concluded if the combined p-value (2-sided) described above is less than 0.05. For each dose group, statistical significance will be determined in a similar way but using a closed test procedure. Formally, this will be computed as the p-value corresponding to the minimum adjusted Z-statistic of all hypotheses involving the particular dose group being considered. However, if one treatment arm with the largest test statistic is selected for the second stage, the rejection of the global hypothesis implies the rejection of the hypothesis related to the selected hypothesis. The pre-determined alpha value for secondary endpoint testing is specified in Section 4.6.

The analysis will be conducted using SAS and RPACT which also produces the combined effect estimates together with multiplicity adjusted 95% CIs. The stagewise inputs for Rpact will be the model Least squares means, standard errors, sample size per group and degrees of freedom (for estimation of the common standard deviation).

The overall confidence intervals at stage 2 are computed separately for each treatment arm that was selected for stage 2. By use of the Inverse-Normal combination function together with the critical value $Z_{alpha/2}$, the lower bound of the 2-sided 95% repeated confidence interval for a given treatment arm is found as the smallest value for which the multiplicity-adjusted combination test yields non-rejection at two-sided alpha=5%. The upper bound of the confidence interval will be found analogously.

8.2.3 Sensitivity analyses of the primary efficacy endpoint

8.2.3.1 Sensitivity Analysis #1

The first sensitivity analysis will be performed based on the FAS using the hypothetical & treatment policy strategy. The method to handle missing MG-ADL scores (including missing data after the intercurrent events) is specified in Section 4.2.1.

The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.2.3.2 Sensitivity Analysis #2

The second sensitivity analysis will be performed based on the RS under the hypothetical & treatment policy strategy. A J2R approach using Multiple Imputation (MI) method under missing not at random (MNAR) assumption will be used to handle any missing MG-ADL scores (including missing data after the intercurrent events). Missing data will be imputed based on the placebo group distribution, irrespective of individual treatment assignment.

The following is a summary of the imputation method.

100 imputed datasets (m) will be created using monotone linear regression imputation methods which will impute the study participants' missing post-baseline scores at each of the scheduled visits in the study (i.e., Days 1, 8, 15, 22, 29, 36 and 43). If the missing data does not follow a monotonic pattern, a sequential approach to imputing the data to produce a monotone missing data pattern will be applied using the MCMC impute=monotone option in PROC MI (SAS System). Then the monotone linear regression imputation methods will be applied.

The MI method allows for a pattern-mixture model approach assuming the data are MNAR. The MNAR option in PROC MI (SAS system) will be used to impute the placebo distribution as described in Yuan (2014).

Each of the imputed datasets will be analyzed via the specified MMRM model (see Section 8.2.2). The treatment effects and standard errors from LSMs and LSMDs will be combined across the 100 imputed datasets to produce an overall LSMs and LSMDs with associated p-value and 97.5 % CI using SAS PROC MIANALYZE.

The following variables will be included in the imputation model:

- Baseline MG-ADL Score (continuous variable)
- MG-ADL Score at Days 8, 15, 22, 29, 36 and 43 (continuous variable)

Note: if the MI model does not converge or produce estimates (e.g., due to over-specification) the set of imputation variables may be modified.

8.2.3.3 Sensitivity Analysis #3

The third sensitivity analysis will be performed based on the subgroup of the RS who received all 6 (sc) doses of IMP in the treatment period, using the hypothetical & treatment policy strategy and same missing data handling method as mentioned in Section 4.2.1.

The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.2.3.4 Sensitivity Analysis #4

The fourth sensitivity analysis will be performed for the primary endpoint on the FAS excluding confirmed COVID-19 cases under the treatment policy strategy.

The method to handle missing MG-ADL scores (including missing data after the intercurrent events) is specified in Section 4.2.1.

The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.2.4 Supplementary analyses of the primary efficacy endpoint

8.2.4.1 Supplementary Analysis #1

The first supplementary analysis will be performed based on the RS, using the composite strategy (see details in Section 8.1). A trimmed mean approach, where missing data are assumed to be missing not at random (MNAR), will be used to impute missing MG-ADL scores (including the intercurrent events) with the worst score of the MG-ADL questionnaire.

The trimmed mean approach will be applied for each stage separately as follows:

1. Perform an analysis using ANCOVA model with treatment group, Baseline MG-ADL score, region, stratification factors (MuSK+/- and AChR+/-) as fixed effects excluding any study participants with missing data at Day 43 or who experienced an intercurrent event by Day 43.
2. Retain the coefficients from the model for Baseline MG-ADL score, region, and stratification factors (MuSK+/- and AChR+/-).
3. Calculate the adjusted endpoint for each study participant as based on the raw CfB and coefficients calculated from the ANCOVA in Step 1: Adjusted CfB = Raw CfB – Stratification Coefficient*Stratification (AChR/ MuSK) – Baseline Score Coefficient*Baseline MG-ADL score – Region Coefficient*Region.
4. Identify any study participants with missing data at Day 43 and any study participants who experienced any intercurrent event by Day 43. A worst score (i.e., 24) will be imputed for these study participants at Day 43 in order to flag them as worse responders than any subject who completes.
5. Determine the trim fraction to be used. This will be the maximum of dropout and intercurrent event rate in each of the three treatment groups. For example, if the rate of dropout/IE in the three groups is 10, 15 and 20% then the worst 20% of each group will be the trimmed.
6. Sort each treatment group in ascending order by adjusted endpoint Day 43 MG-ADL score and trim equal fractions from each treatment group that was calculated in Step 5 from the bottom.

7. Calculate the mean adjusted CfB score of the trimmed sample for each treatment group and the difference between trimmed means of each rozanolixizumab group and placebo.
8. Repeat Steps 5-7 (above) 10,000 times but each time with a new treatment group assignment (which is a permutation of the original treatment labels, i.e. take a 100% random sample of the original treatment variable without replacement) and a new trimming fraction appropriate to the current permutation.
9. Order the 10,000 permuted trimmed mean differences and count the number of those mean differences that exceed the observed trimmed mean difference calculated in Step 7 as n_1.
10. Then the 1-sided empirical p-value of the original trimmed mean difference $= n_1/10000$.

The one-sided p-values will be presented for each rozanolixizumab dose compared to placebo.

The p-values from Stage 1 and Stage 2 will be combined in the same manner as the primary analysis. Specifically, the final one-sided p-value is $p = 1 - \phi[\frac{1}{\sqrt{2}}\{\phi^{-1}(1-p_1) + \phi^{-1}(1-p_2)\}]$.

8.2.4.2 Supplementary Analysis #2

The second supplementary analysis of the primary endpoint will be performed using a treatment policy strategy (see details in Section 8.1) based on the RS. Any missing MG-ADL scores will be handled based on maximum likelihood estimation method under MAR assumption.

The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.2.5 Additional Analysis

An additional analysis of primary endpoint will be performed on RS under the COVID-19 hypothetical strategy (see details in Section 8.1). The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.2.6 Exploratory Analysis

An exploratory analysis of primary endpoint using historical MG-specific auto-antibodies as a covariate instead of Baseline MG-specific auto-antibodies. This analysis will be performed on RS under the hypothetical & treatment policy strategy (see details in Section 8.1). The same stage-wise analysis approach as primary analysis (Section 8.2.2) will be repeated.

8.3 Statistical analysis of the secondary efficacy endpoints

All secondary efficacy endpoints will be tested according to the testing strategy defined in Section 4.6.

Please see below for details about the estimands attributes for the evaluation of the secondary endpoints (secondary and sensitivity analyses).

1. **Treatment Conditions**: same as described in the estimand for the primary endpoint (Table 8-1).
2. **Population**: same as described in the estimand for the primary endpoint (Section 8.2).
3. **Endpoints, ICEs and PLS**: Please see Table 8-3 below.

Table 8-3: Secondary Efficacy Endpoints: Intercurrent Events and Population Level Summary by Statistical Category

Statistical Category	Endpoint	Intercurrent Event Strategy	Population Level Summary
Secondary	MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)	The ICEs are detailed in Section 8.1. A **composite strategy** will be used to handle the ICEs.	Odds ratio at Day 43 (Visit 10) analyzed using a logistic regression model adjusting for covariates for study participants receiving rozanolixizumab versus placebo, using the RS.
Secondary	Change from Baseline to Day 43 (Visit 10) in MG-C score	The ICEs are detailed in Section 8.1. A **hypothetical & treatment policy strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the MG-C score for study participants receiving rozanolixizumab versus placebo.
Sensitivity	Change from Baseline to Day 43 (Visit 10) in MG-C score	The ICEs are detailed in Section 8.1. A **hypothetical & treatment policy strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-C score for study participants receiving rozanolixizumab versus placebo, using the RS. A J2R multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.

Statistical Category	Endpoint	Intercurrent Event Strategy	Population Level Summary
Supplemental	Change from Baseline to Day 43 (Visit 10) in MG-C score	The ICEs are detailed in Section 8.1. A **composite strategy** will be used to handle the ICEs.	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the MG-C score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score of its respected questionnaire. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data, using the RS.
Secondary	Change from Baseline to Day 43 (Visit 10) in QMG score	**Hypothetical & treatment policy strategy**, same as for the MG-C secondary analysis	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the QMG score for study participants receiving rozanolixizumab versus placebo.
Sensitivity	Change from Baseline to Day 43 (Visit 10) in QMG score	**Hypothetical & treatment policy strategy**, same as for the MG-C sensitivity analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the QMG score for study participants receiving rozanolixizumab versus placebo, using the RS. A J2R multiple imputation approach will be utilised, same as the MG-C sensitivity analysis
Supplemental	Change from Baseline to Day 43 (Visit 10) in QMG score	**Composite strategy**, same as for the MG-C supplemental analysis	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the QMG score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used, as the MG-C supplemental analysis

Statistical Category	Endpoint	Intercurrent Event Strategy	Population Level Summary
Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score	**Hypothetical & treatment policy strategy**, same as for the MG-C secondary analysis	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score for study participants receiving rozanolixizumab versus placebo.
Sensitivity	Change from Baseline to Day 43 (Visit 10) in MG Symptoms PRO 'Muscle Weakness Fatigability' score	**Hypothetical & treatment policy strategy**, same as for the MG-C sensitivity analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the QMG score for study participants receiving rozanolixizumab versus placebo, using the RS. A J2R multiple imputation approach will be utilised, same as the MG-C sensitivity analysis
Supplemental	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score	**Composite strategy**, same as for the MG-C supplemental analysis	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used, as the MG-C supplemental analysis
Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score	**Hypothetical & treatment policy strategy**, same as for the MG-C secondary analysis	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score for study participants receiving rozanolixizumab versus placebo.

Statistical Category	Endpoint	Intercurrent Event Strategy	Population Level Summary
Sensitivity	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score	**Hypothetical & treatment policy strategy**, same as for the MG-C sensitivity analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score for study participants receiving rozanolixizumab versus placebo, using the RS. A J2R multiple imputation approach will be utilised, same as the MG-C sensitivity analysis
Supplemental	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score	**Composite strategy**, same as for the MG-C supplemental analysis	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used, as the MG-C supplemental analysis
Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	**Hypothetical & treatment policy strategy**, same as for the MG-C secondary analysis	Difference in mean change from Baseline (LSMD from MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score for study participants receiving rozanolixizumab versus placebo.
Sensitivity	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	**Hypothetical & treatment policy strategy**, same as for the MG-C sensitivity analysis	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score for study participants receiving rozanolixizumab versus placebo, using the RS. A J2R multiple imputation approach will be utilised, same as the MG-C sensitivity analysis

Statistical Category	Endpoint	Intercurrent Event Strategy	Population Level Summary
Supplemental	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	**Composite strategy**, same as for the MG-C supplemental analysis	Difference in mean change from Baseline (LSMD from ANCOVA) to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score for study participants receiving rozanolixizumab versus placebo. A trimmed mean approach will be used, as the MG-C supplemental analysis

Note: CfB=Change from Baseline; LSMD=Least Squares Mean Difference; MMRM=mixed model for repeated measures; ANCOVA= analysis of covariance; MAR=Missing at Random

8.3.1 MG-ADL Responder Rate at Visit 10 (Day 43)

See Section 8.2.1 for the derivation of MG-ADL total score.

Study participants will be classified as responders at Visit 10 if the value is at least a 2-point improvement (decrease) from Baseline at Visit 10 (Day 43).

Analysis will be based on the RS under the composite strategy (see details in Section 8.1). Any missing data scores (including missing data due to the intercurrent events) will also be imputed as non-responders. Note that this endpoint is not part of the formal secondary endpoint testing strategy.

The number and percentage of study participants who are MG-ADL responders at Day 43 will be presented by treatment group and RLZ total for each stage. The odds ratio of the responder rates at Day 43 will be estimated and tested between treatment groups (each rozanolixizumab dose vs placebo) for each stage separately using logistic regression model with factors of treatment group, Baseline MG-ADL score and stratification factors (MuSK+/- and AChR+/-). The odds ratio with associated 95% CI and p-value based on the Wald test will be presented. Region may be added as an additional factor in the logistic regression model if significant in the primary analysis.

The odds ratios, 95% CIs, and p-values from each stage will be combined using the same inverse normal method used in the primary efficacy endpoint.

8.3.2 Change from Baseline to Day 43 (Visit 10) in MG-C score

The complete list of MG-C items and scores are provided in Table 13–2. The total score will be calculated according to the rules set down in Section 13.2. This total score will be used to calculate change from Baseline, in summaries and for efficacy analysis.

The following analyses will be performed:

- Secondary: The same approach as specified in Section 8.2.2 will be implemented.
- Sensitivity: The same approach as Section 8.2.3.2 will be applied.
- Supplemental: The same approach as Section 8.2.4.1 will be applied. The worst MG-C total score is 50.

- Additional: The same approach as Section 8.2.5 will be applied.
- Exploratory: The same approach as Section 8.2.6 will be applied.

8.3.3 Change from Baseline to Day 43 (Visit 10) in QMC score

The complete list of QMG items and scores are provided in Table 13–1. Partially missing total scores will be imputed according to the rules set down in Section 13.1. This total score after single item imputation will be used to calculate change from Baseline, in summaries and for efficacy analysis.

The following analyses will be performed:

- Secondary: The same approach as specified in Section 8.2.2 will be implemented.
- Sensitivity: The same approach as Section 8.2.3.2 will be applied.
- Supplemental: The same approach as Section 8.2.4.1 will be applied. The worst QMG total score is 39.
- Additional: The same approach as Section 8.2.5 will be applied.
- Exploratory: The same approach as Section 8.2.6 will be applied.

8.3.4 Change from Baseline in PRO Muscle Weakness Fatigability score

The PRO Muscle Weakness Fatigability score is based on the MG symptoms PRO instrument items 34-42. See Section 13.4 for the complete list of MG symptoms PRO items and scoring details.

The following analyses will be performed:

- Secondary: The same approach as specified in Section 8.2.2 will be implemented.
- Sensitivity: The same approach as Section 8.2.3.2 will be applied.
- Supplemental: The same approach as Section 8.2.4.1 will be applied. The worst PRO Muscle Weakness Fatigability score is 100.
- Additional: The same approach as Section 8.2.5 will be applied.
- Exploratory: The same approach as Section 8.2.6 will be applied.

8.3.5 Change from Baseline in PRO Physical Fatigue score

The PRO Physical Fatigue score is based on the MG symptoms PRO instrument items 19-33.

The same stage-wise MMRM model and analysis approach as specified in Section 8.2.2 will be implemented to test for superiority.

The following analyses will be performed:

- Secondary: The same approach as specified in Section 8.2.2 will be implemented.
- Sensitivity: The same approach as Section 8.2.3.2 will be applied.
- Supplemental: The same approach as Section 8.2.4.1 will be applied. The worst PRO Physical Fatigue score is 100.

- Additional: The same approach as Section 8.2.5 will be applied.
- Exploratory: The same approach as Section 8.2.6 will be applied.

8.3.6 Change from Baseline in PRO Bulbar Symptoms score

The PRO Bulbar Symptoms score is based on the MG symptoms PRO instrument items 6-15.

The following analyses will be performed:

- Secondary: The same approach as specified in Section 8.2.2 will be implemented.
- Sensitivity: The same approach as Section 8.2.3.2 will be applied.
- Supplemental: The same approach as Section 8.2.4.1 will be applied. The worst PRO Bulbar Symptoms score is 100.
- Additional: The same approach as Section 8.2.5 will be applied.
- Exploratory: The same approach as Section 8.2.6 will be applied.

8.4 Analysis of other efficacy endpoints

All other efficacy variables will be summarized overall using descriptive statistics, unless specified otherwise. No stage-wise summary will be performed, except for time to MG-ADL response. Missing data will be handled as described in Section 4.2.1.

8.4.1 Use of rescue therapy due to worsening (IVIg, PEX)

The use of rescue therapy will be identified by a 'yes' response to the "Rescue Medication?" question on the concomitant medication CRF, or plasma exchange as collected on concomitant medical procedure CRF".

The number of study participants in each treatment group that use rescue therapy due to worsening (IVIg, PEX) will be summarized by treatment group and RLZ total.

The nominal p-value (calculated using a Pearson's Chi-Squared test for independence) will be presented for the difference between each rozanolixizumab dose and placebo in the percent of study participants using rescue therapy at a 2-sided 0.05 alpha level.

8.4.2 Time to first rescue therapy

Time to first rescue therapy (in days) is defined as: Date of first rescue therapy use–- Date of first IMP + 1.

Time to first rescue therapy will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Study participants who do not take rescue therapy will be censored at the date of withdrawal/study completion. Where there are several AEs which led to drop out, consider the earliest starting AE.

The number of study participants with first rescue therapy and number of censored study participants up to 8, 12, 24, 32, 43, 57, 71, 85, 99 days will be summarized using descriptive statistics.

The median time to first rescue therapy, including the two-sided 95% CI, will be calculated for each treatment.

8.4.3 Time to MG-ADL response (≥2.0 points improvement from Baseline)

Time to MG-ADL response (in days) is defined as Date of First MG-ADL Response–- Date of MG-ADL Baseline + 1.

Study participants who use rescue therapy prior to Day 43 or who are withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response will be censored at time of event. Study participants who never achieve a response by Day 43 will be censored at the date of their last MG-ADL assessment.

The number of study participants with 8, 12, 24, 32, 43 days to first MG-ADL response and number of censored study participants will be summarized descriptively.

Time to first MG-ADL response will be analyzed using a Cox Proportional Hazards model including fixed terms for treatment and stratification factors (MuSK+/- or AChR+/-). This model will be performed separately for study participants included in the interim analysis and for all study participants overall. Region may be added as an additional factor in the Cox Proportional Hazards model if it is significant in the primary analysis.

The Hazard Ratio (test/reference), 95% CI and p-values for each treatment comparison of interest will be presented for the Stage 1 (interim analysis), Stage 2 and overall (all data combined).

The log-hazard ratio, standard error estimates and (1-sided) p-values from the separate stage-wise Cox Proportional Hazards models for the relevant treatment group will be used to create overall p-values and repeated confidence intervals using the same methodology as the primary efficacy analysis.

The time to first MG-ADL response will be presented graphically using a Kaplan-Meier curve by treatment group, RLZ total. See details in Section 9.3.2 .

8.4.4 QMG score

The QMG scores and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics. The subgroup summaries will also be performed by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3.

The QMG score (excluding ocular items) change from Baseline will be calculated the same as the change from Baseline in the QMG score. The QMG scores (excluding ocular items) and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics.

Above QMG summaries will be repeated for COVID-19 free participants, where COVID-19 free participants exclude:

- Participants who discontinue treatment due to suspected/confirmed COVID-19 infection (“Confirmed COVID-19” or “Suspected COVID-19” as the relationship to COVID-19 in the COVID-19 Impact eCRF);
- Participants who discontinue treatment due to non-infection related COVID-19 issues (“General circumstances around COVID-19 without infection” or “other” as the relationship to COVID-19 in the COVID-19 Impact eCRF);

- Participants have visits affected in treatment period (e.g. visit performed by video call) due to COVID-19.

A boxplot of change from Baseline at Day 43 and a time plot of mean change and percentage change from Baseline for QMG will also be plotted by the following dose groups: placebo, [redacted].

By-participant listings of QMG scores will be provided.

8.4.5 QMG responder rate (≥3.0 points improvement from Baseline)

Study participants will be classified as responders at a visit if the value is at least a 3-point improvement (decrease) from Baseline. Missing data will be imputed using NRI per Section 4.2.1.

The number and percentage of observed and imputed responders will be summarized separately by treatment group, RLZ total and visit. In addition, QMG responders will be summarized by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3. Same summaries will be repeated for COVID-19 free participants as defined in Section 8.4.4.

8.4.6 MG-C score

The total scores and total score (excluding ocular items) with associated change from Baseline will be summarized by treatment group and RLZ total at scheduled visit using descriptive statistics. The subgroup summaries will also be performed by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3. Same summaries will be repeated for COVID-19 free participants as defined in Section 8.4.4.

A boxplot of change from Baseline at Day 43 and a time plot of mean change and percentage change from Baseline for MG-C will also be plotted by the following dose groups: placebo, [redacted].

By-participant listings of MG-C scores will be provided.

8.4.7 MG-C responder rate (≥3.0 points improvement from Baseline)

Participants will be classified as responders at a visit if the value is at least a 3-point improvement (decrease) from Baseline (Burns, Ted M et al [2010]). Missing data will be imputed using NRI per Section 4.2.1.

The number and percentage of observed and imputed responders will be summarized separately by treatment group, RLZ total and visit. In addition, MG-C responders will be summarized by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3. Same summaries will be repeated for COVID-19 free participants as defined in Section 8.4.4.

8.4.8 MG-ADL score

See Section 8.2.1 for the derivation of MG-ADL total score.

The MG-ADL scores and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics. The subgroup summaries will also be performed by

subgroups in Section 4.9.1 and by administered dose for each weight subgroup as specified in Section 4.9.3.

The MG-ADL score (excluding ocular items) change from Baseline will be calculated the same as the change from Baseline in the MG-ADL score. The MG-ADL scores (excluding ocular items) and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics.

The mean change from Baseline with 95% CI in MG-ADL total score over time with cumulative ADA or NAb status will be plotted by treatment group and RLZ total. See details in Section **Error! Reference source not found.**.

A boxplot of change from Baseline at Day 43 and a time plot of mean change and percentage change from Baseline for MG-ADL will also be plotted by the following dose groups: placebo, [redacted].

The study participants with missing MG-ADL assessment and associated reasons at each scheduled visit will be summarized by treatment group and RLZ total. Same summaries will be repeated for COVID-19 free participants as defined in Section 8.4.4.

By-participant listings of MG-ADL values will be provided.

8.4.9 MG-ADL responder rate (≥2.0 points improvement from Baseline)

Derivation of the responder is detailed in Section 8.3.1.

The number and percentage of observed and imputed responders will be summarized separately by treatment group, RLZ total and visit. In addition, MG-ADL responders will be summarized by subgroups in Section 4.9.1 and by administered dose for each weight subgroup as specified in Section 4.9.3. Same summaries will be repeated for COVID-19 free participants as defined in Section 8.4.4.

8.4.10 MG Symptoms PRO 'Physical Fatigue' score

See Section 8.3.5 for the derivation of MG Symptoms PRO 'Physical Fatigue' score.

The PRO Physical Fatigue scores and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics. The subgroup summaries will also be performed by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3.

In addition, empirical cumulative distribution functions of the change in score from Baseline to Day 43 will be plotted by treatment group and RLZ total.

By-participant listings of all MG Symptoms PRO values will be provided.

8.4.11 MG Symptoms PRO 'Muscle Weakness Fatigability'

See Section 8.3.4 for the derivation of MG Symptoms PRO 'Muscle Weakness Fatigability' score.

The PRO Muscle Weakness Fatigability scores and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics. The subgroup summaries will also be performed by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3.

In addition, empirical cumulative distribution functions of the change in score from Baseline to Day 43 will be plotted by treatment group and RLZ total.

8.4.12 MG Symptoms PRO 'Bulbar Symptoms'

See Section 8.3.6 for the derivation of MG Symptoms PRO 'Bulbar Symptoms' score.

The PRO Bulbar Symptoms scores and change from Baseline will be summarized by treatment group, RLZ total and visit using descriptive statistics. The subgroup summaries will also be performed by MG-specific autoantibody (MuSK+ or AChR+) and by administered dose for each weight subgroup as specified in Section 4.9.1 and Section 4.9.3.

In addition, empirical cumulative distribution functions of the change in score from Baseline to Day 43 will be plotted by treatment group and RLZ total.

8.4.13 Patient Global Impressions of Severity

A frequency table will be produced to summarize answers provided to the PGI-S ("none," "mild," "moderate," "severe," "very severe,") for each visit by treatment group and RLZ total.

A by-participant listing of PGI-S will be provided.

8.4.14 Patient Global Impressions of Change

A frequency table will be produced to summarize answers provided to the PGI-C ("very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse") for each visit by treatment group and RLZ total.

A by-participant listing of PGI-C will be provided.

8.4.15 MGII overall scores, ocular sub-scores, and generalized domain scores

The complete list of MGII items and scores are provided in Table 13-8. The total score will be calculated according to the rules set down in Section 13.5.

Summary statistics of the actual values and change from Baseline values will be used to summarize the MGII overall score and sub-scores separately by treatment group and RLZ total for each visit during Treatment period.

A by-participant listing of MGII scores will be provided.

8.4.16 MG-QOL15r

The total score is calculated by summing all the individual items. See Section 13.6 for scoring details.

Summary statistics of the actual values and change from Baseline values will be used to summarize MG-QOL15r scores by treatment group and RLZ total for each visit.

A by-participant listing of MG-QOL15r scores will be provided.

8.4.17 EQ-5D-5L

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

A frequency table will be produced to summarize answers provided to each of the 5 dimensions of the EQ-5D descriptive system at each scheduled visit by treatment group. The observed values of EQ VAS scores and change from Baseline will be summarized by treatment group and RLZ total at each scheduled visit. No imputation will be applied on missing item in EQ-5D descriptive system and EQ VAS.

A by-participant listings of EQ-5D-5L will be provided.

8.4.18 Minimal symptom expression

Minimum Symptom Expression (MSE) is designed to assess how many study participants become free or virtually free of MG symptoms as measured by achieving an MG-ADL total score of 0 or 1 (Vissing et al. 2020). See Section 8.2.1 for the derivation of MG-ADL total score.

The number and percentage of study participants achieving MSE at any time during the treatment and observation phases will be summarized by treatment group and RLZ total.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

All analyses described in Section 9.1 will be performed on the PK-PPS, and all other analysis will be performed on Safety Set.

9.1 Pharmacokinetics

Individual plasma concentrations of rozanolixizumab will be summarized by treatment group and overall for administered RLZ dose and RLZ total and scheduled sampling day for the PK-PPS using n, arithmetic mean, median, SD, minimum, maximum, geometric mean (geomean) with associated 95% CI, and geometric coefficient of variation (geoCV) (assuming log-normally distributed data).

A scatter plot of combined individual concentration versus time profiles will be presented in linear scale by treatment group with all study participants overlaid on the same plot, including day 3, 6, 24, 38, 41. The same plot will also be presented by administered RLZ dose ([redacted]) and RLZ total.

Furthermore, a plot time course plot of geometric mean concentrations by administered RLZ dose will be presented by treatment group and RLZ total. See details in Section 4.9.3.

All figures will include the lower limit of quantification (LLOQ) on the semi-logarithmic plots.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as below the limit of quantification (BLQ)
- Descriptive statistics of concentrations will be calculated if at most 1/3 of the individual data points at a timepoint are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance. If more than 1/3 of the individual data points at a timepoint are missing or are not quantifiable, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank.
- If n<3, then only the n, minimum and maximum will be presented. If no study participants have data at a given timepoint, then only n=0 will be presented.

- The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geoCV) is 0

  The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data $\text{geoCV}(\%) = \sqrt{\exp(\text{SD}^2) - 1} \times 100$.

Individual concentrations of rozanolixizumab will be listed by treatment group and RLZ total for the PK-PPS and will include the actual sampling time in days relative to the previous dose, the IgG observed at the same visit, the ADA titer observed for the binding assay and the NAb titer for the same visit, and change from Baseline in total IgG and IgG subclasses for the corresponding visit.

9.2 Pharmacodynamics

9.2.1 MG-specific autoantibodies

MG-specific autoantibodies (anti-MuSK/anti-AChR) Baseline values will be based on the last available assessment value prior to first IMP (excluding historical data collected on CRF since the assays were not from the same vendor as specified in this study).

MG-specific autoantibodies (anti-MuSK/anti-AChR) will be summarized by treatment group and RLZ total at scheduled visit for observed values, absolute and percentage changes from Baseline. Additional summary of absolute and percentage changes from Baseline in MG-specific autoantibodies (anti-MuSK/anti-AChR) will be performed by weight subgroup and total for administered dose and RLZ total at scheduled visit (reference Section 4.9.3). The maximum decrease from Baseline in MG-specific autoantibodies (change and percentage change) will be reported in the listing and summarized for each treatment.

Mean and mean percentage change from Baseline values in MG-Specific autoantibodies will be plotted over time by treatment, RLZ total and period with all treatments overlaid on the same plot and the plot will be repeated for the following dose groups: placebo, [redacted].

Mean percent change from baseline of anti-MuSK and Total IgG, and mean change from baseline of MG-ADL, QMG, MG-C will be plotted over time by treatment and RLZ total for only participants who are anti-MuSK positive at baseline; Additionally, data from individual study participant will be plotted representing percentage change from Baseline in anti-MuSK and Total IgG, and MG-ADL, QMG, MG-C change from Baseline for only participants who are anti-MuSK positive at baseline. The same plots will be repeated for percentage change from Baseline values in anti-AChR for only participants who are anti-AChR positive at baseline.

A boxplot of maximum percentage change from Baseline for MG-specific autoantibodies will be plotted by the following dose groups: placebo, [redacted].

MG-specific autoantibodies will be listed, together with total IgG, IgG subclasses, MG-ADL, QMG, MG-C change from Baseline.

The correlation between screening and Baseline assay (positive, negative) will be presented based on the Pearson correlation test.

9.2.2 Total serum IgG and IgG subclasses

Total serum IgG concentrations and IgG subclasses will be summarized by treatment group, RLZ total and time point for observed values, change from Baseline, and percentage change from Baseline. Additional summary of absolute and percentage changes from Baseline in total IgG will be performed by weight subgroup and total for administered dose and RLZ total at scheduled visit (reference section 4.9).

The maximum change and percent change from Baseline in total serum IgG and IgG subclasses will be reported in the listing and summarized for each treatment. In the event that a decrease from Baseline in total serum IgG or IgG subclass is not observed in a given study participant, the maximum change will be reported as the smallest increase from Baseline.

Mean change and percent change from Baseline values in total serum IgG will be plotted over time by treatment and RLZ total with all treatments overlaid on the same plot, and the plot will be repeated by the following dose groups: placebo, [redacted] .

Spaghetti plots will be provided for total IgG and percentage change from baseline in total IgG over time stratified by treatment group, RLZ total and Baseline bodyweight group (<50kg, 50kg-<70 kg, 70-<100kg, ≥100kg) where the Baseline bodyweight group is multipaneled or overlaying with different colors within each treatment group.

For correlation analysis between clinical endpoints and PD data, scatterplots including regression lines and correlation coefficients will be provided for:

- Maximum change from baseline through to and including day 43 in total IgG versus change from baseline at day 43 in MG-ADL, QMG, and MG-C scores;
- Maximum percent change from baseline through to and including day 43 in total IgG versus change from baseline to day 43 in MG-ADL, QMG, and MG-C scores;
- Minimum total IgG through to and including day 43 versus change from baseline to day 43 in MG-ADL, QMG, and MG-C scores.

A boxplot of maximum percentage change from Baseline for total IgG will also be plotted by the following dose groups: placebo, [redacted] .

Serum concentration of change from Baseline in total IgG and IgG subclass will be listed together with concentrations of rozanolixizumab , ADA status and MG-ADL change from Baseline, as specified in Section 9.3.2. In addition, it will be listed with IgG subclasses and MG-specific autoantibodies as described in Section 9.2.1.

9.3 Anti-drug antibody status

Evaluation of rozanolixizumab immunogenicity will be performed using data from all evaluable study participants in the SS, defined as all study participants treated with rozanolixizumab who have an evaluable pretreatment (baseline) sample (negative or positive ADA sample status), and at least 1 evaluable post-baseline value.

Study participants with an evaluable pretreatment (baseline) sample but without a single evaluable sample taken post-baseline will be included in the reporting of pre-existing ADA but excluded from all other immunogenicity analyses.

The ADA of rozanolixizumab will be measured using a three-tiered assay approach: screening assay, confirmatory assay and titration assay. Any sample confirmed positive for ADA will be assayed to determine whether there is neutralizing potential. Samples that are neutralizing antibody (NAb) positive will be evaluated in a titration assay to quantify the NAb level and will be reported as titer. Samples from study participants on placebo will not be tested for anti-drug antibodies.

9.3.1 ADA Data Consideration

ADA Sample Status

The ADA sample status will be determined for each pre-treatment (Baseline) and post-treatment (post-Baseline) visit where samples are taken for ADA analysis.

- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative** if corresponding rozanolixizumab concentrations are equal or below the validated drug tolerance limit of the ADA assay (200µg/mL rozanolixizumab) allowing detection of 100ng/mL ADA
- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immune-depletion', but with corresponding rozanolixizumab concentrations above the validated drug tolerance limit of the ADA assay, will be defined as **ADA inconclusive**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**
- Samples that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc., will be defined as **Missing**.

NAb sample status (positive/negative/missing) will be determined for ADA positive samples.

ADA Baseline

By default, the Day 1 will be the Baseline value if the ADA sample status at screening is ADA negative or missing. If the ADA sample status at screening is ADA positive and ADA status at Day 1 is ADA negative or missing, the screening will be the Baseline value. If the ADA sample status at screening and Day 1 are the same, Day 1 will be the Baseline value.

ADA /NAb Participant Status

The ADA participant status will be classified on study participant and group level as outlined below (Shankar et al. 2014; Rup et al, 2015). A description of how study participants will be categorized for the immunogenicity assessment is provided in Table 9–1.

Individual study participants will be assessed for ADA participant status, composed of 6 categories: ADA negative, inconclusive, and ADA positive, whereby a positive participant's status is determined as originating from a treatment-induced, boosted, reduced or unaffected ADA response.

Study participants who are identified as being treatment-induced or treatment-boosted ADA-positive will be grouped as treatment-emergent (TE)-ADA positive participants. Study participants who are identified as being treatment-reduced or treatment-unaffected ADA-positive will be grouped as non-TE-ADA positive participants. Both TE-ADA positive and non-TE–ADA positive participants will be further classified as NAb negative or NAb positive.

The individual and combined ADA participant categories will be summarized through the end of the 8-week observation week (Day 99), unless specified otherwise.

Table 9–1: Terms and Definitions for ADA Evaluation in Study Participants

Classification	Classification Label	Definition
Individual participant categories		
1	Pre-ADA negative – treatment induced ADA negative (ADA-NEG)	Study participants who have an ADA negative sample at Baseline and all sampling points post-Baseline up to the timepoint of interest.
2	Inconclusive	Study participants who have an ADA positive or negative Baseline sample and some post-Baseline samples are missing or inconclusive, while other post-Baseline samples are ADA negative up to the timepoint of interest.
3	Pre-ADA negative – treatment induced ADA positive (TI-POS)	Study participants who have an ADA negative sample at Baseline and have least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest.
4	Pre-ADA positive – treatment boosted ADA positive (TB-POS)	Study participants who have an ADA positive sample at Baseline and at least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest, with increased titer values compared to Baseline (greater than a predefined fold difference increase from Baseline value which will be defined within the validation of the assay i.e. MSR of the assay[a]).
5	Pre-ADA positive – treatment reduced ADA positive (TR-POS)	Study participants with an ADA positive sample at Baseline, and ADA negative samples at all sampling points post-Baseline up to the timepoint of interest.
6	Pre-ADA positive – treatment unaffected ADA positive (TU-POS)	Study participants with an ADA positive at Baseline and an ADA positive sample at any sampling point post-Baseline up to timepoint of interest with titer values of the same magnitude as Baseline (less than a predefined fold difference from the Baseline value which will be defined within the validation of the assay, i.e. MSR of the assay[a]).
Combined participant categories		

7	Treatment emergent ADA positive (TE-POS)	Includes study participants who are treatment induced ADA positive (category 3) or treatment boosted ADA positive (category 4).
8	Non-treatment emergent ADA positive (Non-TE-POS)	Includes study participants who are treatment reduced ADA positive (category 5) or treatment unaffected ADA positive (category 6).
9	Treatment emergent ADA positive – NAb positive (TE-POS, Nab-POS)	Includes study participants who are treatment emergent positive (category 7) and have at least one NAb positive sample
10	Treatment emergent ADA positive – NAb negative (TE-POS, Nab-NEG)	Includes study participants who are treatment emergent positive (category 7) and have no NAb positive samples
11	Non-treatment emergent ADA positive–- NAb positive (Non-TE-POS, NAb-POS)	Includes study participants who are non-treatment emergent positive (category 8) and have at least one NAb positive sample
12	Non-treatment emergent ADA positive–- NAb negative (Non-TE-POS, NAb-NEG)	Includes study participants who are non-treatment emergent positive (category 8) and have no NAb positive samples

[a] The fold difference increase from baseline value, i.e. the minimum significant ratio (MSR) determined during assay validation, will be reported in the relevant tables, listings and figures. It reflects the fold difference in titer level that considered higher than the assay variation in titer determination

9.3.2 ADA summaries

The following outputs will be presented on the SS.

Tables:

- Number and percentage of study participants with positive, negative, inconclusive or missing ADA sample status at the time of each visit will be summarized by treatment group and RLZ total. Denominator is the number of study participants having a non-missing result at that visit. The same table will be repeated for NAb sample status (positive, negative, missing).
- Number and percentage of study participants in each of the individual and combined ADA participant status categories presented in **Error! Reference source not found.**will be summarized by treatment group and RLZ total.
- Total prevalence of pre-existing ADA and NAb, defined as number and percentage of participants having an ADA positive sample status at baseline, with the denominator being the total number of study participants having an evaluable sample result at Baseline. Missing samples will not be included in the denominator. The same will be repeated for NAb.
- The first occurrence of treatment-emergent ADA positivity: cumulative number and percentage of TE-ADA positive participants (category 7) who are ADA positive for the first time at each visit.
- Summary table of mean maximum percentage CFB in total IgG and mean CFB in MG-ADL total score at Day 43, summarized by ADA participant categories 1, 2, 9, 10, 11 and 12 for the corresponding time period of interest (up to Day 43) and by treatment group and RLZ total.

- Overall summary table of TEAEs within each of the ADA participant categories 1, 2, 7 and 8.
- Summary table of incidence of TEAEs by ADA participant category 1, 2, 7 and 8.
- Summary table of AEOF hypersensitivity reactions, anaphylactic reactions and infusion reactions by ADA participant category 1, 2, 7 and 8.

Figures:

- Individual time course plots for study participants with at least one ADA positive sample, representing ADA and NAb titers (on log-scale), rozanolixizumab plasma concentrations, percentage CFB for total IgG and MG-specific autoantibodies, and CFB for MG-ADL total score. The sub-title of the graph will include the study participant number, bodyweight category, treatment group, ADA participant category (2, 3,4,5,6). The dosing will be represented in the x axis with bars/arrows at the time of dose.
- Spaghetti plots of individual time course of ADA titer for ADA positive participants in categories 9, 10, 11 and 12, whereby all categories are overlaid on the same plot and visualized using different symbols and colors. The ADA titer results will be presented on a log-scale. Dosing time points should be indicated below the x-axis. The same plot will be repeated for NAb titer for NAb positive participants in categories 9 and 11.
- A box-and-whisker plot of maximum post-dose ADA titer (on log-scale) through the end of the observation period versus ADA participant category for categories 9, 10, 11 and 12. The same plot will be repeated for NAb titer for ADA participant categories 9 and 11.
- Scatter dot plot of individual rozanolixizumab post-dose plasma concentrations categorized by Day (i.e. Days 3, 6, 24, 38, 41) and for each Day by ADA participant categories 1, 2, 9, 10, 11 and 12. Individual samples that tested positive for ADA will be visualized using a symbol and/or color.
- Time course plot of mean change from Baseline in MG-ADL total, summarized by ADA participant category 1, 2, 7, and 8. Categories will be determined for the time period from baseline up to Day 43. Separate plots for each treatment group and RLZ total. The sample plot will be repeated for NAb related categories 9, 10, 11, 12.
- Spaghetti plots of individual time course of percentage CFB for total IgG, for each of the ADA participant categories 1, 2, 9, 10, 11 and 12, whereby the ADA participant categories are multipaneled. Separate plots for each treatment group and RLZ total ([redacted] combined). Individual samples that tested positive for ADA will be visualized using a symbol and/or color. Dosing time points should be indicated below the x-axis.
- Scatter dot plot of individual CFB in MG-ADL total score categorized by ADA titer tertile (including category ADA not present) over time. The same plot will be repeated for NAb titer.
- Scatter dot plot of individual percentage CFB for total IgG categorized by ADA titer tertile (including category ADA not present) over time. The same plot will be repeated for NAb titer.

Listings:

- By-subject listing by treatment group, individual ADA participant category, screening and confirmatory assay results, ADA titer, fold change compared to baseline, and whether or not sample contains RLZ concentration above drug tolerance. In addition, the time since administration of IMP will be reported (in days).
- By-subject listing by treatment group, administered RLZ dose and timepoint, of ADA and NAb sample status, ADA titer, NAb titer, rozanolixizumab plasma concentration, CFB for total IgG, CFB for MG-specific autoantibodies, CFB for MG-ADL total score, QMG and MG-C, and individual ADA participant classifications. In addition, the time since administration of IMP will be reported (in days).
- By-subject listing of abovementioned TEAEs, the time of onset, the ADA and NAb sample status and ADA and NAb titers at the closest sampling time point prior to and subsequent to the TEAE, and time since last administration of IMP (in days).

9.4 Immunology

All analyses described in this section will be based on the SS.

9.4.1 Serum complement levels and plasma complement levels

Serum (C3 and C4) and plasma (C3a and C5a) complement variables will be listed by treatment group and RLZ total, visit and time point including changes from Baseline. Descriptive summaries will be presented for both absolute values and changes from Baseline for all study participants, and separately for study participants who experience an infusion reaction or hypersensitivity reaction or anaphylactic reaction. The selection criteria of infusion reaction or hypersensitivity reaction are described in Section 13.8.

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change from Baseline. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper limit of quantification.
Serum (C3 and C4) and plasma (C3a and C5a) complements results will be listed.

9.4.2 Serum cytokines

Serum cytokines will be summarized by treatment group and RLZ total, visit and time point for both absolute values and changes from Baseline, for all study participants, and separately for study participants experiencing with serious or severe headache and/or infusion reactions or hypersensitivity reaction. The selection criteria of those events are described in Section 13.8.

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change from Baseline. Measurements ALQ, if applicable, will be imputed to the upper limit of quantification.

Cytokines results will be listed.

9.4.3 Serum immunoglobulin concentrations

Immunoglobulins (IgE, IgA and IgM) will be summarized by treatment group, RLZ total and visit for absolute values, change from Baseline, and percent change from Baseline.

Individual figures over time (absolute value) will be presented by study participant, with all variables overlaid on the same plot and separate plots each study participant.

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change from Baseline. Measurements ALQ, if applicable, will be imputed to the upper limit of quantification.

Immunoglobulins (IgE, IgA, and IgM) will be listed.

9.4.4 Anti-tetanus toxoid serum titers

Anti-tetanus toxoid serum titers will be summarized by treatment group, RLZ total and visit for both absolute values, change from Baseline, and percent change from Baseline.
The geometric mean change from Baseline with 95% CI in anti-tetanus toxoid serum titers versus time at each scheduled timepoint will be plotted by treatment group excluding all participants with undetectable Baseline titers. IgG values will be overlaid on the same plot.

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change from Baseline. Measurements, if applicable, will be imputed to the upper limit of quantification.

Anti-tetanus toxoid serum titers will be listed.

10 SAFETY ANALYSES

All safety analyses will be presented using the SS. Listings will be presented by treatment group and study participant; tabulations will be presented by treatment group and RLZ total.

Unless otherwise specified, safety analyses will be presented by treatment group as defined in Section 3.6.

10.1 Extent of exposure

The number of weeks on IMP will be summarized by treatment group and RLZ total. The number of days on IMP will be calculated as follows:

$$\text{Number of weeks on IMP} = \frac{[(\text{Date of Last Dose Received}) - (\text{Date of First Dose Received}) + 1]}{7}$$

The total number of infusions will be summarized using descriptive statistics by treatment group and RLZ total. Categorical summaries of the number of infusions (1-6) will also be summarized.

The summaries above will be repeated excluding the mock infusions.

All drug administration details will be listed.

10.2 Adverse events

10.2.1 Data considerations

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 3.8).

In addition, AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 or later for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild,

moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described below:

- Grade 1–- Mild
- Grade 2–- Moderate
- Grade 3, 4, 5–- Severe

These will be tabulated together with the AEs that were not classified according to CTCAE criteria i.e., all Grade 1 AEs as per CTCAE criteria will be included in the 'mild' category together with those AEs classified as mild as per the 'standard' intensity classification. In the case a mapped standard intensity classification per above rule is different from the standard intensity classification on CRF, the worst case will be used as the standard intensity classification (i.e. an AE with Grade 1 and moderate as intensity classification will be classified into moderate).

A TEAE is defined as an AE starting on or after the time of first administration of IMP up to and including 8 weeks (56 days) after the final dose. Adverse events starting before the date of the first administration of IMP or after 8 weeks following the final dose of IMP will not be considered TEAEs. Thus AEs before first dosing and AEs after 8 weeks following the final dose will be combined in one category. Such events will be listed only.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless evidence exists that does not allow the AE to be treatment-emergent. Handling of missing dates for classification of AEs as TEAEs is described in Section 4.2.2.

The following rules will be used to assign a TEAE to a study period:

- **Treatment Period:** a TEAE will be assigned to the Treatment Period for the tabulations if the start date of the event is on or after the date of the first administration of IMP on Day 1, up to 7 days following the final dose of IMP
- **Observation Period:** a TEAE will be assigned to the Observation Period for the tabulations if the start date of the event is greater than 7 days after the date of the final dose of IMP until 8 weeks following the final dose; events starting later than 8 weeks following the final dose of IMP are not considered TEAEs

In the case of early withdrawal in the Treatment Period, a TEAE will be assigned to the Treatment Period based on the last received IMP plus 168 hours (7 days). Subsequent TEAEs (up to 8 weeks post-last dose) will be assigned to the Observation Period.

A TEAE will be counted as a TEAE related to IMP if the response to the question "Relationship to Study Medication" is "Related". Severe TEAEs are those with CTCAE Grade 3 or above, or those without a CTCAE grading classified as 'severe' by the Investigator.

Es will be presented as "number of study participants (percentage of study participants) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual study participants, while "number of study participants" will count each study participant only once.

10.2.2 AE summaries

Summary tables with the number, percentage of study participants and frequency of TEAEs will be provided by treatment group and RLZ total. Additional details are as follows:

1. Overview of TEAEs will include following categories: any TEAEs, serious TEAEs, participant discontinuation due to TEAEs, permanent withdrawal of IMP due to TEAEs, temporary withdrawal of IMP due to TEAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to death, all deaths (AEs leading to death).
2. Incidence of TEAEs will be summarized by SOC, HLT and PT for:
   - Any TEAEs
   - TEAEs during Treatment Period
   - Severe TEAEs
   - Any TEAEs by maximum intensity (mild, moderate and severe)
   - Any TEAEs by relationship
   - Any TEAEs relative to ADA status
   - Any TEAE by Risk Difference ≥5% (by decreasing frequency of Risk Difference)
   - Non-serious TEAEs above reporting threshold of 5% of study participants
   - Fatal TEAEs
   - Fatal TEAEs by relationship
   - Serious TEAEs
   - Serious TEAEs by relationship
   - Participant discontinuation due to TEAEs
   - TEAEs leading to permanent withdrawal of IMP
   - TEAEs leading to temporary withdrawal of IMP
   - Treatment-emergent AESM
   - Treatment-emergent AESI
3. Incidence of TEAEs will be summarized by PT for:
   - Any TEAEs by decreasing frequency of PT

AESMs include severe headache, severe GI disorders (i.e., abdominal pain, diarrhea, vomiting), and opportunistic infection.

AESIs are the cases of potential Hy's Law (see Section 10.3.1).

AESMs and AESIs will be identified based on the assessment by the Investigator as recorded in the CRF. An AE will be counted as an AESM if there is a 'yes' response to the question "Adverse event of Special Monitoring?" and 'no' otherwise. An AE will be counted as an AESI

if there is a 'yes' response to the question "Adverse Event of Special Interest?" and 'no' otherwise.

When applicable adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing frequency of PT in the rozanolixizumab total column for tables.

Listings of all TEAEs, all non-serious TEAEs, serious TEAEs, permanent withdrawal of IMP due to AEs, study participant discontinuation from study due to AEs, AEs leading to death, AESIs, AESMs will be presented by treatment group and study participants.

10.2.3 Adverse Events of Focus

Rozanolixizumab treatment-emergent adverse events of Focus (TEAEOF) include the following categories:

- Headaches
- Gastrointestinal disturbances
- Hypersensitivity reactions
- Anaphylactic reactions
- Injection site reaction
- Infusion reaction
- Opportunistic infections
- Reductions in albumin and plasma proteins
- Effects on the kidney
- Drug related hepatic disorders

A by-subject listing of all treatment-emergent AEOF by category (as listed above) will be provided. The number and percentage of study participants who experience each treatment-emergent AEOF will be summarized by most recent dose level prior to onset of AEOFs and total Rozimab treatment group. The following summaries will be presented by SOC, HLT, and PT:

- Treatment-emergent AEOF
- Serious Treatment-emergent AEOFs
- Treatment-emergent AEOFs by relationship
- Treatment-emergent AEOFs by maximum intensity (mild, moderate and severe)
- Treatment-emergent AEOF hypersensitivity reactions, anaphylactic reactions and infusion reactions by ADA
- Treatment-emergent AEOF headache and GI disturbances in Treatment period by intensity
- Treatment-emergent AEOFs by Risk Difference (by decreasing frequency of Risk Difference)

Graphs for treatment-emergent AEOF headache by time of onset (relative to infusion), severity, causality and duration for each study participant will also be provided.

10.2.4 Safety analysis by weight subgroup and administered dose

To support the goal of a fixed dosing strategy for Rozanolixizumab, additional summary tables with the number, percentage of study participants and frequency of TEAEs (when applicable) will be provided by weight subgroup and administered dose and by SOC, HLT and PT for:

- Overview of TEAEs
- Incidence of TEAEs
- Incidence of Serious TEAEs
- Incidence of Severe TEAEs
- Incidence of AEOF of headache and GI disturbances
- Incidence of AEOF of headache and GI disturbances by maximum intensity (mild, moderate and severe)

10.3 Clinical laboratory evaluations

The following table (Table 10-1) lists safety laboratory assessments that are collected throughout the study:

Table 10-1: Clinical Laboratory Parameters

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine Estimated Glomerular	Sodium	Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic	Total Protein Albumin

Laboratory Assessments	Parameters			
	Filtration Rate (eGFR)[a]		Transaminase (SGPT)	
	Glucose (fasting state, preferred)	Calcium [b]	Alkaline phosphatase	C-reactive protein (CRP)
	Lactate dehydrogenase (LDH)	High-density lipoprotein (HDL) [c]	Total Cholesterol (TC)	Triglycerides (TRIG)
Routine Urinalysis	• Specific gravity • Albumin, albumin/creatinine, creatinine • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, hemoglobin by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[d] • PTT, INR, and HbA1c tests • Serology testing (for Hepatitis B, Hepatitis C, and HIV) All study-required laboratory assessments will be performed by a central laboratory. • The results of each test must be entered into the CRF.			

NOTES:

All study-required laboratory assessments will be performed by a central laboratory.

The results of each test must be entered into the CRF.

[a] eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula which is eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 [if female] * 1.159 [if black]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. If race is not captured, participant will be assumed not Black in the calculation.

[b] Corrected Calcium (mmol/L) =0.02 * (40 – Albumin (g/L)) + Calcium (mmol/L).

[c] Calculation of Low-density lipoprotein (LDL) will follow Friedewald equation, where LDL in mmol/L= TC - HDL - TRIG/2.22; LDL in mg/dL= LDL=TC-HDL-TRIG/5 (if all values are in mg/dL). This formula is applicable only if Triglycerides is less than or equal to 400 mg/dL (4.52 mmol/L).

[d] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Institutional Review Board (IRB)/ Independent Ethics Committee (IEC).

Chemistry, hematology and quantitative urinalysis (observed value, absolute change from Baseline) will be summarized in standard unit using descriptive statistics by treatment group and RLZ total at each scheduled visit.

The central data will be used for the summary tables. Measurements BLQ will be imputed with half of the lower limit of quantification LLOQ, and measurements ALQ will be imputed to the upper quantification limit for the purpose of quantitative summaries.

The number and percentage of study participants who meet each of the markedly abnormal (MA) criteria outlined in Section 13.7 will be summarized by treatment group at any visit (including unscheduled visit).

The laboratory variables that are categorized as normal, high or low based on the reference range supplied by the analytical laboratory will be presented in shift tables from Baseline to any post-Baseline visit (including unscheduled visit) by treatment group.

Mean values in albumin, C-reactive protein and White Blood Cell Count with absolute count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) plotted over time by treatment, RLZ total with all treatments overlaid on the same plot. Lipids including High-density Lipoprotein, Low-density lipoprotein, Total Cholesterol, Triglycerides will be plotted the same way if data are available.

All laboratory test results will be listed, including Baseline, scheduled and unscheduled visits with results in standard unit. Values outside the reference range for the continuous variables will be flagged in the listings. The reference ranges will also be reported in the listings. In addition, the listings will include a flag for values identified as MA. Additional lab test, including pregnancy testing, will also be listed.

10.3.1 Potential drug-induced liver injury

The number and percentage of study participants who meet one or more of the following potential drug-induced liver injury (pDILI) criteria will be summarized by treatment group and RLZ total:

- Participants with at least one post-Baseline liver laboratory assessment
- Incidence of potential hepatotoxicity with symptoms potentially associated with hepatitis or hypersensitivity
- Incidence of potential hepatotoxicity with no symptoms potentially associated with hepatitis or hypersensitivity
- Laboratory criteria for pDILI:
  - (AST or ALT > 3 x ULN) and TBL > 1.5 x ULN
  - (AST or ALT > 3 x ULN) and TBL > 2 x ULN
  - (AST or ALT > 3 x ULN) and TBL > 2 x ULN and ALP < 2 x ULN (Hy's Law)

In order to meet the above criteria, a study participant must experience the elevation in bilirubin and ALT or AST (and the absence of the ALP elevation) at the same visit. For example, a study participant who experiences a > 2x ULN elevation of bilirubin at one visit and a> 3x ULN

elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. If participant meets part of one criterion but at least one parameter is unknown, then he/she should not be considered for meeting the criterion.

Additional analyses for liver function tests (LFTs) will be performed to assess the potential for liver toxicities in accordance with the United States Food and Drug Administration guidelines. Per guidelines, the following criteria will be used to define levels of LFT elevation:

- Aspartate aminotransferase (AST): >3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
- Alanine aminotransferase (ALT): >3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
- AST or ALT: >3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN
- Total bilirubin (TBL): >1.5 x ULN, >2 x ULN
- Alkaline phosphatase (ALP) >1.5 x ULN

A listing will also be provided for study participants who meet at least one of the above criteria. All results obtained at that visit for the specified parameters will be displayed.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

Observed values and changes from Baseline will be summarized by vital signs variables (pulse rate, systolic and diastolic blood pressure, and temperature) and timepoint by treatment group.

The number and percentage of study participants who meet each of the MA criteria outlined in Section 13.7 will be summarized by treatment group and RLZ total at any visit (including unscheduled visit).

A by-participant listing of all vital sign measurements and change from Baseline will be presented by treatment group and timepoint. The listing will include a flag for values identified as MA.

Repeated and unscheduled measurements will be handled as described in Section 4.2.3.

10.4.2 Electrocardiograms

The following variables will be reported:

- Heart rate
- PR interval
- RR interval
- QRS duration
- QT interval
- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$)

Observed values and changes from Baseline will be summarized by treatment group and RLZ total at scheduled visit and by ECG variable. The number and percentage of study participants

with normal, abnormal not clinically significant and abnormal clinically significant ECG results will be provided in a shift table from Baseline to worst post-Baseline interpretation during the study.

For the ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each timepoint. In the event that there are not 3 available measurements at a given timepoint, the mean will be calculated based on the number of measurements for which data are provided.

The number and percentage of study participants who meet each of the MA criteria outlined in Section 13.6 will be summarized by treatment group at any visit (including unscheduled visit).

A listing of electrocardiogram data will be presented, including repeated and unscheduled measurements.

10.4.3 Other safety endpoints

10.4.3.1 Physical examination

Results of physical examination abnormalities will be listed.

10.4.3.2 Suicidal risk monitoring

The C-SSRS include: (i) suicidal ideation, (iii) suicidal behavior, (iii) suicidal ideation or behavior, and (iv) self-injurious behavior without suicidal intent.

Suicidal ideation is defined as an event in any of the following 5 categories:

- [redacted]

Suicidal behavior is defined as an event in any of the following 5 categories:

- [redacted]

Suicidal behavior or ideation is defined as an event in any of the above 10 categories.

Self-injurious behavior without suicidal intent is corresponding to the response to “Has subject engaged in Non-Suicidal Self-Injurious Behavior?” in questionnaire.

A by-participant listing of the C-SSRS questionnaire data will be provided by treatment group.

10.4.3.3 Assessment and management of Tuberculosis (TB)

By-participant listings of interferon gamma release assay (IGRA) TB test, chest X-ray and TB signs and symptoms questionnaire for TB will be provided.

11 OTHER ANALYSES

11.1 Specific analyses for Pharmaceuticals and Medical Devices Agency (PMDA)

The following endpoints will be summarized for study participants in Japan only:

- Study participant characteristics (as specified in Section 5)
- Demographics and other Baseline characteristics (as specified in Section 6)
- Primary efficacy endpoint (as specified in Section 8.2.2)
  - Change from Baseline in MG-ADL to Day 43 (Visit 10)
- Secondary efficacy endpoints (as mentioned in Section 8.3):
  - MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)
  - Change from Baseline to Day 43 (Visit 10) in MG-C score
  - Change from Baseline to Day 43 (Visit 10) in QMG score
- Other efficacy endpoints (as mentioned in Section 8.4):
  - Use of rescue therapy due to worsening (IVIg, PEX)
  - Change from Baseline in MG-ADL at each scheduled assessment during Treatment and Observation Periods
    - In addition to the overall summary, the MG-ADL scores and change from Baseline will be summarized by the subgroup (MuSK+ or AChR+).
  - MG-ADL responder (≥2.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
  - Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods
  - QMG responder (≥3.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
  - Change from Baseline in MG-C score at each scheduled assessment during Treatment and Observation Periods
  - MG-C responder (≥3 .0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
  - Change from Baseline in MG-QOL15r at each scheduled assessment during Treatment and Observation Periods
- ADA summaries (as mentioned in Section 9.3.2):

- Number and percentage of study participants with positive, negative or missing ADA status at the time of each visit and overall will be summarized by treatment group and RLZ total.
- Number and percentage of study participants in each of the ADA classifications will be summarized by treatment group and RLZ total.
- Number and percentage of study participants with first occurrence of treatment-emergent ADA positive at each visit will be summarized by treatment group and RLZ total.
- The cumulative number of study participants with treatment-emergent ADA positive will also be presented.
- The time to achieving treatment-emergent ADA positive, separated by treatment group and ADA category, will be analyzed based on Kaplan-Meier methods.
- The incidence of NAb, defined as (cumulative) proportion of study participants having NAb positive samples at any point up to and including that time point will be summarized by treatment group and RLZ total. Missing samples will not be included in the denominator. This will be also plotted graphically overlaying the treatment groups.
- A summary table of all immune related TEAEs by ADA status will be presented by treatment group. For this summary, study participants will be presented for TEAEs occurring prior to becoming treatment emergent ADA positive, TEAEs occurring after becoming TE ADA positive, and TEAEs for study participants who remained TE ADA negative.

Safety endpoints

The number, percentage of study participants and frequency of TEAEs will be summarized by treatment group and RLZ total. Additional details are as follows:

- An TEAE overview table will be provided, include following categories: any TEAEs, serious TEAEs, participant discontinuation due to TEAEs, permanent withdrawal of IMP due to TEAEs, temporary withdrawal of IMP due to TEAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to death, all deaths (AEs leading to death).
- Incidence of TEAE will be summarized by SOC, HLT, and PT for:
  - Any TEAEs
  - Severe TEAEs
  - Any TEAEs by maximum intensity (mild, moderate and severe)
  - Any TEAEs by relationship
  - Fatal TEAEs
  - Serious TEAEs
  - Serious TEAEs by relationship
  - Participant discontinuation due to TEAEs
  - TEAEs leading to permanent withdrawal of IMP

Treatment-emergent AESMs (Headache, Gastrointestinal disturbances and Opportunistic infections)

11.2 Headache questionnaire

The results of the headache questionnaire will be listed for each applicable study participant using ES. No summary tabulations will be provided for these assessments.

12 REFERENCES

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13 APPENDICES

13.1 QMG Scale

The QMG scale comprises 13 items, including ocular and facial movement, swallowing, speech, limb strength and forced vital capacity. Scoring for each item ranges from no weakness (0) to severe weakness (3), with an overall score range from 0 to 39, i.e., a higher score indicates more severe disease. A 3-point change in the overall score is considered to be clinically relevant.

The QMG testing form is provided in Table 13–1. The total score is obtained by summing the responses to each individual item.

[redacted] The score ranges from 0 to 33.

In the event of missing data, the following rules will be applied:

- If 1 or 2 items are not answered, the overall score will be obtained by imputing the missing items with the average score across the remaining items at the specific visit. The imputed value will be rounded to one decimal place
- If more than 2 items are missing the overall score will not be calculated at the specific visit

Table 13–1: Quantitative myasthenia gravis testing form

[redacted]

F=female; M=male.

13.2 MG-C score

The MG-C score items and associated scores are provided in Table 13–2.

The MG-C score comprises 10 items, each of which is weighted differently in the calculation of the overall score. The overall score ranges from 0 to 50, with a higher score indicating more severe disease.

The total score is obtained by summing the responses to each individual item.

The score ranges from 0 to 41.

In the event of missing data at a particular timepoint, the MG-C score will not be calculated. Due to the different weighting applied to each item it is not possible to impute the missing data with the average score across the remaining items.

Table 13–2: MG-C score items and scoring algorithm

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

13.3 MG-Activities of Daily Living

The MG-ADL score comprises 8 items, each with a score of 0 to 3. The total score is obtained by summing the responses to each individual item. Thus, the score ranges from 0 to 24 with a higher score indicating more disability. The MG-ADL testing form is provided in Table 13–3.

In the event of missing data, the following rules will be applied:

- If 1 or 2 items are not answered, the overall score will be obtained by imputing the missing items with the average score across the remaining items at the specific visit. The imputed value will be rounded to one decimal place.
- If more than 2 items are missing the overall score will not be calculated.

Table 13–3: MG-Activities of Daily Living

13.4 MG Symptoms PRO

The MG Symptoms PRO includes two steps: 1) rescoring the item responses; and 2) calculation of the final scores. Details of the scoring is found in the Myasthenia Gravis Symptoms PRO Instrument Scoring Manual date 28 February 2019.

Step 1: Rescoring the item responses. The item responses should be rescored so as the lowest item-level score is 0. Rescoring rules are provided in Table 13-4, Table 13-5, and Table 13-6.

Step 2: Calculation of the MG Symptoms PRO Scores

The scores are calculated using the formula below, i.e. the sum of item scores is linearly transformed to have all domain scores ranging from 0 to 100:

$$MG\ Symptom\ PRO\ scale\ score = \frac{Sum\ of\ item\ scores\ within\ the\ scale}{Raw\ score\ range} \times \frac{Total\ number\ of\ items\ in\ the\ scale}{Number\ of\ non\ missing\ items\ in\ the\ scale} \times 100$$

The score for each scale is calculated only when at least 70% of the items are completed. Details on the minimum number of items needed for score calculation and the range of raw score are provided in Table 13-7.

Table 13-4: MG Symptoms: Ocular, Bulbar, and Respiratory Symptoms Rescoring

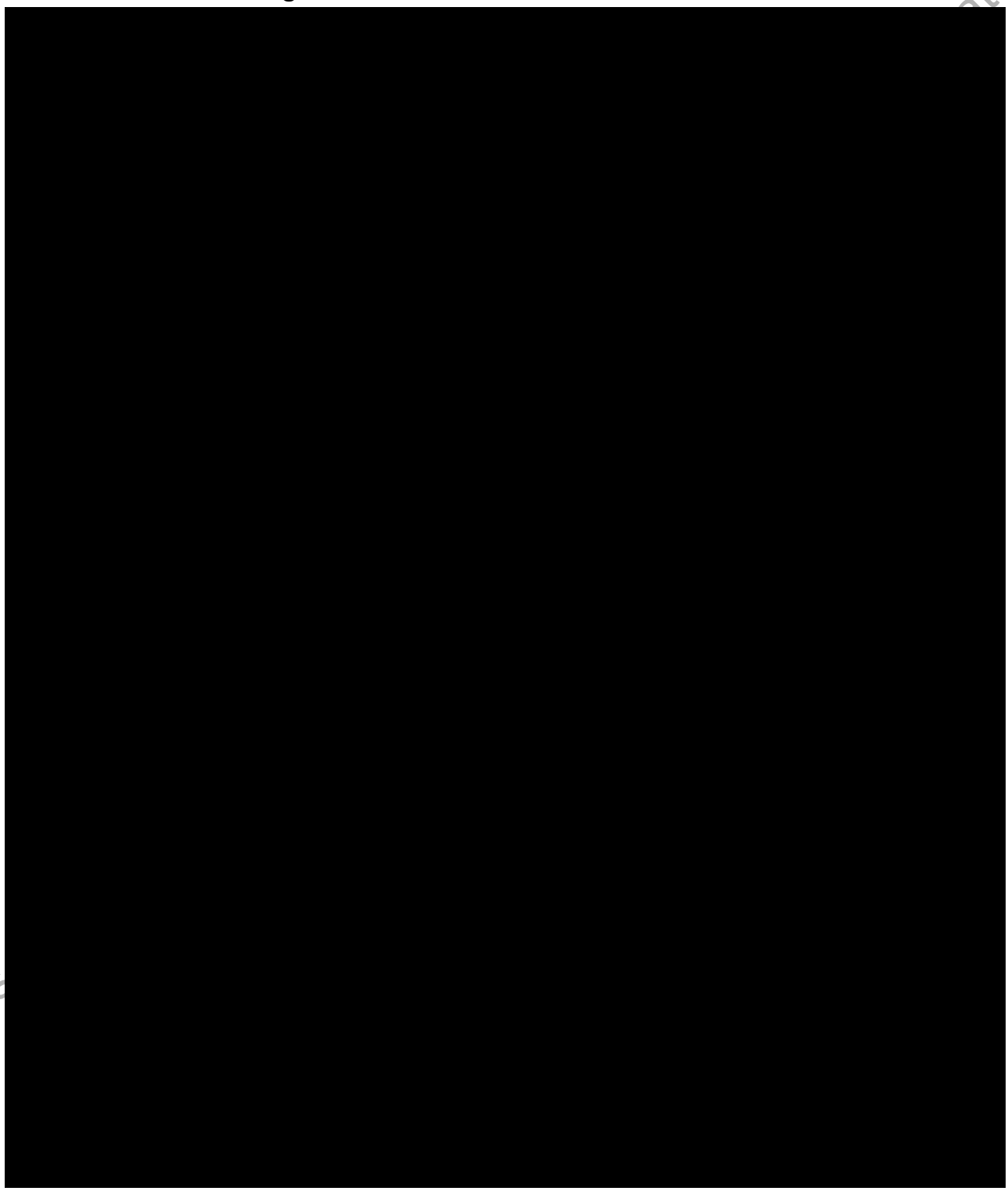

Table 13-4: MG Symptoms: Ocular, Bulbar, and Respiratory Symptoms Rescoring

Table 13-5: MG Symptoms: Physical Fatigue Rescoring

Table 13-6: MG Symptoms: Muscle Weakness Fatigability

Table 13-7: Description of the MG Symptoms PRO Scale Scores

Scale	Number of Items	Number of items needed for score	Raw score range	Listing of items included (MG Symptoms PRO item number)
Ocular symptoms	5	4	0-15	1-5
Bulbar symptoms	10	7	0-30	6-15
Respiratory symptoms	3	3	0-9	16-18
Physical fatigue	15	11	0-60	19-33
Muscle weakness fatigability	9	7	0-36	34-42

13.5 MG Impairment Index

The MG-II is provided in Table 13-8. The MGII can be summarized as a total score and also as 2 sub-scores reflecting an Ocular and a Generalized domain.

The total score is the raw sum of all the items, including the clinical examination and the patient-reported questionnaire.

The ocular score is calculated by summing 8 items reflecting ocular impairments. These items are patient questionnaire items 1 to 6 and examination items 1 and 2.

The generalized score is calculated by adding items 7 to 22 from the patient questionnaire and items 3 to 6 from the examination.

In the event of missing data, the following rules will be applied:

- In the case where at least 7 of the 8 items from the Ocular subscale are answered, the Ocular subscale score will be generated after imputing the missing response by the average of non-missing responses, by adding all item scores. If there are 2 or more missing data out of the 8 Ocular subscale items, then the Ocular subscale score will be missing.
- In the case where at least 18 of the 20 items from the Generalized subscale are answered, the Generalized subscale score will be generated after imputing the missing response(s) by the average of non-missing responses, by adding all item scores. If there are 3 or more missing

data out of the 20 Generalized subscale items, then the Generalized subscale score will be missing.

- In the case where both the Ocular and the Generalized subscale scores are non-missing, then the Total score will be calculated as the sum of the Ocular and the Generalized subscale scores. If one of the two subscale scores are missing, then the Total score will be missing.

Table 13-8: MG Impairment Index

MG Impairment Index (MGII)™ - Patient Questionnaire

ID: _____
Date: _____

INSTRUCTIONS:
Please answer the following questions regarding your symptoms. Only consider those that you think are related to myasthenia. Check the answer that best describes your symptoms over the past 2 weeks.

PROBLEMS WITH YOUR EYES: Please answer regarding the past 2 weeks.

1. Double vision throughout the day				
Have you experienced episodes of double vision? If yes, at what time do they occur (on average)?	☐ No Double Vision 0	☐ Episodes only in the evenings 1	☐ Episodes starting in the afternoons 2	☐ Constant or present most of the day 3
2. Double vision with activities				
Have you experienced double vision with activities such as reading, driving, watching TV or using a computer? If yes, how long does it take (on average) before the double vision occurs?	☐ No Double Vision 0	☐ After more than 1 hour 1	☐ After less than 1 hour, but not immediately 2	☐ Constant double vision or it starts immediately 3
3. Severity of double vision				
Have you experienced double vision? If yes, how severe has it been (at your worst)?	☐ No Double Vision 0	☐ Mild: it doesn't affect my daily activities 1	☐ It affects my activities but no need to cover one eye 2	☐ I need to cover one eye to be able to function 3
4. Eyelid drooping throghout the day				
Have you experienced drooping of your eyelid(s)? If yes, when does it occur (on average)?	☐ No eyelid drooping 0	☐ Only in the evenings 1	☐ Drooping starts in the afternoons 2	☐ Constant drooping or present most of the day 3
5. Eyelid drooping with activities				
Have you experienced drooping of your eyelid(s) with activities such as reading, driving, watching TV or using a computer? If yes, how long does it take (on average) before the drooping occurs?	☐ No eyelid drooping 0	☐ After more than 1 hour 1	☐ After less than 1 hour, but not immediately 2	☐ Constant drooping or it starts immediately 3
6. Severity of eyelid drooping				
Have you experienced drooping of your eyelids? If yes, how severe has it been (at your worst)?	☐ No eyelid drooping 0	☐ Mild: it doesn't affect my vision 1	☐ It affects my vision but no need to lift my eyelid 2	☐ I need to lift my eyelid or tilt my head to be able to see 3

MGII. V1.0. English- Canada

Table 13-8: MG Impairment Index

MG Impairment Index (MGII)™ - Patient Questionnaire

ID: _____

PROBLEMS EATING: Please answer regarding the past 2 weeks.

7. Difficulty swallowing

Have you experienced difficulty swallowing? How severe has it been (at your worst)?	No swallowing problems ☐ 0	Occasional episodes of choking/coughing with food or liquids ☐ 1	Liquids return through my nose, but no problems with solid food ☐ 2	Difficulty swallowing hard food, requiring a change in diet ☐ 3	Unable to swallow or using a feeding tube ☐ 4

8. Chewing different types of food

Have you experienced difficulty chewing? How severe has it been (at your worst)?	No difficulty chewing ☐ 0	Difficulty chewing hard foods (e.g. steak, raw carrots) ☐ 1	Difficulty chewing soft foods (e.g. hard boiled egg) ☐ 2	Unable to chew (eating only liquids or feeding tube) ☐ 3

9. Chewing tiredness/fatigue

At your worst, how long does it take to develop fatigue or tiredness in your jaw?	No difficulty chewing ☐ 0	Difficulty chewing at the end of the meal ☐ 1	Difficulty chewing from the beginning of the meal ☐ 2	Unable to chew (eating only liquids or feeding tube) ☐ 3

PROBLEMS SPEAKING AND BREATHING: Please answer regarding the past 2 weeks.

10. Voice changes through the day

Have you experienced episodes of nasal, hoarse or weak voice? When do they occur on average?	No voice changes ☐ 0	Voice changes only in the evenings ☐ 1	Voice changes starting in the afternoons ☐ 2	Constant voice changes or present most of the day ☐ 3

11. Voice changes with prolonged conversation

How long can you talk (on average), before developing voice changes, such as nasal, hoarse or weak voice? (Normal conversation, with pauses for other speakers)	No voice changes ☐ 0	Voice changes after more than 30 minutes ☐ 1	Voice changes after less than 30 minutes, but not immediately ☐ 2	Constant voice changes or they start immediately (less than 1 minute) ☐ 3

12. Severity of voice changes

At your worst, how severe have your voice changes been? (Nasal, hoarse, weak voice)	No voice changes ☐ 0	Mild changes: my voice is mostly clear ☐ 1	Moderate changes: it can be hard to understand me ☐ 2	Severe changes: it is impossible to understand me ☐ 3

MGII. V1.0. English- Canada

Table 13-8: MG Impairment Index

MG Impairment Index (MGII)™ - Patient Questionnaire

ID: _____

PROBLEMS SPEAKING AND BREATHING (Cont.): Please answer regarding the past 2 weeks.

13. Speech clarity through the day

Have you experienced difficulty pronouncing words or slurred speech? When does it occur on average?	No episodes of slurred speech ☐ 0	Slurred speech only in the evenings ☐ 1	Slurred speech starting in the afternoons ☐ 2	Constant slurring, or present most of the day ☐ 3

14. Speech clarity with prolonged conversation

How long can you talk (on average), before developing slurred speech? (Normal conversation, with pauses for other speakers)	No episodes of slurred speech ☐ 0	Slurred speech after 30 minutes ☐ 1	Slurred speech after less than 30 minutes, but not immediately ☐ 2	Constant slurring, or it starts immediately (less than 1 minute) ☐ 3

15. Severity of speech changes

At your worst, how severe have your speech changes been? (Slurring, difficulty pronouncing words)	No episodes of slurred speech ☐ 0	Mild slurring: It is easy to understand me ☐ 1	Moderate slurring: There are some difficulties understanding me ☐ 2	Severe slurring: it is impossible to understand me ☐ 3

16. Difficulty breathing

Have you experienced shortness of breath that is caused by myasthenia? (i.e. not caused by asthma, or other lung/heart disease) If yes, when has it occurred (at your worst)?	No shortness of breath (except for strenuous exercise) ☐ 0	With moderate effort (e.g. walking several blocks at my own pace) ☐ 1	With minimal effort (e.g. getting dressed, walking inside the house) ☐ 2	At rest or when lying on my back ☐ 3	Requiring assisted ventilation ☐ 4

GENERALIZED SYMPTOMS: Please answer regarding the past 2 weeks.

17. Overall physical tiredness

Have you experienced overall physical tiredness caused by myasthenia gravis? (i.e. not by sleeplessness, depression or other medical conditions)	No physical tiredness ☐ 0	Overall physical tiredness in the evenings ☐ 1	Overall physical tiredness starting in the afternoons ☐ 2	Constant physical tiredness, or present most of the day ☐ 3

MGII. V1.0. English- Canada

Table 13-8: MG Impairment Index

MG Impairment Index (MGII)™ - Patient Questionnaire

ID: _____

GENERALIZED SYMPTOMS: Please answer regarding the past 2 weeks.

18. Arm weakness severity

Have you experienced weakness in your arms? If yes, how severe has it been (at your worst)?	No arm weakness ☐ 0	Mild weakness (e.g. difficulty lifting heavy objects) ☐ 1	Moderate weakness (e.g. difficulty lifting arms above the shoulders, but I can do it) ☐ 2	Severe weakness (unable to lift arms above the shoulders) ☐ 3

19. Arm weakness with prolonged use

Have you experienced weakness in your arms after prolonged use? When does it happen (on average)?	No arm weakness ☐ 0	Weakness when keeping arms up for long (e.g. washing or drying my hair) ☐ 1	Weakness with prolonged activities at shoulder level (organizing objects on a shelf, holding a phone to the ear) ☐ 2	Weakness with minimal effort (e.g. desk work, chopping vegetables) ☐ 3

20. Leg weakness severity

Have you experienced weakness in your legs? If yes, how severe has it been (at your worst)?	No leg weakness ☐ 0	Mild weakness (e.g. difficulty standing from a squat or from tying my shoes) ☐ 1	Moderate weakness (e.g difficulty standing from a chair, I need to push up with my arms) ☐ 2	Severe weakness (e.g unable to stand from a chair without assistance) ☐ 3

21. Leg weakness with prolonged use

Have you experienced weakness in your legs after prolonged use? When does it happen (on average)?	No leg weakness ☐ 0	Weakness when walking more than 10 blocks at my own pace ☐ 1	Weakness when walking less than 10 blocks at my own pace ☐ 2	Constant weakness or with minimal effort (standing, walking inside the house) ☐ 3

22. Neck weakness

Have you experienced weakness in your neck? When does it happen (on average)?	No neck weakness ☐ 0	Weakness only in the evenings ☐ 1	Weakness starting in the afternoons ☐ 2	Constant weakness or present most of the day ☐ 3

MGII. V1.0. English- Canada

Table 13-8: MG Impairment Index

MG Impairment Index (MGII) - Examination

ID:_____
Date:_____

This sheet refers to the physical examination. Detailed instructions are found in the instruction manual. You will need a stopwatch.

	0	1	2	3	Score
E1. Diplopia	No Diplopia	Diplopia in only 1 direction.	Diplopia in 2 directions.	Diplopia in ≥3 directions OR in primary gaze.	
E2. Ptosis	No ptosis	Ptosis between 10-60 seconds.	Spontaneous ptosis or in less than 10 seconds.		
E3. Lower Facial Strength	Normal strength	Can resist with cheeks, but air escapes through lips.	Unable to seal lips or provide resistance with cheeks.		
E4. Arm Endurance	Holds arms for 180 seconds.	Holds arms for 91-179 seconds.	Holds arms for 30-90 seconds.	Holds arms for < 30 seconds.	
E5. Leg Endurance	Holds leg for 90 seconds.	Holds leg for 40-89 seconds.	Holds leg for 16-39 seconds.	Holds leg for ≤ 15 seconds.	
E6. Neck Endurance	Holds head for 60 seconds.	Holds head for 35-59 seconds.	Holds head for 11-34 seconds.	Holds head for ≤ 10 seconds.	

MGII. V1.0. English- Canada

13.6 MG-QOL15r

The MG-QOL15r is a brief survey, completed by the study participant, that is designed to assess some aspects of "quality of life" related to MG. The total score is calculated by summing all 15 individual items.

In the event of missing data, the following rules will be applied:

- In the case where at least 70% of the items (i.e. 11 items out of the 15) are answered, the total score will be generated after imputing the missing responses by the average of available (ie non-missing) responses, by adding all item scores.
- In the case where more than 30% (i.e. 5 items or more) are missing, the total score will not be generated.

Table 13-9: MG-QOL15r

Please indicate how true each statement has been (over the past few weeks).

	Not at all	Somewhat	Very much
	0	1	2
1. I am frustrated by my MG			
2. I have trouble using my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

MG-QOL15r
Muscle and Nerve 2016 Dec;54(6):1015-1022.

Total MG-QOL15r score

MG-QOL15r - United States/English.
MG-QOL15r_AU1.0_eng-USorl.doc

13.7 Markedly abnormal criteria for Rozanolixizumab program

The following criteria will be applied in the determination of marked abnormalities for laboratory assessment values. They are based on Version 5 of the Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher criteria unless otherwise noted. If both high and low criteria are shown for a parameter, the criteria should be summarized separately in tabular or graphical data summaries.

Table 13-10: Hematology

Parameter	Unit (conventional)	Unit (standard)	Marked Abnormality Criteria
Hemoglobin	g/dL	g/L	<8.0 g/dL ; <80 g/L
WBC (Leukocytes)[1]	10^9/L	10^9/L	Low : <2.0 x 10^9/L
			High : >30 x 10^9/L
Lymphocytes Absolute	10^9/L	10^9/L	Low : <0.5 x 10^9/L
			High : >20 x 10^9/L
Neutrophils Absolute	10^9/L	10^9/L	<1.0 x 10^9/L
Platelets[2]	10^9/L	10^9/L	<50.0 x 10^9/L

[1]WBC (Leukocytes) markedly abnormal high criterion is not based on Version 5 CTCAE Grade 3 or higher criteria. Due to the mechanism of action of RLZ, the safety alert is related to infection risk which would be identified by a lower cut-point than the standard which is related to acute leukemias. A markedly abnormal high cut-point >30 x 10^9/L is applied to flag leukocytosis (George 2012).

Table 13-9: Chemistry

Parameter	Unit (conventional)	Unit (standard)	Marked Abnormality Criteria
AST (SGOT)	U/L	U/L	>5.0 x ULN
ALT (SGPT)	U/L	U/L	>5.0 x ULN
ALP (Alkaline Phosphatase)	U/L	U/L	>5.0 x ULN
GGT (Gamma Glutamyl Transferase)	U/L	U/L	>5.0 x ULN
Bilirubin (Total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal; >3.0 x Baseline value if Baseline is abnormal
Albumin	g/dL	g/L	<2 g/dL; <20 g/L
Creatinine	mg/dL	umol/L	>3.0 x ULN
Estimate glomerular filtrate rate (eGFR)[1]	mL/min/1.73 m^2	mL/min/1.73 m^2	eGFR <29 mL/min/1.73 m^2
C reactive protein (CRP)[2]	mg/L	mg/L	>10 mg/dL; >100mg/L

Calcium[3]	mg/dL	mmol/L	Low: Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L
			High: Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L
Immunoglobulin G[4]	(g/L)	(g/L)	≤1 g/L
Potassium	mmol/L	mmol/L	Low: <2.5 mmol/L
			High: >6.0 mmol/L
Sodium	mmol/L	mmol/L	Low: <125 mmol/L
			High: >155 mmol/L
Glucose[5]	mg/dL	mmol/L	Low: <40 mg/dL; <2.2 mmol/L
			High: > 250 mg/dL; >13.9 mmol/L
Total Cholesterol	mg/dL	mmol/L	>400 /dl; >10.34 mmol/L
Triglycerides	mg/dL	mmol/L	>500 mg/dl; >5.7 mmol/L

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; dL = deciliter; GGT: gamma-glutamyltransferase; L = liter; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal

Note: Marked abnormality criteria are defined by Grade 3 or higher events according to the Common Terminology for Adverse Events (CTCAE), Version 5.0, November 17, 2017 unless otherwise noted.

[1]eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration or CKD-EPI formula (https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi) which is eGFR = 141 * min(Scr/κ,1)$^{\alpha}$ * max(Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 [if female] * 1.159 [if black]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. For derivation from values in standard units (umol/L) the κ values are 61.88 for females and 79.56 for males.

[2]Includes CRP and High Sensitivity (HS) CRP. Reference for marked abnormality criteria: Nehring, S.M.; Goyal, A.; Patel, B.C. (2020). StatPearls Publishing, web link: https://www.ncbi.nlm.nih.gov/books/NBK441843/.

[3]Corrected Calcium (mmol/L) =0.02 * (40 – Albumin (g/L)) + Calcium (mmol/L).

[4]Immunoglobulin G criterion based on immunodeficiency literature and noted in RLZ study protocols.

[5]Glucose high criterion defined by Grade 3 and higher events according to CTCAE, Version 4.03, June 14, 2010.

Table 13-10: Vital Signs

Parameter	Abnormality Criteria
Pulse Rate (beats/minute)	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	≤ 90 and a decrease from Baseline of ≥20 ≥180 and an increase from Baseline of ≥ 20
Diastolic Blood Pressure (mmHg)	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥15
Temperature	>101 ^{0}F (38.3 ^{0}C)
Body Weight	≥ 10% decrease from Baseline ≥ 10% increase from Baseline

Table 13-11: Electrocardiogram

Parameter	Abnormality Criteria
QT interval (ms)	≥500ms
	≥60ms increase from Baseline
QTc(F) (ms)	≥500ms
	≥60ms increase from Baseline
PR interval (ms)	Treatment-emergent value >200ms
QRS interval (ms)	Treatment-emergent value >100ms
Heart rate (bpm)	<50bpm
	>120bpm

Abbreviations: bpm = beats per minute; ms = milliseconds; QTc(F) = Fridericia corrected QT interval;
Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit after the first infusion of study medication and within 56-days of the last infusion and not meeting the same criteria during Baseline

13.8 AEs of focus for Rozanolixizumab program

The AEOF selection criteria is specified in the Rozimab Safety AEs of Focus document developed by UCB. The purpose of this document is to detail the approach to identifying TEAEs meeting criteria for AEOF for the Rozanolixizumab (also called Rozimab) program.

Following Events are AEOFs for Rozimab for MG studies:

No	Event (also included in Title of TFL output)	Selection criteria
1	Headache (Note: also included in AESM if severe)	TEAE with HLGT='Headaches'
2	Gastrointestinal disturbances (Note: also included in AESM if severe)	TEAE with HLT='Gastrointestinal and abdominal pains (excl oral and throat)' or HLT='Gastrointestinal signs and symptoms NEC' or HLT='Nausea and vomiting symptoms' or HLT='Diarrhoea (excl infective)' or HLT='Gastritis (excl infective)'
3	Hypersensitivity reactions	SMQ='Hypersensitivity'
4	Anaphylactic reactions	SMQ='Anaphylactic reaction' and TEAEs that either emerged on the **same day** as when a study medication injection reaction was received, or that emerged **one day after** a study medication injection was received, and which fulfill any of the following 3 criteria should be included in the summary table:

		1. If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. 2. If a subject reports any TEAE which codes to a PT included in Category B **AND** reports any TEAE which codes to a PT included in Category C, **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions. 3. If a subject reports any TEAE which codes to a PT included in Category D **AND** reports (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.
5	Injection site reactions	TEAE with HLT='Injection site reactions' or HLT='Infusion site reactions' or HLT='Administration site reactions NEC'
6	Infusion Reactions	Infusion reaction marked on AE CRF page (based on the assessment by the Investigator)
7	Opportunistic infections (Note: also included in AESM)	Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table using UCB-defined search criteria. Opportunistic infections are identified in two steps using the attached spreadsheet for MedDRA v24.0 in UCB Rozimab Safety AEs of focus document. Step 1: Refer to column B of the spreadsheet which identifies the Preferred Terms (PTs) to be classified as opportunistic infections using either a single 'x' or a double 'xx'. • TEAEs which code to a PT flagged with a single 'x' need to also be serious in order to be considered an opportunistic infection. • All TEAEs which code to a PT flagged with a double 'xx' are considered to be an opportunistic infection, regardless of seriousness. All serious TEAEs in the study database which code to a PT flagged with a single 'x' and all TEAEs in the study database which code to a PT flagged with a double 'xx' will be summarized as an opportunistic infection in the stand-alone table. [CQ97NAM= 'Opportunistic Infection–- Automatic'] Step 2: Refer to column C of the spreadsheet which identifies the PTs that need to be evaluated on a case-by-case basis by the

		study physician and safety physician in order to determine whether it is a true opportunistic infection or not. The process for physician review is as follows: 1. Study programming team creates a spreadsheet which lists all of the subjects with a TEAE present in the database which codes to a PT identified as case-by-case. [CQ98NAM= Opportunistic Infection–- Manual Review Candidate] Information from the AE dataset to be included in the spreadsheet: Subject ID, AE verbatim term, System Organ Class (SOC), High Level Term (HLT), Lower Level Term (LLT), PT, AE start date, AE end date, seriousness, severity, relationship to study medication, action taken. Additionally, a column will be included where the study physician/safety physician can document their decision on the case. 2. Study physician/safety physician (SPs) reviews the cases in the spreadsheet separately and reconciles final decision, and indicates in the additional column which AEs are confirmed to be opportunistic infections via a single 'x'. 3. Study programming team incorporates these decisions into the AE dataset by merging the SPs decisions for individual subjects / PTs and flagging both the automatic and the confirmed opportunistic infections as such in the dataset. [CQ99NAM= 'Opportunistic Infection – Adjudicated'] The SPs reviews the context of all of a subject's data (AEs and possibly other) and concludes individually. Indicators of relevant cases may be e.g. repetitive occurrences, conjunction of other events or findings considered relevant. All subjects with a case-by-case PT reported that has been confirmed by the SPs to be an OI will be summarized as such in the stand-alone table, along with all of the events identified in Step 1 of this process. [CQ99NAM= 'Opportunistic Infection – Adjudicated'] The timing and frequency of Step 2 should be outlined and agreed to by the study team at the beginning of the study. It is suggested that this process be executed multiple times throughout the course of the study, more frequently in the weeks leading up to database lock, and one final time immediately prior to database lock. Following the initial physician review of case-by-case events, subsequent reviews will be based on the cumulative set of case-

		by-case events present in the database at each time point of spreadsheet creation. Physician decisions from previous runs should be retained in each subsequent run. The final run of the spreadsheet, with all SP decisions on the full set of case-by-case events, will be archived at the conclusion of the study analysis prepared for agency submission.
8	Reductions in albumin and plasma proteins	TEAEs with PT='Blood albumin decreased' or PT='Protein albumin ratio' or LLT='Plasma protein abnormal' or LLT='Proteins serum plasma low'
9	Effects on the kidney	TEAEs in SMQ= 'Acute renal failure'
10	Drug related hepatic disorders	TEAEs in SMQ='Drug related hepatic disorders–- comprehensive search'
11	Drug related hepatic disorders	TEAEs in SMQ='Drug related hepatic disorders - comprehensive search'
12	Effect on lipids	TEAEs with PT= 'Blood cholesterol increased' or PT= 'Low density lipoprotein increased' or PT= 'Blood triglycerides increased' or PT= 'Hypercholesterolaemia' or PT= 'Hypertriglyceridaemia' or PT= 'Hyperlipidaemia' or PT= 'Dyslipidaemia' or PT= 'Lipids increased'

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN

14.1 Amendment 1

Rationale for the amendment

This amendment is to apply following changes:

- Modifications introduced in Protocol Amendment 3,
- COVID-19 strategy on the analyses,
- Specific analyses requests for PMDA,
- Additional analyses requested by sponsor
- Other cosmetics changes.

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of SAP.
Global	Re-organized the paragraphs in some sections and added some clarifications.	For better understand and avoid misunderstanding of the analyses.
Global	"study drug" has been changed to "IMP"	Keep consistent terminology
Global	Updated abbreviations	Ensure abbreviations are used in the appropriate way.
1. Introduction	Protocol Amendment 2 has been replaced with Protocol Amendment 3	Protocol Amendment 3 has been approved.
2.1.3 Other objectives	The objective relating to anti-drug antibody (ADA) was updated to include the impact it has on pharmacokinetics (PK) and pharmacodynamics (PD).	Updated in Protocol Amendment 3
2.1.3 Other objectives	Evaluation of the effects of rozanolixizumab on serum cytokines was added to the study objectives.	Updated in Protocol Amendment 3
2.1.3 Other objectives	Evaluation of the effects of rozanolixizumab on the α- and β-globulins was removed from the study objectives.	Removed from Protocol Amendment 3
2.1.3 Other objectives	Assessment of the effect of rozanolixizumab on deoxyribonucleic acid (DNA) and ribonucleic acid	Removed from Protocol Amendment 3

	(RNA) was removed from the study objectives and associated endpoints	
2.1.3 Other objectives	Genetics was removed from the study objective.	Removed from Protocol Amendment 3
2.1.3 Other objectives	The objective for exploratory biomarkers was made more general.	Updated in Protocol Amendment 3
2.2.1.3 Efficacy endpoints	Other efficacy endpoints related to MG Impairment Index (MGII) scores have been moved to the end of the list.	Updated in Protocol Amendment 3
2.2.1.3 Efficacy endpoints	An additional other efficacy endpoint has been added: "Minimal Symptom Expression (MG-ADL score of 0 or 1) at Day 43 (Visit 10)"	Updated in Protocol Amendment 3
2.2.2.2 Pharmacodynamic endpoints	The pharmacodynamic endpoint for neurofilament-light (NF-L) levels has been removed.	Removed from Protocol Amendment 3
2.2.4 Anti-drug antibody endpoints	New section was created for ADA endpoints	Separated from immunology endpoints
2.2.5 Immunological endpoints	'Observation Period' was removed from the endpoint relating to serum cytokines.	Updated in Protocol Amendment 3
2.2.6 Other and exploratory endpoints	Genetics was removed from the study endpoint.	Removed from Protocol Amendment 3
2.2.6 Other and exploratory endpoints	The endpoints for exploratory biomarkers was made more general.	Updated in Protocol Amendment 3
2.3 Study design and conduct	The number of sites has been changed from 125 to 135. In addition, Asia has been added as a region for the study to be performed.	Updated in Protocol Amendment 3
2.3 Study design and conduct	All reference to the rollover OLE study, MG0004, has been replaced to introduce the new OLE study, MG0007.	Updated in Protocol Amendment 3
2.4 Determination of sample Size	Specify the calculation of second stage sample size	Clarifications on the sample size calculation
Figure 1-1	The study schematic was updated with new figure.	Updated in Protocol Amendment 3
3.2.1 Analysis time points	Added "Mapping to analysis visit windows is not applied, except for premature end of treatment (PEOT) visits (specified in Section 3.2.3)"	Clarified the mapping rule at PEOT visit
3.2.2 Study periods	In Treatment Period definition, "ends after Day 43 assessment" has been	Clarified the end point of Treatment Period

	changed to "ends after Day 43/PEOT assessments."	
3.2.2 Study periods	Clarified both Treatment and Observation periods are completed when study participants have a completed status in the Study Termination CRF	Ensured to be consistent with CRF guideline.
3.5 Analysis sets	Remove "Analysis of the Safety Set (SS) will be according to the treatment the study participants actually received. Analysis of the Full Analysis Set (FAS) and Randomized Set (RS) will be according to the treatment to which the study participants were randomized." And explain the randomized or actual treatment used in section 3.5.2. and 3.5.3 Clarified that FAS is based on RS.	Simplified the sections.
3.6 Treatment assignment and treatment groups	Added PK/PD analyses in the case study participants will be analyzed per actual treatment group	PK/PD analyses are also based on actual treatment group.
3.8 Coding dictionaries	Updated MedDRA version to 23.0	Latest coding version will be used in the study.
3.9 Changes to protocol-defined analyses	Removed some changes that have been already incorporated into Protocol Amendment 3 and added interaction term used in the model of primary analysis.	Consistent with Protocol Amendment 3
4.1 Adjustments for covariates	Specified the region category–- North America, Europe, and Asia [excluding Japan], Japan	Clarification
4.1 Adjustments for covariates	Clarified randomized stratification factor will be adjusted in the analysis model	Actual baseline stratification factor could be different from randomized one if it has been entered by error in IRWS at randomization
4.2.1 Efficacy data	Added MGII scores and MG-QOL15r in this section regarding the rules for handling missing data	Missing in last version
4.2.1 Efficacy data	Added a table to clarify the imputation methods for primary and secondary efficacy endpoints.	Further clarification
4.2.2 Dates and times	Clarified the reasons for imputation of missing dates and times	Further clarification

4.2.2 Dates and times	Added imputation rule for complete missing end date	Used for the calculation of AE duration
4.2.2 Dates and times	Updated the rules in Table 4-1	Further clarification
4.2.3 Missing data due to COVID-19	Added the new section for the approaches and strategies used to handle missing data due to COVID-19	To address the impact of COVID-19 on the study data
4.4.1 Timing of and basis for periodic data reviews and interim analysis	Updated the description of periodic data reviews and re-organize the section	Updated in Protocol Amendment 3
4.4.1 Timing of and basis for periodic data reviews and interim analysis	Clarified the futility stopping rule is non-blinding and correct p-value at each dose to 0.025	Clarification and mistake correction
4.4.2 Data required for periodic data reviews and interim analyses	Updated the section and sub-sections title.	Further clarification
4.6 Multiple comparisons/multiplicity	Updated the step number proceeded to in Scenario 1	Incorrect step numbers in last version
4.6 Multiple comparisons/multiplicity	In Scenario 2 Step 5, clarified that "Both doses are significant if the larger 2-sided p-value lesser than 0.5(1+1)*0.05=0.05. If not, then one dose is significant if the smaller p-value less than 0.025."	Truncation fraction is 1 for family 6.
4.9 Examination of subgroups	Clarified randomized stratification factor will be used in the subgroup analyses	Actual baseline stratification factor could be different from randomized one if it has been entered by error in IRWS at randomization
4.9 Examination of subgroups	Added additional subgroups for MG-ADL and subgroup only derived in analysis datasets	Additional subgroups were requested for PMDA submission
4.9.1 Examination of COVID-19 Subgroups	New section was added to specify additional summary on COVID-19 subgroups, pre-, during and post- the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.
5.1 Participant disposition	Added additional summaries of screen failure and disposition by pre-, during and post- the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.
5.2 Protocol deviations	Added PD relationship to COVID-19 in summary table and additional summaries by pre-, during and post-the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.

6.1 Demographics	Added "Notes: Missing age will be calculated as year of informed consent signed – year of birth"	Handling of missing age.
6.1 Demographics	Added "A by-participant listing of demographics will be provided using the RS. Childbearing potential and lifestyle will be listed using the ES separately."	Missing in last version
6.1 Demographics	Added additional summaries by pre-, during and post- the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.
6.2 Other Baseline characteristics	Specified where to locate those baseline characteristics	Further clarification
6.2 Other Baseline characteristics	Added "Thymectomy (yes, no)", "MG-specific autoantibody (MuSK+ /aChR+)" and Baseline MG-ADL category	Additional Baseline characteristics were requested for PMDA submission
6.2 Other Baseline characteristics	Added age at initial MG diagnosis	Missing in last version
6.2 Other Baseline characteristics	Added additional summaries by pre-, during and post- the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.
6.3 Medical history and concomitant diseases	Added additional summaries by pre-, during and post- the COVID-19 pandemic	To analyze the amount of data pre-, during and post-the COVID-19 pandemic.
6.4.1 Categories of prior and concomitant medications	Updated the definition in 5 categories and added table to clarify it	Further clarification
6.4.2 Assignment of medications to study period	Clarified the assignment of mediation to Treatment and Observation Period	Further clarification
8.1 Handling of intercurrent events	New section was added to specify the intercurrent events and 2 new intercurrent events related to COVID-19. Listed the strategies for the intercurrent events.	Further clarification
8.2 Statistical analysis of the primary efficacy endpoint	Added the paragraph to briefly describe the analyses for primary endpoint and list the estimand attributes in Table 8-1 and 8-2	Estimand attributes of primary endpoint were not clear in last version.
8.2.2 Primary analysis of the primary efficacy endpoint	Updated sequential test formula and descriptions	Incorrect in last version
8.2.3.2 Sensitivity Analysis #2	New sensitivity analysis using jump-to-reference approach is added	Updated in Protocol Amendment 3

8.2.4.1 Supplementary Analysis #1	The analysis using trimmed mean approach is downgraded to supplementary analysis. Methodology updated.	Updated in Protocol Amendment 3
8.2.5 Additional analysis	Additional analysis was added using study participant not affected by COVID-19	To check the COVID-19 impact on primary endpoint
8.3.1 MG-ADL Responder Rate at Visit 10 (Day 43)	Added "Any missing data scores (including missing data due to the intercurrent events) due to other reasons will also be imputed as non-responders."	Further clarifications on how to handle missing MG-ADL responder
8.4 Analysis of other efficacy endpoints	Clarified summary of other efficacy endpoints will be performed overall, except for time to MG-ADL response.	Further clarification
8.4.1 Use of rescue therapy due to worsening (IVIg, PEX)	Specified the alpha level to be used in the statistical test	Missing in last version
8.4.2 Time to first rescue therapy	Updated the censoring rule and added summary of study participants with 8, 12, 24, 32, 43, 57, 71, 85, 99 days to first rescue therapy and number of censored study participants	Missing in last version
8.4.3 Time to MG-ADL response (≥2.0 points improvement from Baseline)	Updated the censoring rule and added summary of study participants with 8, 12, 24, 32, 43 days to first rescue therapy and number of censored study participants.	Missing in last version
8.4.3 Time to MG-ADL response (≥2.0 points improvement from Baseline)	Clarified the censoring rule and the KM plot by treatment group and cumulative ADA/NAb positivity	Further clarification
8.4.4 QMG score	Added "The subgroup summaries will also be performed as specified in Section 4.9." and "By-participant listings of QMG scores will be provided."	Missing in last version
8.4.5 QMG responder rate (≥3.0 points improvement from Baseline)	Added "In addition, QMG responders will be summarized by the subgroup (MuSK+ or aChR+)."	Additional subgroups were requested for PMDA submission
8.4.5 QMG responder rate (≥3.0 points improvement from Baseline)	Specified both observed and imputed responders will be summarized.	Further clarification
8.4.6 MG-C score	Added "The subgroup summaries will also be performed as specified in Section 4.9." and "By-participant	Missing in last version

	listings of QMG scores will be provided."	
8.4.7 MG-C responder rate (≥5.0 points improvement from Baseline)	Added "In addition, MG-C responders will be summarized by the subgroup (MuSK+ or aChR+)."	Additional subgroups were requested for PMDA submission
8.4.7 MG-C responder rate (≥5.0 points improvement from Baseline)	Specified both observed and imputed responders will be summarized.	Further clarification
8.4.8 MG-ADL score	Added "The subgroup summaries will also be performed as specified in Section 4.9."	Missing in last version
8.4.8 MG-ADL score	Added "Additionally, a table will summarize missing MG-ADL assessment at each scheduled visit by treatment group."	Assess the COVID-19 impact on the efficacy data
8.4.8 MG-ADL score	Clarified the KM plot by treatment group and cumulative ADA/NAb positivity	Clarification of the plot
8.4.9 MG-ADL responder rate (≥2.0 points improvement from Baseline)	Added "In addition, MG-ADL responders will be summarized by the subgroup (MuSK+ or aChR+)."	Additional subgroups were requested for PMDA submission
8.4.9 MG-ADL responder rate (≥2.0 points improvement from Baseline)	Specified both observed and imputed responders will be summarized.	Further clarification
8.4.10 MG Symptoms PRO 'Physical Fatigue' score	Added "The subgroup summaries will also be performed as specified in Section 4.9." and "By-participant listings of all MG Symptoms PRO values will be provided."	Missing in last version
8.4.11 MG Symptoms PRO 'Muscle Weakness Fatigability'	Added "The subgroup summaries will also be performed as specified in Section 4.9."	Missing in last version
8.4.12 MG Symptoms PRO 'Bulbar Symptoms'	Added "The subgroup summaries will also be performed as specified in Section 4.9."	Missing in last version
8.4.13 MG Symptoms PRO 'Respiratory Symptoms' score	Removed description of the score	Details of PRO items can be found in the protocol.
8.4.14 MG Symptoms PRO 'Ocular Symptoms' score	Removed description of the score	Details of PRO items can be found in the protocol.
8.4.15 Patient Global Impressions of Severity	Removed description of the score	Details of PRO items can be found in the protocol.

8.4.15 Patient Global Impressions of Severity	Added "A by-participant listing of PGI-S will be provided."	Missing in last version
8.4.16 Patient Global Impressions of Change	Removed description of the score	Details of PRO items can be found in the protocol.
8.4.16 Patient Global Impressions of Change	Added "A by-participant listing of PGI-C will be provided."	Missing in last version
8.4.17 MGII overall scores, ocular sub-scores, and generalized domain scores	Removed description of the score	Details of PRO items can be found in the protocol.
8.4.17 MGII overall scores, ocular sub-scores, and generalized domain scores	Added "A by-participant listing of MGII scores will be provided.	Missing in last version
8.4.18 MG-QOL15r	Removed description of the score	Details of PRO items can be found in the protocol.
8.4.18 MG-QOL15r	Added "A by-participant listing of MG-QOL15r scores will be provided."	Missing in last version
8.4.20 Minimal symptom expression	New efficacy endpoint was added.	Added in Protocol Amendment 3
9.2 Pharmacodynamics	Removed NF-L	Removed in Protocol Amendment 3
9.2.1 MG-specific autoantibodies	Added additional plots and correlation tables. Added efficacy data in listings.	Requested by sponsor
9.3 Anti-drug antibody	Created separate section for ADA	Separated it with immunology endpoints.
9.3 Anti-drug antibody	Clarified the ADA analyses	Requested by sponsor
9.4.2 Cytokines	Added summary for study participants experiencing with serious or severe headache and/or infusion reactions or hypersensitivity reaction.	Updated in in Protocol Amendment 3
10.2.2 AE summaries	Updated the AE summaries.	Requested by sponsor
11.1 Specific analyses for Pharmaceuticals and Medical Devices Agency (PMDA)	Listed specific analyses for PMDA	Specific analyses were requested for patients in Japan only
13.6 MG-QOL15r	Added scoring details of MG-QOL15r	Missing in last version
13.7 Markedly abnormal criteria for Rozanolixizumab program	Updated the criteria per new MA document provided by UCB	Document is updated by sponsor
13.8 AEs of focus of Rozanolixizumab	Updated the criteria per new UCB Rozimab Safety AEs of Focus document	Document is updated by sponsor

14.2 Amendment 2

Rationale for the amendment

- Update and/or Clarification on various wording, definition and cutoff values.
- Update to be consistent across MG studies and follow Protocol Amendment 4 edits.
- Incorporate regulatory feedback on ICE handling.
- Additional analyses requested by sponsor.
- Other cosmetics changes.

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
2.2.1.3 Other efficacy endpoints	Add "(excluding ocular items)" to Change from Baseline in MG-ADL at each scheduled assessment during Treatment and Observation Period	Updated as it was an omission from the previous protocol amendment.
	Add "at any time up to and including" to Minimal symptom expression (MG-ADL score of 0 or 1) at Day 43 (Visit 10)	Updated as it was an omission from the previous protocol amendment.
	Remove "and Observation" in Change from Baseline in MG Impairment Index (MGII) scores at each scheduled assessment during Treatment and Observation Periods. Remove "and Observation" in Change from Baseline in MGII ocular sub-scores at each scheduled assessment during Treatment and Observation Periods. Remove "and Observation" in Change from Baseline in MGII generalized domain sub-scores at each scheduled assessment during Treatment Periods.	These PRO will not be assessed during the Observation Period.
3.3 Definition of Baseline values	Baseline definition to include using of IMP date, if time is missing, but assessment date is on same date as first IMP	Updated to provide Clarification on baseline values.

3.9 Changes to protocol-defined analysis	Add “estimand and ICE strategies to be based on regulatory feedback”. Update Potential Hy’s Law to Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) >3x Upper Limit of Normal (ULN) and total Bilirubin (TBL) >2xULN, and Alkaline Phosphatase (ALP) <2 x ULN. The Full Analysis Set (FAS) will consist of all study participants in the RS. Update MG specific autoantibodies stratification factor from a single two category factor to two binary factors, MuSK (+/-) and aChR (+/-). Minimal Symptom Expression (MG-ADL score of 0 or 1) at any time up to and include both treatment and observation phase, where the protocol only states to include up to Day43 (Visit10).	Update as PD to PA4
4.1Adjustment for covariates	Change MG-specific autoantibody stratification factor in statical modeling to be based on values evaluated at Baseline instead of IWRS at randomization. Add explanation on handling of missing MG-specific autoantibody stratification factors.	Updated to provide further clarification on source of the baseline MG-specific autoantibody values as stratification factor.
4.4.2.2 Data required for interim analysis	Remove MG Symptoms PRO tables from IA list	Updated to meet IA meeting decision, not necessary for IA and for DMC.
4.9 Examination of subgroups	Change MG-specific autoantibody stratification factor in the subgroup analysis to be based on values evaluated at Baseline instead of IWRS at randomization.	Updated to provide further clarification. On source of the baseline MG-specific autoantibody values as stratification factor.

	For Baseline Characteristics table, MG-ADL cut off value was set to be <5, >=5	Updated to set cutoff value for clarification.
5.1 Participant Disposition	Add primary reason for participants roll over from MG3 to MG4/7. "Mandatory withdrawal due to need for rescue therapy and roll over to extension study" to be under "Other".	Add explanation for participants that has completed the treatment in MG0003 and then needs rescue treatment and instead roll over to the MG0004/7 extension studies.
5.1, 6.1, 6.2, 6.3 8.1, 8.3.1, 8.4.1, 8.4.3-8.4.20 9.1, 9.2, 9.2.1, 9.2.2, 9.3.2, 9.4.1-9.4.4 10.1	Add "RLZ total" as a group for all summaries and plots	General update.
6.2 Other Baseline characteristics	Change and separate "Baseline" and "historical" MG-specific autoantibodies summary, and add comparison.	Updated to provide further clarification on data source of "Historical" and "Baseline" MG-specific antibodies.
6.2 Other Baseline characteristics	Change Age at initial MG diagnosis = (Date of Initial MG Diagnosis–- Date of Birth+1)/365.25	Updated to correct error in formula.
8.1 Handling of intercurrent events	Change ICE2 treatment discontinuation to permanent treatment discontinuation. Combine previously hypothetical strategy with new edits to Target treatment strategy as Hypothetical &Treatment Strategy to handle ICEs,	Update based on regulatory suggestions.
8.1 Handling of intercurrent events	Clarified that study participants with visits in treatment period affected by COVID-19 will be removed for COVID-19 free analysis.	To clarify when to remove study participant, as it doesn't make sense to remove the study participant if COVID only affected visit (s) during the observation period of the study participant.
8.2 Statistical analysis of the primary efficacy endpoint	Change "Treatment condition of interest" to "Treatment Conditions". Change "Population of interest(targeted)" to "Population".	Update in accordance to ICH GCP estimand attributes.

8.3 Statistical analysis of the secondary efficacy endpoint		
8.2 Statistical analysis of the primary efficacy endpoint 8.2.4.1 Supplementary analysis #1	Define "worst score" for imputation to be from its respected questionnaire.	Updated to provide further clarification.
8.2.3.4 Sensitivity Analysis #4	Add an additional sensitivity analysis of the primary endpoint (on the FAS), excluding confirmed COVID-19 cases	Update based on regulatory suggestions.
8.4 Analysis of other efficacy endpoints	Add analyses for COVID-19 free patients for QMG and MG-C as well.	To check the impact of COVID-19.
9.3 Anti-drug antibody status	ADA related modification	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.2.2 AE summaries	Added AESM definition.	For better understanding and reminder to check the data.
	Added TEAEs leading to death by relationship	Required for final CSR.
	Define risk difference of > 5% to be displayed.	Further clarity on % risk difference for display.
10.3 Clinical laboratory evaluations	Remove "If multiple central lab data were captured at scheduled visits, the average would be used for continuous values, or the worst will be used for categorical values" Remove HDL, total cholesterol, and Triglycerides from Clinical Chemistry	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.3.1 Potential drug-induced liver injury	Update criteria for pDILI	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
11.1 Specific analysis for Pharmaceuticals and Medical Devices Agency	Remove MG Symptoms PRO related secondary efficacy endpoints Remove Time to first rescue, EQ-5D-5L from other efficacy endpoints	Update to align with Japanese table review.

	Remove AESM, AEOFs, lab, vital signs and ECG from safety endpoints.	
11.2 Headache Questionnaire	Change each study participant to each applicable study participant using ES	Update to provide further clarification
13.1 QMG Scale	Update table 13-1 with new scale values based on updates in QMG CRF.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
13.8 AEs of focus	Update to include MedDRA 23.1	Update to current version of MedDRA

14.3 Amendment 3

Rationale for the amendment

- Update PK/PD related sections
- Update to be consistent across MG studies and follow Protocol Amendment 4 edits.
- Update to add additional exploratory analysis and figures for display
- Clarification on various definitions.

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
Throughout	Update to MedDRA v24.0 MG-C responder rate from ≥ 5 points improvement from Baseline to ≥ 3 points Correction to typos and abbreviations.	General update
2.2.1.3 Other efficacy endpoints	Patient Global Impressions of Severity (PGI-S) at each scheduled assessment during the Treatment and Observation Periods instead of change from Baseline of PGI-S.	Correction.
3.3 Definition of Baseline	Add "and time if time is collected for the individual assessment)" Add "MG-specific autoantibodies MuSK and aChR Baseline is detailed in Section 9.2.1"	Clarification and to be consistent with all MG studies.
3.5.4 Pharmacokinetic Per-Protocol Set	Change to "at least 1 dose of rozanolixizumab, had at least 1quanifiable concentration"; Add "Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PK-PPS but may lead to exclusion of specific data."	Clarification
3.7 Center Pooling Strategy	Add region categorization.	Clarification

3.8 Coding Dictionaries	Update version and date.	General update and to be consistent with all MG studies.
3.9 Changes to protocol-defined analysis	MG-C responder definition will be 3-point improvement instead of 5-point. PGI-S instead of change from Baseline of PGI-S LDL calculation	Update as PD to PA4
4.1 Adjustments for covariate	Add “a post-Baseline measurement may be used. If this is not available, then”	Clarification
4.2.1 Efficacy data	Apply NRI imputation to include timepoints after use of rescue medication.	Clarification
4.2.2 Dates and Time	Remove duplication in calculation rules in Table 4-1	Correction to typo
4.9.1 General subgroups	Add “using the same algorithm for missing values as specified in Section 4.1”. Add “Historical MuSK (+/non +) and historical AChR (+/non +) will also be examined in the subgroup analysis, in this case, Baseline MuSK(+/-) and Baseline AChR(+/-) will replaced by Historical MuSK (+/non +) and historical AChR(+/non +). ”	Clarification
4.9.1 General subgroups	Add “Forest plot will be provided”; Remove MG Baseline medication definition and add to section 6.4.3	General summary
5.1 Participant Disposition	Add summary table to show count of participant by visit.	General summary

6.1 Demographic	Add “The same summary will also be presented by stages”.	General summary
6.2 Other Baseline characteristics	Add reference to 6.4.3 Add “The same summary will also be presented by stages”. Add “Procedure History CRF” to Thymectomy	Clarification
6.3 Medical History and Concomitant Diseases	Add “history of headache”	Clarification
6.4.3 Baseline MG medication definition	Add new section to define MG Baseline medication definition.	Clarification
8.2.6 Exploratory Analysis	Repeat section 8.2.2 using historical MG-specific auto-antibodies status.	Add exploratory analysis
8.3.2 -8.3.6	Add “Exploratory: The same approach as Section 8.2.6 will be applied”	Add exploratory analysis
8.4.3 Time to MG-ADL Response	Update for clarification. Remove KP plot by “overall ADA or neutralizing antibody (NAb) status”	Clarification Remove plots to be consistent with PK section.
9 PHARMACOKINETICS AND PHARMACODYNAMICS	Add “all other analysis will be performed on Safety Set. .”	Clarification
9.1 Pharmacokinetics	Remove paragraph on plots for ADA titer and ADA status	Remove duplication
	Explain spaghetti plot to be plotted “by treatment group” and “administered RLZ dose ([redacted]) and RLZ total”	Clarification

	Remove geometric mean plot by cumulative ADA status	Remove plots
	Replace arithmetic mean plot by geometric time course plot	Remove plots
	Adding guidelines on data to be presented "If more than 1/3 of the individual data points at a timepoint are missing or are not quantifiable, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank. • If n<3, then only the n, minimum and maximum will be presented. If no study participants have data at a given timepoint, then only n=0 will be presented."	Clarification
	Add "Change from baseline" for IgG and IgG subclass, and remove "MG-ADL change from Baseline" from graph.	Further Clarification
9.2.1 MG-specific autoantibodies	Add MG-specific autoantibodies Baseline definition	Further clarification
9.2.1 MG-specific autoantibodies	Adding reference	General update
	Add "The maximum decrease from Baseline in MG-specific autoantibodies (change absolute and percentage change decrease) will be reported in the listing and summarized for each treatment." For MG-specific auto antibodies summaries.	Clarification
	Add "and the plot will be repeated for the following dose groups: placebo, [redacted]	Clarification

	[redacted]"	
	Add "Mean percent change from baseline of anti-MuSK and Total IgG, and mean change from baseline of MG-ADL, QMG, MG-C will be plotted over time by treatment and RLZ total for only participants who are anti-MuSK positive at baseline"	Add plots
	Change time course plots to "boxplot of maximum percent change" for MG-Specific autoantibodies	Change plot style
9.2.2 Total serum IgG and IgG subclasses	Replace "decrease" and "absolute change " as "change and percent change "	Clarification
	Clarify "mean change" instead of "mean" plot will be plotted, also add dose group plots to IgG mean change and percentage graph	Clarification
	Remove "absolute", add "Total" to IgG	Clarification
	Remove " Individual plots per study participant will be plotted representing total IgG, MG-specific autoantibodies, NAb titer, MG-ADL total score. See details in Section 9.3.2." and "A plot of geometric mean of total IgG (absolute) and arithmetic mean of percentage change from Baseline by cumulative ADA status will be presented by treatment group and RLZ total. See details in Section 9.3.2."	Remove plots

	Change “Absolute reduction” to “Change” ; “to” day 43 to “at” day 43; “relative reduction “ to “Percent change”	Clarification
	Remove “up to day 43 and time plot of mean change and percent change “	Remove plots and Clarification
	Add “change from baseline concentration of total IgG and IgG subclass” to listing	General update
9.3 Anti-drug antibody status	Add “Samples that are NAb positive will be evaluated in a titration assay to quantify the NAb level and will be reported as titer. Samples from study participants on placebo will not be tested for anti-drug antibodies.”	Clarification
9.3.1 ADA Data Consideration	add “if corresponding rozanolixizumab concentrations are equal or below the validated drug tolerance limit of the ADA assay (200µg/mL rozanolixizumab) allowing detection of 100ng/mL ADA” to ADA negative definition; Add definition of ADA inconclusive “Sample values that are either ‘negative screen’ or the combination of ‘positive screen’ and ‘negative immune-depletion’, but with corresponding rozanolixizumab concentrations above the validated drug tolerance limit of the ADA assay, will be defined as ADA inconclusive “	Update ADA sample status definition
	change “ADA Classification “ to “ADA/NAb participant Status”	Update ADA sample status definition

	Update Table 9-1 for participant ADA/NAb classification	Update ADA sample status definition
	Remove Cumulative ADA status and Overall ADA status	Update ADA sample status definition
9.3.2 ADA Summaries	Update tables, figures and listings based on new definition of ADA participant category. Also add scatter plots, and remove geometrics mean plots	Clarification
	Remove Time to MG-ADL KP plots by ADA/NAb status	Remove plots
10.2.3 AE of Focus	Add Treatment-emergent to all tables; Add AEOF table by Risk Difference ≥5% (by decreasing frequency of Risk Difference)	Clarification
10.3 Clinical laboratory evaluations	Replace "Change from Baseline" with "Mean" value for plotting. Update Table 10-1.	Clarification and update per PA4
	Add plots for lipids if data available.	Clarification
12 Reference	Add reference for "The MG Composite" by Burns, Ted M et al.	Add reference
13.7 Markedly abnormal criteria for Rozanolixizumab program	Added corrected calcium algorithm and updated the marked abnormality criteria for corrected calcium and eGFR formula parameters.	Clarification to align with literature values
13.8 AEs of focus	Updated definitions of AEOF	To be consistent across MG studies

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.