STATISTICAL ANALYSIS PLAN

AMENDMENT 5.0

Study: MG0010 (RAISE)

Product: Zilucoplan

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY TO CONFIRM THE SAFETY, TOLERABILITY, AND EFFICACY OF ZILUCOPLAN IN PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

Sponsor Name: Ra Pharmaceuticals, Inc. (now part of UCB)

Legal Registered Address: 87 Cambridge Park Drive

Cambridge, MA, 02140 | USA

Regulatory Agency Identifier Number:

Registry	ID
EudraCT Number	2019-001564-30

Confidentiality Statement

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This Statistical Analysis Plan (SAP) for study MG0010 is based on the protocol amendment 2.0 dated 18 Dec 2020.

SAP Version	Approval Date	Change	Rationale
1.0	06 Nov 2019	Not Applicable	Original version
amendment 1.0	01 Feb 2021	Described Below	Update to UCB standards
amendment 2.0	13 May 2021	Described Below	Anti-PEG antibodies analyses added Refractory definition updated
amendment 3.0	17 June 2021	Described Below	Multiplicity strategy for secondary endpoints modified
amendment 4.0	13 Oct 2021	Described Below	Update following FDA's feed-back
amendment 5.0	06 Dec 2021	Described Below	Clarification added and typos corrected.

Amendment 1.0

The purpose of the SAP amendment 1.0 was to make the following changes based on the SAP Version 1.0 dated 6 Nov 2019:

– The SAP was updated considering the protocol amendment version 2.0 (18 Dec 2020)

– Additional analyses were added to consider the impact of the COVID-19 pandemic on the reliability of the results of the study

– Specific analyses were added for the Japanese population

– Additional analyses were requested by sponsor

– SAP was written according to UCB SAP template

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
Global	Re-organized the paragraphs and added some clarifications.	To comply with UCB format
Global	"subject" has been changed to "participant"	To keep consistent terminology

Section # and Name	Description of Change	Brief Rationale
Global	Updated abbreviations	Updates
Title page	Updated version number and date; added UCB study number	Updates
1 Introduction	Change Protocol to protocol amendment 2.0	Updates
1.1 Objectives and Estimands/Endpoints	Added safety objectives and exploratory objectives	As per protocol amendment 2.0
2 Statistical Hypotheses	Added Statistical Hypotheses for primary and secondary endpoints	To comply with UCB SAP format
3 Sample Size	Increased total sample size to 156 participants (78 participants per treatment group)	As per protocol amendment 2.0
4. Population for analysis	Per protocol set: changed 'major' to 'important' protocol deviations. The definition: 'If a participant receives both doses of study drug (i.e., placebo and 0.3 mg/kg), the participant will be assigned to the dose group which they received at the highest frequency within the study' has been removed	A switch of treatment should be reported as an important PD and therefore such a participant would be excluded from the PPS.
4. Population for analysis	Added population $ITT_{NOCOVID}$ and $SS_{NOCOVID}$	To comply with FDA's guidance on conduct of clinical trials of medical products during COVID-19 Public Health Emergency.
4. Population for analysis	Added PK Set	Need for PK analysis
4. Population for analysis	Added PD Set	Need for PD analysis
5.1. General Considerations	Some baseline characteristics, efficacy and safety data will be summarized by pre-, during COVID-19 relative to the pandemic cut-off date, using WHO defined date of 11Mar2020. $ITT_{NOCOVID}$ and $SS_{NOCOVID}$ analyses will be done if respectively ITT and SS includes at least 15% of participants infected with COVID-19.	To comply with FDA's guidance on conduct of clinical trials of medical products during COVID-19 Public Health Emergency.
5.1. General Considerations	Added interim database lock after last recruited participant has completed Week 12 or has withdrawn before Week 12	As per protocol amendment 2.0

Section # and Name	Description of Change	Brief Rationale
5.1.1 General study level definitions	Some sections have been added: Analysis Time points Relative Day Mapping of End date of the treatment period in case of IMP withdrawal Study Periods Missing data due to COVID-19 Handling of repeated and unscheduled measurements Handling of missing dates and times for AEs and concomitant medications.	More details for programming on how to handle missing dates, missing data, mapping of visits, etc…
5.1.1.3 Treatment assignment and treatment groups	Added that for PK/PD analyses, participants will be analyzed per actual treatment group	PK/PD analyses are also based on actual treatment group.
5.1.1.5 Coding dictionaries	Updated MedDRA version to 23.0	Latest coding version will be used in the study.
5.2 Participant disposition	Summaries of impact of Covid-19 by visit added	To consider the COVID-19 pandemic
5.2 Participant disposition	Added additional summaries of screen failure and disposition by pre-, during the COVID-19 pandemic	To analyze the amount of data pre-, during COVID-19 pandemic.
5.3.2.1 Primary Analysis	Some interaction terms in the main model removed	As per protocol amendment 2.0
5.3.2.1 Primary Analysis	Change to AR (1) autocorrelation structure if an unstructured correlation structure does not converge.	More likely to converge in case there are some issues in terms of convergence
5.3.2.1 Primary Analysis	Added figures for LSMs (idem for secondary endpoints)	To improve the presentation of results
5.3.3 Sensitivity analysis	Removed MMRM with LOCF	LOCF would not be acceptable.
5.3.3 Sensitivity analysis	Removed MMRM with Treatment interaction terms for primary endpoint and all secondary endpoints	Model is very unlikely to converge due to the number of parameters and number of participants. Moreover, the model can become very difficult to interpret
5.3.3 Sensitivity analysis	Removed MMRM with Additional Covariates	Subgroup analyses are sufficient

Section # and Name	Description of Change	Brief Rationale
5.3.3 Sensitivity analysis	Added Tipping point analysis for primary endpoint	Added as sensitivity analyses
5.3.4 Supplementary analysis	Move MMRM on PPS from sensitivity analysis to supplementary analysis	To comply with ICH E9 Addendum
5.3.4 Supplementary analysis	Added MMRM under treatment policy approach and removed MMRM using Observed Case.	Recommended during EMA scientific Advice
5.3.4 Supplementary analysis	MMRM using ITT$_{NOCOVID}$ added	To take into account the COVID-19 pandemic
5.4.2 Time to receive rescue therapy over the 12-week Treatment period	Added table for statistical analyses with median time to receive rescue therapy, 95%CI	Statistical analysis for time-to-event data
5.4.2 Time to receive rescue therapy over the 12-week Treatment period	Removed Time-to-event analysis using Observed Case	Analysis where discontinued subjects were excluded from the model would not reflect the treatment effect.
5.4.3 Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Removed sensitivity analysis using Observed Case	Analysis where missing and censored observations are missing. Since a non-responder imputation is done for these endpoints, this analysis is not needed.
5.4.3. Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Changed Logistic Regression at each visit by GEE model	Better to use a repeated measure model
5.4.3. Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Forest Plots added	To improve the presentation of the results
5.4.3. Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Removed Logistic regression with treatment interaction term and Logistic Regression with additional covariates	Too many covariates in the model, unlikely to converge

Section # and Name	Description of Change	Brief Rationale
5.4.3. Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Removed Chi-square test on the ITT population.	Main model with 95%CI and p-value are a better estimate
5.4.3 Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12	Changed Logistic Regression using LOCF by Logistic Regression using NRI	LOCF will not be used
5.5 Tertiary/Exploratory Endpoints analysis	On additional endpoints (EQ-5D-5L, MGFA status and sub scores of QMG, MGC, MG-ADL, Mg-Qol15r) only summary statistics are provided (no statistical analysis)	No statistical analyses on minor endpoints.
5.5 Tertiary/Exploratory Endpoints analysis	Neuro-QOL and WPAI: change LOCF approach by using MMRM with multiple imputation (same as main analysis for the primary endpoint) Time to Response (defined as CFB MG-ADL ≥2, CFB MG-ADL ≥3, CFB QMG ≥3, CFB QMG ≥5) analyzed as time to event data using KM curves and log rank test. Additional graphs added.	LOCF will not be used
5.6.1 Extent of exposure	IMP duration added	As per UCB standards
5.6.2 Adverse Events	New section was added to specify additional summary on TEAE before/during COVID-19 pandemic	To analyze the amount of data pre-, during the COVID-19 pandemic.
5.6.2.2 AE summaries	AEs summaries may be done on the $SS_{NOCOVID}$ if there is at least 15% of participants in the SS are infected by COVID-19	To analyze the safety on participants not impacted by COVID
5.6.2.2 AE summaries	Added summary of any TEAEs above threshold of 5% of participants in any treatment group	To comply with study reporting requirements
5.6.2.2 AE summaries	Added summary of treatment related TEAEs above threshold of 5% of participants in any treatment group	To comply with study reporting requirements
5.6.2.2 AE summaries	Added Non-serious TEAEs above threshold of 5% of participants in any treatment group	To comply with study reporting requirements
5.6.3.1 AE of Interest (AEIs)	Added	To better understand the safety profile of Zilucoplan

Section # and Name	Description of Change	Brief Rationale
5.6.3.2 Clinical laboratory evaluations	Added Shift tables from baseline to each post-baseline visit	To better understand the safety profile of Zilucoplan
5.6.3.2 Clinical laboratory evaluations	Added marked abnormalities	To better understand the safety profile of Zilucoplan
5.6.3.2 Clinical laboratory evaluations	Added Potential drug-induced liver injury	To better understand the safety profile of Zilucoplan
5.6.3.3 Vital Signs	Added Shift tables from baseline to each post-baseline visit	To better understand the safety profile of Zilucoplan
5.6.3.3 Vital Signs	Added marked abnormalities	To better understand the safety profile of Zilucoplan
5.6.3.4 ECGs	Added marked abnormalities	To better understand the safety profile of Zilucoplan
5.6.3.4 ECGs	Added Shift tables from baseline to each post-baseline visit	To better understand the safety profile of Zilucoplan
5.6.3.6 Total serum IgG and IgG subclasses	Added	As per protocol
5.6.3.7 Immunogenicity	New section was created for ADAs and neutralizing antibodies	To better understand the immunogenicity profile of Zilucoplan
5.7.1.1 Pharmacokinetics	More details given in this section	To better understand the PK profile of Zilucoplan
5.7.2 Specific analyses for Japanese population	All set of analyses asked for PMDA submission	Specific analyses were requested for patients in Japan only

Section # and Name	Description of Change	Brief Rationale
5.8 Subgroup analyses	Following subgroups have been added: Ethnicity (Hispanic or Latino, Not Hispanic or Latino) Race (Asian, Black, White, Other/Mixed) Weight in Kg (<56, 56-<77, 77-<150≥ 150) Duration of disease at Baseline (<median, ≥ median) MGFA disease class at Baseline (Class II (IIa, IIb), III (IIIa, IIIb), or IV (IVa or IVb)) CKD Stage Only summary statistics will be provided. Some safety analyses on TEAE will be provided on some subgroups.	As suggested in FDA's guidance
6.1.1 Demographics	Added additional summaries by pre-, during the COVID-19 pandemic	To analyze the amount of data pre and during the COVID-19 pandemic.
6.1.1 Demographics	Removed p-value to compare similarity of the distribution of demographics and baseline characteristics	As per UCB standards
6.1.2 Protocol deviations	Added PD relationship to COVID-19 in summary table	To analyze PD due to the COVID-19 pandemic.
6.1.3 Medical history	Added additional summaries by pre-, during the COVID-19 pandemic	To analyze the amount of data pre and during the COVID-19 pandemic.
6.1.4 Prior/Concomitant medications	Updated categories of past/Prior/Baseline/Concomitant/Concomitant only categories	Further clarification
6.1.4.4 Refractory criteria	Updates to reflect what is collected in eCRF	Further clarification
6.1.5.9 Neuro-QoL SF	Total score will be calculated	Further clarification
6.3 Changes to Protocol-Planned Analyses	Updated after protocol amendment 2.0	Protocol amendment 2.0

Amendment 2.0

The purpose of the SAP amendment 2.0 was to make the following changes based on the SAP Amendment 1.0 dated 01 February 2021:

− Anti-PEG antibodies analyses added in Immunogenicity section

- Refractory definition updated

- Minor changes to add clarity

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
Abbreviations	Updated Abbreviations	To add clarity
5.1.1.5 Coding dictionaries	Updated MedDRA version 24.0 Update WHODD version March 2021	Latest coding version will be used in the study.
5.2 Participant Dispositions	Pre- and during the COVID-19 period will be based on the enrollment date relative to the pandemic cut-off. Rewording for the differentiation of visits between those done on video call and those on site	To add clarity for programming
5.5.5 Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MG Composite Scores from baseline without rescue therapy	The improvement values will start at the maximum level of worsening and will continue to the maximum level of improvement seen in the study	To add clarity for programming
5.5.6 Sub-scores of the QMG, MG-ADL, MG-QOL15r, and MG-Composite scores	Exploratory analysis added: The individual items for each total score (i.e. QMG, MG-ADL, MG-QOL15r, MGC) will also be summarized by treatment group in a shift table from Baseline to Week 12 visit.	To add insight
5.6.2.2 AE summaries	"leading to study discontinuation" reworded to "leading to permanent withdrawal from IMP"	To add clarity for programming
5.6.2.2 AE summaries	Number, percentage of participants and frequency of fatal TEAEs summarized by relationship, SOC, PT added	To comply with regulatory requirements
5.6.2.2 AE summaries	Summaries of TEAE during COVID infection was added	To better describe TEAEs during COVID-19 infection
5.6.3.1 AE of Interest (AEIs)	Each summary of TEAE of interest will be provided for each AE of interest separately	To add clarity
5.6.3.7 Immunogenicity	Immunogenicity will be provided for both active and placebo treatment group. Anti-PEG antibodies summaries were added	To better describe analyses done for immunogenicity

Section # and Name	Description of Change	Brief Rationale
5.7.2 Specific analyses for Japanese Participants	Treatment-related TEAEs and Treatment-related TEAEs resulting in permanent withdrawal of IMP due to TEAEs were added.	To support submission in Japan
5.7.2 Specific analyses for Japanese Participants	Chemistry, Vital Signs and ECG summaries were removed	Removed since not necessary for PMDA submission
5.8 Subgroup analyses	Age group changed to: Age (<65 years / ≥ 65 years)	Typo error in previous version.
5.8 Subgroup analyses	'Japan' region changed to 'East Asia'	Stratification factor was re-labelled from 'Japan' to 'East Asia' as additional participants from East Asia were included in the stratum.
5.8 Subgroup analyses	Chronic Kidney Disease Stages subgroup added	To comply with guidelines
6.1.1 Baseline characteristics and demographics	Age definition updated	To account for data collected in the eCRF
6.1.3.1 Medical history (other than MG disease history)	Sorting within HLT added	More details for programming
6.1.4.3 MG Specific Prior and Concomitant Medications	MG Specific Concomitant only summaries added	To give more insight
6.1.4.4 Refractory criteria	Refractory definition was updated to account for other corticosteroids that were taken for at least one year and any other immunosuppressive therapy.	Refractory definition updated after eCRF was updated.
Table 6–8	Updated PT list for anaphylactic reactions categories	Two PT missed from the previous list
6.2.1 Laboratory Assessments Marked Abnormality Criteria	Conventional units updated Triglycerides removed Typos corrected	To reflect data transfer specifications

Amendment 3.0

The purpose of the SAP amendment 3.0 was to make the following changes based on the SAP amendment 2.0 dated 13 May 2021:

Section # and Name	Description of Change	Brief Rationale
2.2 Secondary endpoints and multiplicity	The fixed sequential testing procedure using a pre-defined order of the secondary endpoints was modified using a Holm procedure for the last 4 secondary endpoints in the hierarchy within a gatekeeping framework.	To account for the low number of events of the lowest secondary endpoints in the hierarchy.
6.3 Appendix 3 Changes to Protocol-Planned Analyses	Explanation given for the change in the multiplicity procedure	To describe additional changes between SAP Amendment 3.0 and the protocol.

Amendment 4.0

The purpose of this SAP amendment 4.0 is to make the following changes based on FDA's feedback on the SAP Amendment 3.0 dated 17 June 2021:

Section # and Name	Description of Change	Brief Rationale
Abbreviations	NRI, LOCF, J2R, PD-PPS, PK-PPS, TEMA were added.	Missing in previous version.
1.1 Objectives and Estimands/Endpoints	Intercurrent event handling was updated in the primary estimand where use of rescue therapy (ICE1), adverse event of death or myasthenic crisis (ICE2) were assumed to be treatment failure whereas any other missing data is assumed to be missing at random in the primary analysis. Other secondary Estimands were updated accordingly.	FDA suggested this change for the primary estimand
1.1 Objectives and Estimands/Endpoints	Difference for time to first administration of rescue will be assessed using Kaplan-Meier plots	Update due to the low number of expected events
4 Population for analysis	ITT population was removed. RS and mITT were added.	FDA suggested this change in population from ITT to mITT due to the change in the primary estimand.
4 Population for analysis	ITT no COVID and SS No Covid used only if 15% of the population is infected by COVID was removed.	FDA suggested that the efficacy and safety analyses should be done on the total study populations followed by

Section # and Name	Description of Change	Brief Rationale
	To analyze the impact of COVID-19 infection on the primary estimand, a COVID-19 Free Set was added defined as study participants having neither a COVID-19 related IPD, nor impacted visits on the COVID-19 eCRF page, nor a COVID-19 related AE.	sensitivity analyses to assess the effects of COVID-19 infections on the study results.
4 Population for analysis	Population PKS updated to PK-PPS and PDS updated to PD-PPS.	This change is to remove subjects with important protocol deviations affecting the PD or the PK of the drug.
5.1 General Considerations	Changed ITT to mITT. Population CFS added. Population ITTnoCovid et SS noCovid removed.	Changes needed due to the changes in population
5.1.1.1.3.2 Coronavirus Disease 2019 pandemic periods	COVID-19 pandemic periods (prior/during/post) added	More details provided compared to previous version
5.1.1.1.4 Mapping of assessment	Clarification added on early termination visit	Clarified for programming
5.1.1.3	Updated populations	as per FDA's recommendation
5.1.1.7.2 Efficacy endpoints	Summary of Primary, Sensitivity and supplementary for primary and secondary efficacy endpoint added, with handling of missing data.	Based on FDA's proposal
5.1.1.7.4 Missing data due to COVID-19	Missing data due to COVID updated with additional sensitivity and subgroup analysis on the CFS.	Based on FDA's comments
5.1.1.9 Handling of rescue therapy visits	Paragraph added to clarify handling of rescue therapy visit	Clarification in the SAP
5.2 Participant dispositions	Populations updated	Due to changes in populations suggested by the FDA
5.3.2.2 Handling of missing data	Imputation rules for intercurrent events updated	Based on FDA's proposal
5.3.3.1 Sensitivity 1	Clarification added for the jump to reference approach	To add clarity
5.3.3.2 Sensitivity 2	Tipping point analysis slightly modified due to the change in the primary estimand	Due to the change in primary estimand

Section # and Name	Description of Change	Brief Rationale
5.3.3 Sensitivity 3	MMRM on CFS	Added as per FDA's comment
5.3.4.3 Supplementary 3	MMRM using PMM changed from primary analysis to supplementary analysis	Based on FDA's proposal
5.3.4.4 Exploratory	Worst-rank analysis added	Based on FDA's proposal
5.4.1.2 Main analytical approach	Imputation method updated	Based on FDA's proposal
5.4.1.3 Sensitivity	Part updated to reflect the change in the primary estimand	Based on FDA's proposal
5.4.2.2 Main analytical approach	Median time to rescue removed	Difficult to interpret due to the low number of events expected
5.4.2.3.2 Sensitivity	Additional sensitivity analysis on the CFS/ Analysis on ITT no COVID removed.	Added as per FDA's comment
5.4.3.1 Definition of endpoint	Algorithm updated to reflect the change in imputation rules	Change of imputation rules suggested by the FDA
5.4.3.3.3 Sensitivity 3	GEE changed to weighted GEE	GEE could produce invalid estimates
5.4.3.3.4 Sensitivity 4	Analysis on CFS added	Added as per FDA's comment
5.5.5 Responder analysis	MMRM added as exploratory for MG-ADL responder (defined as improvement ≥2) and QMG responder (defined as improvement ≥3)	To add defined threshold in the literature used for MG-ADL and QMG.
5.6.1 Extent of exposure	Exposure duration added	To be consistent across the gMG Zilucoplan studies.
5.6.2 Adverse Events	Analyses to assess the impact of COVID-19 on the safety as well as the impact of COVID-19 vaccination	COVID 19 related analysis added based on feedback from FDA
5.6.2 Adverse Events	Definition of treatment-emergence updated	To include the 5 half-lives of Zilucoplan after the last dose when defining treatment emergent adverse events.
5.6.3.2 Clinical Laboratory evaluations	Treatment-emergence defined	To add clarity and consistency across the gMG Zilucoplan studies
5.7.2 Specific analyses for Japanese Participants	Summary on prior and concomitant medications (other	To comply with PMDA's requirements

Section # and Name	Description of Change	Brief Rationale
	than MG therapy) on Japanese removed Added plot on observed and standard errors for MG-ADL and QMG added	
5.8 Subgroup analyses	Safety analyses on the subgroup MG Refractory was added	To comply with PMDA's requirements
5.8 Subgroup analyses	Subgroup based on the pandemic period was added	Based on FDA's guidance
6.1.2 Protocol Deviations	Clarification added on how the relationship to COVID will be assessed	Added clarification for programming
6.1.5.4 MG-QOL-15r	Clarification added	To add clarity
6.1.8 COVID-19 terms	COVID-19 terms added	To identify study participants infected by COVID-19
Table 6-10	Table updated	To add clarity and consistency across the gMG Zilucoplan studies.
6.3	Changes to protocol-Planned analysis updated to reflect these changes	To reflect additional changes in SAP Amendment 4.0 compared to the protocol.

Amendment 5.0

The purpose of the SAP amendment 5.0 was to make the following changes based on the SAP Amendment 4.0 dated 13 Oct 2021:

− Typos were corrected

− Rationales for changes for SAP Amendment 4.0 were clarified

Section # and Name	Description of Change	Brief Rationale
Version History	Rationale for change was updated	To document with more clarity changes in various SAP Amendments.
Table 1-1	Any other monotone missing data was renamed as ICE3 Clarification was added on ICE2	To add clarity for programming

Section # and Name	Description of Change	Brief Rationale
5.1	MMRM on PPS done as a supplementary analysis	To be consistent with the rest of the SAP.
5.1.1.1.2	End of Study Visit (defined in the protocol) defined as well as Early Termination Visit	To clarify for programming purposes
Table 5-1	Any other monotone missing data was renamed as ICE3 Added clarification on how to program intercurrent events	To add clarity for programming
5.1.1.7.2 Efficacy Endpoints	Handling on how to identify ICE1, ICE2 and ICE3 was added	To add clarity for programming
5.2 Participant Disposition	Spaghetti plot was replaced by a linear plot for each study participants	To improve the presentation of results
5.3.2.1 Primary Analysis	Standard errors were added for LSMs	To add clarity for programming
5.3.2.2 Handling of missing data	Definition of intercurrent event was homogenized	To be consistent throughout the document
5.3.3.1 Sensitivity 1	Plot added	To improve the presentation of results
5.3.3.2.2 Algorithm 5.3.4.3 Supplementary 3 5.3.4.4 Exploratory 5.4.1.2 Main Analytical Approach 5.4.3.1 Definition of endpoints	Typos corrected	To be consistent with the rest of the document
5.5.5 Responder analysis	The wording of waterfall plot replaced by a cumulative frequency plot	To add clarity for programming
5.6.2.2 AE summaries	COVID-19 tables not repeated for each period	Not needed as only one treatment period in MG0010
5.7.2 Specific Analyses for Japanese Participants	All summaries presented for all visits	To add clarity for programming
5.8 Subgroups	MMRM used separately for Refractory/non-Refractory participants	To assess treatment effect in both strata of these populations separately.
Table 6-10	Amylase and lipase added in the Laboratory marked abnormalities	Missing in the previous version and to be consistent across the Zilucoplan's program.

Section # and Name	Description of Change	Brief Rationale
6.2 Appendix 2: Abnormality criteria for Laboratory, Vital Sign and Electrocardiogram Parameters	Typos corrected	

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	Adverse Event
AEIs	Adverse Events of Interest
ALP	alkaline phosphatase
ALQ	above the limit of quantification
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Autoregressive
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	Body Mass Index
BP	Blood Pressure
BUN	blood urea nitrogen
C5	Complement component 5
CFB	Change from Baseline
CI	confidence interval
CKD	Chronic Kidney Disease
COVID-19	Coronavirus Disease 2019
CPStat	Clinical Program Biostatistician
CRF	Case Report Form
CS	Completer Set
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTStat	Clinical Trial Biostatistician
CV	coefficient of variation
DAP	Data Analysis Plan
DEM	data evaluation meeting
DRM	Data Review Meeting

ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ VAS	EQ visual analogue scale
EQ-5D-5L	Euro-Quality of Life 5-Dimensions, 5 levels
ES	Enrolled Set
ESV	End of Study Visit
FDA	US 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
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICE	intercurrent event
IMP	investigational medicinal product
INR	international normalized ratio
IPD	important protocol deviation
IST	Immunosuppressive therapy
J2R	Jump to reference
LFT	Liver Function Test
LLoQ	Lower Limit of Quantification
LLT	Lower Level Term
LOCF	Last Observation Carried Forward
LSM	Least Squares Mean
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
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	minimal symptom expression
n	number of participants
NAb	neutralizing antibody
NRI	non-responder imputation
PEG	Polyethylene glycol
PBO	Placebo
PD	Pharmacodynamic
PD-PPS	Pharmacodynamic Per Protocol Set
PDILI	Potential Drug Induced Liver Injury
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PTT	partial thromboplastin time
QMG	Quantitative Myasthenia Gravis
RBC	red blood cell
sRBC	Sheep red blood cell
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event

TEMA	treatment-emergent marked abnormalities
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 MG0010 (Ra-Pharma reference number RA101495-02.301). It also defines the summary tables, figures and listings (TFLs) to be included in the Clinical Study Report (CSR) according to the protocol.

This SAP includes efficacy, safety, immunogenicity, pharmacokinetics [PK], pharmacodynamics [PD] analyses. Changes to protocol-planned analysis are documented in Section 6.3. Table, Figure and Listing (TFL) specifications are contained in a separate document.

This SAP is based upon and assumes familiarity with protocol amendment 2.0 dated 18 December 2020.

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

The statistical analyses and production of the outputs described in the SAP will be conducted by eClinical Solutions using SAS software version 9.3. The final analyses and outputs will be approved by UCB.

1.1   Objectives and Estimands/Endpoints

The estimand corresponding to the primary objective and primary efficacy analyses are described below. The estimands corresponding to the secondary objectives and secondary efficacy analyses are also described below.

Table 1–1:   Estimands

Objectives	Estimands/Endpoints
Primary Efficacy Objective	
To confirm the efficacy of zilucoplan in participants with gMG	Primary Estimand: **Treatment:** Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs Placebo **Target Population:** Adults with generalized myasthenia gravis (gMG) with inclusion/exclusion criteria provided in section 8.1 and 8.2 of the protocol. **Endpoint:** Change from Baseline (CFB) in Week 12 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score **Intercurrent event handling:** Administration of rescue therapy (ICE1): will be assumed to be a treatment failure from the time of the intercurrent event. Any death or myasthenic crisis (ICE2) will be assumed to be a treatment failure from the time of the intercurrent event. Any other monotone missing data (ICE3) will be assumed to be missing at random: it is assumed that the participant had remained on their treatment throughout the study (i.e., a "Hypothetical-strategy" assuming participants did not discontinue the study and remained on treatment). **Population level summary:** The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MG-ADL.
Secondary Efficacy Objective	
To confirm the efficacy of zilucoplan in participants with gMG	Secondary Estimand: **Treatment:** Same as primary estimand. **Target Population:** Same as primary estimand. **Endpoint:** CFB to Week 12 in the Quantitative Myasthenia Gravis (QMG) Score **Intercurrent event handling:** Same as primary estimand. **Population level summary:** The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 QMG Secondary Estimand: **Treatment:** Same as primary estimand. **Target Population:** Same as primary estimand.

Endpoint: CFB to Week 12 in the Myasthenia Gravis Composite (MGC) Score

Intercurrent event handling: Same as primary estimand.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MGC.

Secondary Estimand:

Treatment: Same as primary estimand.

Target Population: Same as primary estimand.

Endpoint: CFB to Week 12 in the Myasthenia Gravis – Quality of Life revised (MG-QOL15r) Score

Intercurrent event handling: Same as primary estimand.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MG-QOL15r.

Secondary Estimand:

Treatment: Same as primary estimand.

Target Population: Same as primary estimand.

Endpoint: Time to first administration of rescue therapy over the 12-week Treatment Period

Intercurrent event handling: For participants that discontinue from the study without having previously received rescue therapy, the "while on treatment approach" will be assumed, such that a participant will be censored at the time of discontinuation.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the Kaplan-Meier curves.

Secondary Estimand:

Treatment: Same as primary estimand.

Target Population: Same as primary estimand.

Endpoint: Achieving Minimal Symptom Expression (MSE), defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy

Intercurrent event handling: Any participant using rescue therapy (ICE1) and any death or myasthenic crisis (ICE2) will be assumed to be non-responder from the time of the intercurrent event. Any other monotone missing data (ICE3) will be assumed to be missing at random before the endpoint is dichotomized.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the proportion of participants achieving MSE.

Secondary Estimand:

Treatment: Same as primary estimand.

Target Population: Same as primary estimand.

Endpoint: Achieving a ≥ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy

Intercurrent event handling: Any participant using rescue therapy (ICE1) and any death or myasthenic crisis (ICE2) will be assumed to be non-responder from the time of the intercurrent event. Any other monotone missing data (ICE3) will be assumed to be missing at random before the endpoint is dichotomized.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the proportion of participants achieving a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy.

Secondary Estimand:

Treatment: Same as primary estimand.

Target Population: Same as primary estimand.

Endpoint: Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy

Intercurrent event handling: Any participant using rescue therapy (ICE1) and any death or myasthenic crisis (ICE2) will be assumed to be non-responder from the time of the intercurrent event. Any other monotone missing data will be assumed to be missing at random before the endpoint is dichotomized.

Population level summary: The difference between the zilucoplan and placebo treatment groups in the proportion of participants achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy.

Secondary Safety Objective	
To confirm the safety and tolerability of zilucoplan in participants with gMG	**Secondary Safety Endpoint** Incidence of Treatment Emergent Adverse Events (TEAEs) **Other Safety Endpoints** Adverse events of interest (AEIs)

	Physical Examination
	Vital Signs
	ECG
	Clinical Laboratory Tests
	Immunogenicity (i.e. ADAs and neutralizing antibodies, anti-PEG antibodies)
	C-SSRS
Exploratory Objectives	
To assess the PK of zilucoplan	Plasma concentrations of zilucoplan and its major metabolites
To assess the PD of zilucoplan	Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation
	Complement component 5 (C5) levels
To explore the efficacy on additional efficacy endpoints	Achievement of Minimal Manifestation Status per MGFA Post-Intervention Status (MGFA-PIS) at Week 12 without rescue therapy
	CFB to Week 12 in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
	CFB to Week 12 in EQ-5D-5L [5-item questionnaire and visual analog scale (VAS)]
	CFB to Week 12 in QMG sub-scores: ocular, bulbar, respiratory, limb
	CFB to Week 12 in Neuro-QOL Short Form Fatigue Scale
	Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MG Composite Scores from baseline without rescue therapy
	Sub-scores of the QMG, MG-ADL, MG-QOL15r, and MG-Composite scores
To assess the effect on biomarkers	Mechanistic biomarkers pertinent to MG pathophysiology [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers]

1.2 Study design

Study MG0010 is a phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the efficacy, safety, and tolerability of zilucoplan in participants with gMG. The planned enrollment is approximately 156 participants.

Participants will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Randomization will be stratified based on the baseline MG-ADL Score (≤9 versus ≥10), QMG Score (≤17 versus ≥18), and geographical region.

In order to ensure a gradual initiation of the study in Japan, each Japanese site will be capped to an enrollment rate of no more than one participant per week (i.e., one participant per site per week).

The study includes a Screening Period of up to 4 weeks and a 12-week Treatment Period. During the Treatment Period, participants will return to the clinic at Week 1, Week 2, and monthly visits at Week 4, Week 8, and Week 12 to evaluate efficacy, safety, and tolerability. Additional assessments will include questionnaires, biomarker samples, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics. Safety assessments will include physical examinations, vital signs, ECG, clinical laboratory tests, AE monitoring, immunogenicity, and C-SSRS.

Randomized participants will receive 0.3 mg/kg zilucoplan or placebo administered SC at the Day 1 visit. Following in-clinic education and training, all participants will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks. Single use pre-filled syringes in injection devices will be provided for use during the study.

In Japan, following their Day 1 dose, participants will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, participants will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Participants will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

Participants are expected to remain on stable doses of all medications unless medically indicated changes become necessary. All SOC therapy medications for gMG should be kept at the same dose throughout the study, including corticosteroids and IST drugs. If escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to major deterioration of a participant's clinical status, or risk of MG crisis as per the investigator's judgment, the participant may receive IVIG or PLEX treatment or eculizumab as 'rescue therapy'. In Germany, the choice of eculizumab as 'rescue therapy' will not be withheld, if the investigator considers this to be the best course of action.

The safety of participants will be monitored in a blinded manner on an ongoing basis. If an unblinded data review should become necessary to ensure participant safety, a SMC will convene and evaluate study data as appropriate.

At the conclusion of the Treatment Period, all participants will have the option to receive zilucoplan in a separate Extension Study (Study MG0011), provided they meet the Extension Study inclusion criteria.

If a participant discontinues study drug treatment prior to the Week 12 visit for any reason, he/she will not be eligible for the MG0011 Extension Study. For participants who permanently discontinue study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new SAEs since the last study visit.

2 STATISTICAL HYPOTHESES

2.1 Primary Endpoint

The null statistical hypothesis for the primary endpoint is that the treatment difference between zilucoplan and placebo in CFB in Week 12 MG-ADL score is zero. The alternative statistical hypothesis is that the treatment difference between zilucoplan and placebo in CFB in Week 12 MG-ADL score is different from zero.

The primary efficacy endpoint will be tested at the 2-sided 0.05 significance level.

2.2 Secondary Endpoints and multiplicity

The statistical analysis of the 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 framework with different testing procedure for each of the 2 type I error families. This will only be done if the primary endpoint is significant at 2-sided type 1 error of 0.05.

Family 1:

Family 1 will include the key secondary endpoints. Testing will be done using a fixed-sequential testing procedure in the following order:

1. CFB to Week 12 in the QMG score
2. CFB to Week 12 in the MGC score
3. CFB to Week 12 in the MG-QOL15r Survey

A secondary endpoint analysis in Family 1 will be considered statistically significant if the 2-sided p-value is ≤ 0.05 for the endpoint analysis, providing that the primary efficacy endpoint analysis, and all the secondary endpoint analyses occurring earlier in the fixed-sequence are also statistically significant (i.e., have a 2-sided p-value ≤ 0.05). This method provides strong control of the family-wise error rate at the two-sided 0.05 level. At the first endpoint that is not significant, no further testing will be done.

Family 2:

If all secondary endpoints in the Family 1 are significant at 2-sided type 1 error of 5%, family 2 will be tested using a Holm procedure at 2-sided type 1 error. Family 2 includes the following secondary endpoints:

- Time to receive rescue therapy over the 12-week Treatment Period
- Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy
- Achieving a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy
- Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy

The Holm procedure is a multi-step, step-down procedure. The procedure starts with the smallest p-value that will be compared to 0.0125. If the first test shows statistical significance, treatment effect for the respective endpoint is considered significant. Then, testing will proceed comparing

the next-smallest p-value to 0.017. If the second test shows statistical significance, testing will proceed comparing the third smallest p-value to 0.025. If the third test shows statistical significance, testing will proceed comparing the largest p-value to 0.05. The procedure stops whenever a step yields a non-significant result. Once an ordered p-value is not significant, the remaining larger p-values are not evaluated. In this case, treatment effect cannot be concluded for the remaining secondary endpoints.

3   SAMPLE SIZE DETERMINATION

For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, assuming a difference in treatment group least squares means of 2.3, a SD of 3.7, and 78 participants per group (156 in total), the study has approximately 94% power to detect a difference between an active and placebo treatment group based on a 2-sided alpha of 0.05. This assumes rates of rescue and dropout of up to 10% and 5%, respectively.

4   POPULATIONS FOR ANALYSIS

- **Enrolled Set:** The Enrolled Set (ES) will consist in all screened participants including screen failures

- **Randomized Set:** The Randomized Set (RS) will include all randomized participants.

- **Modified Intention-to-Treat Population:** The modified Intention-to-Treat (mITT) Population will include all randomized participants who received at least 1 dose of study drug and have at least 1 post-dosing MG-ADL score.

- **Per Protocol Set:** The Per Protocol Set (PPS) will include all participants in the mITT Population who have completed the 12-week Treatment Period and have no important protocol deviations affecting the primary efficacy endpoint. Important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

- **Safety Set:** The Safety Set (SS) will include all participants who received at least 1 dose of study drug with participants to be analyzed based on the actual study treatment received.

- **COVID-19 Free Set:** The Covid-19 Free Set (CFS) will include all participants in the mITT who have neither:

  – a COVID-19 IPD

  – Nor impacted visits on the COVID-19 impact eCRF page

  – Nor a COVID-19 AE reported in the Adverse Event eCRF form using Appendix 6.1.8.

- **Pharmacokinetic Per-Protocol Set:** The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all participants in the safety population who received at least 1 dose of study drug and had at least 1 quantifiable PK measurement post-dose of study treatment without important protocol deviations that would affect the PK.

- **Pharmacodynamic Per-Protocol Set:** The Pharmacodynamic Per-Protocol Set (PD-PPS) will consist of all participants in the safety population who received at least 1 dose of study drug and had at least 1 quantifiable PD measurement post-dose of study treatment without important protocol deviations that would affect the PD .

5   STATISTICAL ANALYSES

5.1   General Considerations

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.

All clinical study data will be presented in participant data listings.

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.

For PK concentrations, summary statistics will include geometric mean, geometric coefficient of variation (CV), 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.

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.

Statistical tests of efficacy variables will be presented as p-values rounded to four 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 2.2 .

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.

Demographics and baseline characteristics will be analyzed in the mITT population. Prior and Concomitant medications will be done in the SS. Efficacy analyses will be done in the mITT population, in the CFS as sensitivity analyses and in PPS as supplementary analysis. Safety, PK and PD analyses will be done respectively in the SS, PK-PPS and PD-PPS.

Once the last study participant has completed the Week 12 visit, or the last study participant has prematurely discontinued prior to reaching Week 12, the study database will be locked (interim database lock). The study will be unblinded and all the TFLs will be produced. The purpose of this unblinded interim analysis is to perform a comprehensive evaluation of all available double-blind data to prepare regulatory submissions for approval of the MG indication. All TFLs will be produced again once all data (through to the SFU visit) have been collected. If all the participants have completed the study at the interim database lock (the last participants entered the extension study), then the interim database lock will be the final lock.

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

All data will be analyzed based on the visits identified per the Schedule of Activities in the protocol. Mapping to analysis visit windows is not applied, except for early termination visits (specified in Section 5.1.1.1.4).

5.1.1.1.1 Relative day

Relative day will be provided in different listings and will be calculated as follows:

– If the start (stop) date occurred on or after the first dose, but prior to the double-blind drug stop date, relative day is calculated as start (stop) date minus first dose date + 1 (the day of first dose will be Day 1).

– If the start (stop) date occurred before the first dose, the relative day is calculated as date of first dose of IMP minus the start (stop) date (the day prior to first dose will be Day -1)

– If the start (stop) date occurred after the last dose of IMP, the relative day to the most recent dose is calculated as start (stop) date minus last dose of IMP including a '+'to denote posttreatment days (e.g. the day after last dose will be Day +1).

Relative day will only be computed for fully completed dates and will be missing for partial dates. In such cases, relative day should be presented as '- -' in the participant data listings. Relative day will be calculated from first dose of IMP for all treatment groups.

5.1.1.1.2   End date of the Treatment Period

The end date of the Treatment period will be either the date of the Week 12 visit for participants completing the Treatment Period or the date of the End of Study Visit (ESV) (i.e., Early Termination Visit) for participants who discontinued during the Treatment Period. If a participant does not have a Week 12 visit or ESV, then either the date of the last scheduled or unscheduled visit during Treatment Period or the date of the last known dose of study drug during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

5.1.1.1.3   Study periods

Based on the specific requirements of safety and efficacy analyses, two concepts of the definition of periods need to be considered for the study, which will be defined in detail in the sections below.

5.1.1.1.3.1   Study periods for safety and efficacy data

The total duration of study participation for all participants will be up to approximately 16 weeks, including a Screening Period of up to 4 weeks and a 12-week Treatment Period. The participants who choose not to enter the Extension Study or who terminate the study prior to Week 12 will return to the clinic for a Follow-up Visit 40 days +/- 7 days after their last dose.

- Screening Period: 1 to 28 days

- Treatment Period: 12 weeks

- Follow-up Period: up to 7 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 at the end date of treatment period defined in Section 5.1.1.1.2 . 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 Week 12 Visit are completed.

•   Follow-up Period starts one day after the end of the Treatment Period and ends after the final assessments on the Safety Follow-up visit. Participants with assessment after the Treatment period are considered to have started the Follow-up Period. Participants who entered the Extension Study will not do the Follow-up period.

5.1.1.1.3.2   Coronavirus Disease 2019 (COVID-19) pandemic periods

The following COVID-19 pandemic periods will be defined:

- Prior to COVID-19 pandemic period: Period prior to COVID-19 pandemic start date, which is defined as 11-Mar-2020 by the World Health organization (WHO), not including the pandemic start date.

- COVID-19 pandemic period: Period from 11-Mar-2020 through the COVID-19 pandemic end date (which is currently not defined), including the dates of pandemic start and end.

- Post COVID-19 pandemic period: Period after the WHO declaration of the end of the pandemic, beginning on the day after the pandemic end date. The end of the pandemic had

not yet been declared at the time of SAP finalization. As a result, this period will only be included in analyses if the WHO declares an end to the pandemic prior to the end of the study.

These periods will be used to classify the timing of the following relative to COVID-19 pandemic:

- study participant enrolment in the study,

- study participant Week 12 Visit,

- AE onset date.

5.1.1.1.4 Mapping of assessments performed at Early Termination Visit

If a participant prematurely discontinues study drug at any time prior to Week 12, the participant should return to clinic for a stand-alone Early Termination Visit. These assessments will be mapped to the next scheduled visit, where each assessment is done as per protocol.

5.1.1.1.5 Definition of Baseline values

Unless otherwise specified, Baseline will be the last available pre-dose value prior to the first injection 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.

Change from Baseline (CFB) is defined as the value minus baseline value. Percent Change from Baseline is defined as 100 x (Change from Baseline/Baseline).

5.1.1.2 Protocol Deviations

Analyses related to protocol deviations are given in Appendix 6.1.2 .

5.1.1.3 Treatment assignment and treatment groups

RS, mITT and CFS analyses will be based on the randomized treatment.

PPS analyses will be based on the actual treatment received.

SS, PK-PPS and PD-PPS analyses will be based on the actual treatment received. If after unblinding it is determined that participants at any time receive incorrect treatment from their randomized assignment, these participants will be reallocated to the appropriate treatment group. For example, if participants randomized to placebo received zilucoplan, then for the safety and PK/PD analyses, these participants will be reallocated to zilucoplan. Participants randomized to zilucoplan will only be reallocated to the placebo treatment group if they never received zilucoplan.

Treatment groups will be shown as below:

- Placebo

- Zilucoplan 0.3mg/kg

5.1.1.4   Center pooling strategy

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

5.1.1.5   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 version March 2021 or later of the World Health Organization Drug Dictionary (WHODD).

5.1.1.6   Multicenter studies

Individual center results will not be displayed.

5.1.1.7   Missing data

5.1.1.7.1   Censoring values due to Rescue therapy

If a participant receives rescue therapy, efficacy endpoints occurring after rescue therapy will be censored.

5.1.1.7.2   Efficacy endpoints

Rules for calculating total scores (i.e. MG-ADL, QMG, MG-C, MG-QOL15r) when an individual item is missing from an instrument are provided in Section 6.1.5. Imputation methods for overall missing scores for the analyses of the primary and secondary endpoints are listed below. The estimands corresponding to these analyses are described in Section 1.1.

Table 5-1:   Primary and Secondary Estimands

Efficacy Endpoints	Statistical Analysis Type	Statistical Analysis Methods	Imputation Methods	Population
Primary	Primary	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	mITT
	Sensitivity 1	MMRM	Imputation: J2R	mITT
	Sensitivity 2	MMRM	Imputation: Tipping point	mITT
	Sensitivity 3	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	CFS
	Supplemental 1	MMRM	Imputation: maximum likelihood estimation	mITT

Efficacy Endpoints	Statistical Analysis Type	Statistical Analysis Methods	Imputation Methods	Population
	Supplemental 2	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	PPS
	Supplemental 3	MMRM	Imputation: Pattern-mixture approach	mITT
	Exploratory	ANCOVA	Imputation: worst rank	mITT
Secondary (continuous)	Main	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	mITT
	Sensitivity 1	MMRM	Imputation: J2R	mITT
	Sensitivity 2	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	CFS
	Supplemental 1	MMRM	Imputation: maximum likelihood estimation	mITT
	Supplemental 2	MMRM	Imputation: Baseline or last score whichever is worse from time of ICE1 and ICE2 and maximum likelihood estimation for ICE3.	PPS
	Supplemental 3	MMRM	Imputation: Pattern-mixture	mITT
Secondary (binary)	Main	Logistic	Imputation: NRI for ICE1 and ICE2 and maximum likelihood estimation for ICE3.	mITT
	Sensitivity 1	Logistic model	Imputation: J2R	mITT
	Sensitivity 2	Logistic model	Imputation: NRI	mITT
	Sensitivity 3	Weighted GEE model	Imputation: NRI	mITT
	Sensitivity 4	Logistic	Imputation: NRI for ICE1 and ICE2 and maximum	CFS

Efficacy Endpoints	Statistical Analysis Type	Statistical Analysis Methods	Imputation Methods	Population
			likelihood estimation for ICE3.	
	Supplementary	Logistic	Imputation: NRI for ICE1 and ICE2 and maximum likelihood estimation for ICE3.	PPS
Secondary (Time to Event)	Main	Kaplan-Meier plots	No imputation	mITT
	Sensitivity 1	Kaplan-Meier plots	Imputation: Discontinued participants assumed to have taken rescue therapy	mITT
	Sensitivity 2	Kaplan-Meier plots	No imputation	CFS
	Supplementary	Kaplan-Meier Plots	No imputation	PPS
MMRM=mixed model for repeated measures; ANCOVA= analysis of covariance; J2R=Jump to reference; NRI= non-responder imputation				

If a study participant is administered a rescue therapy (ICE1), any data strictly after the start date of the first rescue therapy administration (in the Rescue Therapy Cycle Administration eCRF page) will be flagged as intercurrent event 1 (ICE1).

If a study participant experiences a death (ICE2), then data after the death date on the Early Termination eCRF page will be flagged as intercurrent event 2 (ICE2).

If a study participant experiences a myasthenic crisis (i.e., MedDRA PT = 'myasthenia gravis crisis'), then any data after the start date of the adverse event on the AE eCRF page will be flagged as intercurrent event 2 (ICE2).

Any other monotone missing data will be flagged as intercurrent event 3 (ICE3) in each relevant dataset (depending on the efficacy endpoint). ICE3 is defined as any missing value where all values at subsequent visits are missing.

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

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

5.1.1.7.3   Safety, PK and PD endpoints

Missing data for Safety, PK and PD endpoints will not be imputed; observed cases will be used. This will include observations occurring after a participant receives rescue-medication.

5.1.1.7.4   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 in this study.

- Added an eCRF page "COVID-19 Impact", including impacted visits, impacted assessments and reason why these assessments were impacted

- Protocol deviations related to COVID-19 will be documented

- Included additional summary analyses based on the COVID-19 pandemic period (prior/during). A post COVID-19 time period may be added if relevant.

- Sensitivity analyses on the primary efficacy endpoint using the same method as the primary analysis on the Covid-19 Free Set and by timing of the Week 12 Visit relative to the start and end date (if applicable) of the COVID-19 pandemic period.

- Subgroups analyses will be performed on the primary efficacy endpoint based on the timing of participant enrollment and timing of the Week 12 visit relative to the COVID-19 pandemic period as exploratory.

5.1.1.8   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) as defined in Section 5.1.1.1.5.

- For repeated or unscheduled measurements obtained at Day 1 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 original values (if non-missing) will be used in the calculation of changes from Baseline and for the descriptive statistics (i.e. in summaries by time point).

5.1.1.9   Handling of rescue therapy visits

All rescue therapy visits will be presented in the listings, where applicable. However, the rescue therapy visits will not be presented for descriptive statistics (i.e. summaries by time point). The statistical analyses will present summaries at each scheduled visit as well as outputs of the statistical modelling using the imputation rules defined in Section 5.1.1.7.2.

5.1.1.10   Handling of missing 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, baseline or concomitant medications;

- Duration 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 participants or the date of discontinuation for 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 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.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant. Any medication with a start date on the first dosing date and time unknown, will be assumed to be concomitant. In the event of ambiguity or incomplete data which makes it impossible to determine whether an adverse event was treatment-emergent or not, the adverse event will be considered as treatment-emergent.

Imputed AE dates will be used for the calculation of duration of AEs, defined as:

Duration of AE = stop date – start date + 1

5.2   Participant Dispositions

The following summaries will be created.

- **Reasons for screen failures** will be summarized using the ES for overall. Additionally, the reasons for screen failures will be summarized by pre- and during the COVID-19 pandemic based on the enrollment date relative to the pandemic cut-off date.

- **Disposition of analysis sets** will be summarized by treatments groups and overall, by analysis sets (RS, mITT, CFS, SS, PPS, PK-PPS, PD-PPS). Percentages will be based on the number of participants in the RS in the respective treatment groups and overall. Disposition of analysis sets will also be summarized in the ES by region, with number of sites, principal investigator name, dates of first participant in and last participant out as well as the number of participants screened/screen failures

- **Disposition and discontinuation reasons** using the RS and mITT population will contain the number and percentage of study participants who started, completed, permanently discontinued Treatment Period with primary reason of discontinuation and entered into the extension study RAISE-XT overall. Percentages will be based on the number of participants in the RS and mITT population in the respective treatment group and overall.

- **Discontinuation due to AEs** using the RS and mITT population will summarize the total number of study participants who discontinued the study due to AEs by treatment group and the categories: AE, serious fatal, AE non-fatal and other (AE non-serious fatal).

- **Impact of COVID-19** using the mITT population will summarize number and percentage of participants in each impact category by visit. This table will be done overall and by country. Visits and assessments done via video calls will be listed. For both the listing and the summary table, only visits at which efficacy or safety assessments are scheduled will be included.

Listings of study participant disposition and study discontinuation, analysis set and study participants who did not meet study eligibility criteria will be provided. Listing of all participants impacted by COVID-19 will also be provided.

Additionally, a linear plot of MG-ADL score versus scheduled visit will be presented by treatment group for each participant having performed at least one video call. Visits will be differentiated between those performed by video call and visits performed on site.

Finally, the number of study participants enrolled during each COVID-19 pandemic period as well as the number of study participants still in the study during each COVID-19 pandemic period will be summarized in one table on the randomized set. The table will be done overall and by region (North America, Europe and East Asia).

5.3   Primary Endpoint Analysis

The primary efficacy analysis will be the comparison of zilucoplan 0.3 mg/kg dose group versus placebo in CFB to Week 12 in MG-ADL Score at a 2-sided 0.05 significance level based on the mITT population using least squares means.

5.3.1   Definition of endpoint

The primary endpoint is the CFB in Week 12 MG-ADL Score. The complete list of MG-ADL items and scores and calculation of total score are provided in Appendix 6.1.5.1 . The total score calculated after single item imputation will be used to calculate change from Baseline, in summaries and for efficacy analyses.

5.3.2 Main analytical approach

5.3.2.1 Primary Analysis

For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, treatment group differences will be assessed using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment, baseline MG-ADL Score, baseline QMG Score, geographical region, treatment-by-visit (interaction term), baseline MG-ADL Score-by-visit (interaction term) as fixed effects and participant as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12.

The treatment and geographical region (North America, Europe and East Asia) terms in the MMRM model will be treated as categorical, visit as an ordinal (categorial) variable, and baseline MG-ADL and QMG Scores will be treated as continuous.

The MMRM will use an "unstructured" covariance structure for the repeated measures. In the event the "unstructured" covariance structure model fails to converge, an AR (1) covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means (LSMs) and standard errors (SE) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo will be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs and p-values. Statistical outputs such as LSM and 95% Confidence Intervals (95% CI) will be plotted from Week 1 to Week 12. The least squares mean (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo at Weeks 1, 2, 4, and 8 will also be reported with the corresponding 2-sided 95% CIs.

Model assumptions (Independence, Normality, Homoscedasticity) will be checked by using normal probability plots of studentized residuals by actual residuals and a random variation plot of studentized residuals by predicted values. Results of the diagnostics procedures may be included in the CSR appendix "Documentation of statistical methods" if deemed relevant.

CFB in MG-ADL score will be summarized by treatment group and by visit using descriptive statistics in the mITT. The same summary will be done by subgroup as defined in Section 5.8. CFB MG-ADL will be listed for all participants of the RS with visit flagged if the visit was done prior to the COVID-19 pandemic cut-off date. For participants infected with COVID-19 as per the AE page, CFB in MG-ADL will be listed by visit separately.

5.3.2.2 Handling of missing data

The number of missing values by visit for primary and secondary endpoints will be provided by treatment group and overall using descriptive statistics on the mITT. Additionally, the number of missing values by visit due to COVID-19 will be summarized by treatment group for the primary and secondary endpoints (using the "COVID-19 Impact" e-CRF page) as explained in Section 5.2.

For the primary efficacy analysis, missing or censored data will be imputed the baseline or the last available MG-ADL score (including unscheduled visit), whichever is worse from the time of the following intercurrent events:

- ICE1: Data occurring after a participant received rescue therapy

- ICE2: Data occurring after a participant had any death or myasthenic crisis

Any other monotone missing data (ICE3) will be assumed to be missing at random.

Note: if a MG-ADL assessment is done on the rescue therapy visit, then this will be considered as the last score available prior to rescue therapy. The number and percentage of participants with each intercurrent event (ICE1, ICE2 and ICE3) will be summarized by treatment group.

5.3.3 Sensitivity analysis

5.3.3.1 Sensitivity #1: MMRM using J2R approach

Deviations from the missing at random pattern will be evaluated using a J2R approach using Multiple Imputation (MI method) under the missing not at random assumption (MNAR) to handle any missing scores. Intermittent missing data will be imputed using the Markov-Chain Monte Carlo method, using the MCMC impute=monotone option in PROC MI (SAS System). Monotone missing/censored data will be imputed using the placebo distribution irrespective of individual treatment assignment. The MNAR option in PROC MI (SAS system) will be used to impute the placebo distribution.

The following variables will be included in the imputation model:

- Baseline MG-ADL Score (continuous variable)

- The participant's MG-ADL scores at previous visits (e.g. Week 12 CFB MG-ADL imputed score will use scores at Week 1, 2, 4 and 8). If a participant starts rescue therapy, then the most recent MG-ADL score will be used which may occur at an unscheduled visit

The seed used for these imputations will be 2021 (note that all other multiple imputation procedures described in this SAP related to MCMC/Monotone regression analyses will use this same seed as well). If the MI model does not converge or produce estimates (e.g., due to over-specification) the set of imputation variables may be modified.

Each of the imputed datasets will be analyzed via the specified MMRM model (see Section 5.3.2.1). The treatment effects and standard errors from the least squares means (LSMeans) treatment difference will be combined across the 100 imputed datasets using Rubin's rule to produce an overall p-value using SAS PROC MIANALYZE. LSMs and 95% Confidence Intervals (95% CI) will be plotted from Week 1 to Week 12.

5.3.3.2 Sensitivity #2: Tipping point analysis

5.3.3.2.1 Methodology

An additional sensitivity analysis using the tipping-point approach will be conducted to assess the robustness of the MAR assumptions in the primary analysis. These tipping point analyses will only be performed if the primary efficacy analysis results in a statistically significant treatment effect (p<0.05). Various delta adjustments will be made to the assumed responses on the monotone missing data (ICE3) in each treatment group independently with various degrees of plausibility. It will include scenarios where study participants who have missing data and are randomized to zilucoplan are less likely to respond than compared to study participants who have missing data and were randomized to placebo.

Tipping point analysis is a means of exploring the influence of missingness on the overall conclusion from statistical inference by positing a wide spectrum of assumptions regarding the missingness mechanism (from less conservative to more conservative). The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified while the result is no longer statistically significant.

Participants that receive rescue therapy (ICE1) or participants with a death or myasthenic crisis (ICE2) will be imputed as baseline or the last available MG-ADL score (including unscheduled visit), whichever is worse from the time of the intercurrent events as in the primary analysis. The tipping point analysis will be used for ICE3 assumed to be missing at random in the primary analysis.

5.3.3.2.2 Algorithm

Delta adjustments will be made to the imputed values for observations in each treatment group (for ICE3 only) with various degrees of plausibility with the goal to find for each treatment group the "tipping point" that will significantly reverse the primary result that yielded a p-value less than 0.05.

These delta adjustments (by adding a positive or a negative shift) will be done on the MG-ADL score and will be implemented as follows:

- Step 1: Intermittent missing data will be imputed using the Markov-Chain Monte Carlo method, using the MCMC impute=monotone option in PROC MI (SAS System).

- Step 2: A set of 100 sets of imputations will be produced:

A monotone regression model will be applied while adjusting the imputed values by various shift parameters. These shift parameters will be defined within the pre-defined range of values. A positive shift will be applied to the imputed value for study participants randomized to zilucoplan to decrease the imputed value, whereas a negative shift will be applied to the placebo group to increase the imputed value. Assumptions will be varied independently in each treatment group (i.e. whenever a shift will be applied to the Zilucoplan treatment group, then the placebo group will be fixed). Shift parameters will be chosen according to the range of values observed at baseline. Once defined, the same shift parameter value will be applied on the imputed endpoint value for all visits.

- Step 3: Each of the 100 imputed datasets will then be analyzed using the same MMRM model used for the main analytical approach as the primary endpoint.

- Step 4: The 100 LSMDs will then be combined for overall inference using Rubin's rules, and the results obtained for each shift parameter will be presented in a single table.

- Step 5: Step 2 to 4 will be repeated using a bisection algorithm. The tipping point will be found, if it exists, when the difference between the p-value obtained for the LSMD between zilucoplan and placebo and the target p-value (0.05) is very small (<0.0000001).

The LSMD and 95%CI and p-values obtained for each shift parameter will be combined in one single table. Results will be displayed graphically in a contour plot where y-axis display the

Zilucoplan shift and x-axis is the placebo shift, with contours at selected p-value levels: 0.01, 0.025, 0.05 and 0.1.

5.3.3.3   Sensitivity #3: MMRM on CFS

To assess the impact of the COVID-19 pandemic on the primary efficacy endpoint, the same analysis method as the primary analysis described in Section 5.3.2 will be done on the COVID-19 Free Set.

5.3.4   Supplementary analyses

5.3.4.1   Supplementary #1: MMRM under treatment policy approach

The primary efficacy endpoint analyses will be performed on the mITT population using a treatment policy approach, where all the data will be used regardless of any intercurrent events (i.e. no data will be censored) using the treatment initially assigned at randomisation. Any missing MG-ADL score will be handled based on the maximum likelihood estimation method under the MAR assumption. The same model as the main analytical approach will be implemented.

5.3.4.2   Supplementary #2: MMRM on the PPS

The primary efficacy endpoint analysis will be performed on the PPS.

5.3.4.3   Supplementary #3: MMRM using Pattern-Mixture Model (PMM)

Multiple imputation (MI) methods will be used to handle missing data and data after rescue therapy use (i.e., data collected after a participant has used rescue therapy will be censored and treated as missing data for the primary efficacy analysis).

For this supplementary analysis, 100 imputed datasets will be created using monotone linear regression imputation methods which will impute the participants' missing post-baseline scores at each of the scheduled visits in the study (i.e., Weeks 1, 2, 4, 8, and 12). 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. Imputation will be performed by treatment group, with the underlying imputation distribution based on the reason for the missing data.

Missing and censored data will be imputed based on the placebo group distribution, irrespective of individual treatment assignment, under the following intercurrent events:

–   ICE1: Data occurring after a participant received rescue therapy

–   ICE2: Data occurring after a participant had a death or myasthenic crisis.

Missing data will be imputed based on the participant's assigned treatment group distribution under the following scenarios:

–   ICE3: Monotone missing data for any other reason.

This MI method allows for a pattern-mixture model approach assuming the data are missing not at random (MNAR) under ICE1 and ICE2 (i.e., treatment failure). 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 5.3.2.1). The treatment effects and standard errors from the least squares means (LSMeans) treatment difference will be combined across the 100 imputed datasets to produce an overall p-value using SAS PROC MIANALYZE.

The following variables will be included in the imputation model:

− Baseline MG-ADL Score (continuous variable)

− The participant's CFB MG-ADL scores at previous visits (e.g. Week12 CFB MG-ADL imputed score will use scores at Week 1, 2, 4 and 8). If a participant starts rescue therapy, then the most recent CFB MG-ADL score will be used which may occur at an unscheduled visit

Note that the imputations will be such that they will either be performed by treatment or only the placebo distribution will be used for the imputation (i.e., for MNAR).

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.

5.3.4.4   Exploratory: Worst-Rank analysis of covariance at Week 12

A worst-rank analysis of covariance will be used on the mITT population at Week 12, where participants with poor outcomes will be assigned the highest rank in the following order:

(a) participants who died by Week 12

(b) participants who experienced myasthenic crisis

(c) participants who received rescue therapy, or those who discontinued the study having deteriorated. Deterioration will be defined as a positive change from baseline MG-ADL.

(d) all other participants (ranked in ascending order of the improvement from baseline in MG-ADL total score at Week 12 [LOCF])

Participants with the same outcome will be assigned ranks depending on the timing of the event, where an event occurring earlier will have a higher rank. Participants with the best outcome (i.e. largest improvement) will be assigned the lowest rank. Any missing data (other than due to death, myasthenic crisis, rescue therapy or discontinuation due to deterioration) will be imputed with a last observation carried forward (LOCF) approach. Therefore, each participant will be ranked from 1 (best outcome) to the number of participants in the mITT population (poorest outcome).

Ranks will then be analyzed using an analysis of covariance (ANCOVA) with treatment as fixed effect and baseline MG-ADL score. LS Means rank and 95% confidence intervals will be provided as well as LS means difference and 95% confidence intervals. The p-value will be provided as exploratory.

5.4   Secondary Endpoint Analysis

All secondary endpoints will be listed for all participants of the RS with visit flagged if the visit was done prior to the COVID-19 pandemic cut-off date. For participants infected with COVID-19 as per the AE page, secondary endpoints will be listed by visit separately.

5.4.1   Week 12 CFB in the QMG score, in MGC score, in MG-QoL15r Survey

5.4.1.1   Definition of endpoints

The change from Baseline to Week 12 in the QMG score, in the MGC score and in the MG-QoL15r Survey will be analyzed on the mITT population. More details on how these scores are calculated can be found respectively in Appendix 6.1.5.2 , Appendix 6.1.5.3 and Appendix 6.1.5.4.

5.4.1.2   Main analytical approach

Each of the continuous secondary endpoints (i.e. Week 12 CFB in QMG Score, MGC Score, and MG-QOL15r Survey) will be analyzed using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA). As for the primary endpoint, data after use of rescue therapy (ICE1) and death or myasthenic crisis (ICE2) will be imputed baseline or the last available corresponding score (including unscheduled visit), whichever is worse from the time of the following intercurrent events. Any other monotone missing data (ICE3) will be assumed to be missing at random.

For Week 12 CFB QMG Score, MMRM ANCOVA will include treatment, baseline MG-ADL Score, baseline QMG Score, geographical region (North America, Europe and East Asia), treatment-by-visit (interaction term), baseline QMG Score-by-visit (interaction term) as fixed effects and participant as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12.

Similarly, for Week 12 CFB MGC Score, MMRM ANCOVA will include treatment, baseline MG-ADL Score, baseline QMG Score, geographical region (North America, Europe and East Asia), baseline MGC, treatment-by-visit (interaction term), baseline MGC Score-by-visit (interaction term) as fixed effects and participant as a random effect.

Similarly, for Week 12 CFB in MG-QOL15r, MMRM ANCOVA will be include treatment, baseline MG-ADL Score, baseline QMG Score, geographical region (North America, Europe and East Asia), baseline MG-QOL15r, treatment-by-visit (interaction term), baseline MG-QOL15r Score-by-visit (interaction term) as fixed effects and participant as a random effect.

For each secondary endpoint, the MMRM will use an "unstructured" covariance structure for the repeated measures. In the event that the "unstructured" covariance structure model fails to converge, an AR (1) covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo will be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs and p-values. The least squares mean (LSMs) of each treatment group with standard errors (SE), and the least squares mean differences (LSMDs) between zilucoplan and placebo at Weeks 1, 2, 4, and 8 will also be reported with the corresponding 2-sided 95% CIs. Statistical outputs such as LSMs and 95% CIs will be plotted from Week 1 to Week 12.

These secondary endpoints will be summarized by treatment group and by visit using descriptive statistics on the mITT. The same summaries will be done by subgroup as defined in Section 5.8.

5.4.1.3 Sensitivity analysis

5.4.1.3.1 Sensitivity #1: MMRM using J2R approach

The same approach as Section 5.3.3.1 will be done on these secondary endpoints in the mITT.

5.4.1.3.2 Sensitivity #2: MMRM in CFS

The same approach as Section 5.3.3.3 will be done on these secondary endpoints in the CFS.

5.4.1.4 Supplementary analyses

5.4.1.4.1 Supplementary #1: MMRM under treatment policy approach

The same approach as Section 5.3.4.1 will be done on these secondary endpoints in the mITT.

5.4.1.4.2 Supplementary #2: MMRM on the PPS

The same approach as Section 5.3.4.2 will be done on these secondary endpoints in the PPS.

5.4.1.4.3 Supplementary #3: MMRM using Pattern-Mixture Model (PMM)

The same approach as Section 5.3.4.3 will be done on these secondary endpoints in the mITT.

5.4.2 Time first administration of rescue therapy over the 12-week Treatment period

5.4.2.1 Definition of endpoint

Time to receive rescue therapy over the 12-week treatment period (in days) is defined as: Date of first rescue therapy use – date of first IMP + 1.

Participants who do not take rescue therapy will be censored at the date of withdrawal/study completion.

5.4.2.2 Main analytical approach

Time to receive rescue therapy over the 12-week treatment period will be analyzed as time-to-event on the mITT, using Kaplan-Meier plots. KM estimated survival up to Week 12 will be calculated. Treatment difference will be evaluated using a Log Rank test.

5.4.2.3 Sensitivity analysis

5.4.2.3.1 Sensitivity #1: Assuming Discontinued Participants took Rescue Medication

The time-to-event analyses will be repeated assuming the participants who discontinued took rescue medication at the time they discontinued.

5.4.2.3.2 Sensitivity #2: CFS

The time-to-event analyses as described in Section 5.4.2.2 will be performed on the CFS.

5.4.2.4 Supplementary analyses

5.4.2.4.1 Supplementary #1: Time-to-event on PPS

The time-to-event analyses as described in Section 5.4.2.2 will be performed on the PPS.

5.4.3   Achieving MSE, MG-ADL score responder rate, QMG score responder rate without rescue therapy at Week 12

5.4.3.1   Definition of endpoints

These dichotomous secondary endpoints are defined as below:

- Achieving MSE is defined as achieving a MG-ADL value of a 0 or 1 at Week 12 and not having taken rescue therapy

- MG-ADL score responder rate is defined as achieving $\geq$ 3-point improvement from Baseline (decrease) at Week 12 and not having taken rescue therapy

- QMG score responder rate is defined as achieving $\geq$ 5-point improvement from Baseline (decrease) at Week 12 and not having taken rescue therapy

Intermittent missing data will be imputed using Markov Chain Monte Carlo (MCMC) to obtain monotone missing pattern. Any monotone missing data will be imputed using MAR assumption. Participants who received rescue therapy or who had an event of death or myasthenic crisis will be considered as non-responders. The endpoints above will then be dichotomized at Week 12 from the imputed continuous endpoint.

Achieving MSE is defined as achieving a MG-ADL value of a 0 or 1 at Week 12 (after multiple imputation where appropriate), calculated as:

Week 12 MG-ADL value = Baseline MG-ADL + Week 12 CFB in MG-ADL.

The criteria for success will be a value $\leq$ 1.0 to account to imputed Week 12 MG-ADL value that may not be integers.

5.4.3.2   Main analytical approach

Achieving MSE without rescue therapy will be analyzed in the mITT in each imputed dataset using a logistic regression with treatment as factor and baseline MG-ADL score as covariate. Odd Ratios, 95% Confidence interval and associated p-value will be provided. The treatment effects and standard errors will then be combined across the 100 imputed datasets to produce an overall p-value using the SAS proc MIANALYZE.

A $\geq$ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy and a $\geq$ 5-point reduction in QMG Score at Week 12 without rescue therapy will be analyzed in the mITT in each imputed datasets with treatment as a factor, baseline MG-ADL Score, baseline QMG score, and geographical regions (North America, Europe and East Asia) as covariates. The treatment effects and standard errors will then be combined across the 100 imputed datasets to produce an overall p-value using the SAS proc MIANALYZE.

Note: the logistic regression model for Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy endpoint has a reduced number of covariates as the anticipated number of events for this endpoint will be lower.

Odds Ratios and 95% confidence intervals of these 3 endpoints will be plotted on a forest plot.

The number and percentages of participants achieving MSE without rescue therapy will be summarized by treatment group for each scheduled visit. Similarly, descriptive statistics for each scheduled visit will be provided for MG-ADL responder rate and QMG responder rate without

rescue therapy. The same summary will be done by subgroup as defined in Section 5.8. Proportion of responder rates will be plotted on a bar chart with all scheduled visits on the same graph. Chi-square p-value will be added on the graph for Week 12 visit only, as exploratory.

5.4.3.3 Sensitivity analysis

5.4.3.3.1 Sensitivity #1: J2R

Deviations from the missing at random pattern for any other missing data will be evaluated using a J2R approach using Multiple Imputation (MI method) under the missing not at random assumption (MNAR) to handle any missing scores as explained in Section 5.3.3.1. Endpoints will then be dichotomized. Participants who received rescue therapy or who had any death or myasthenic crisis will be considered as non-responders. Each imputed dataset will be analyzed using a logistic regression as described in Section 5.4.3.2 for each of these secondary endpoints to provide Odd Ratios, 95% confidence intervals and p-values. The treatment effects and standard errors will then be combined across the 100 imputed datasets to produce an overall p-value using the SAS proc MIANALYZE.

5.4.3.3.2 Sensitivity #2: Logistic Regression using NRI at Week 12

Logistic regression analysis will be performed on the mITT population using non responder imputation (NRI). If a participant is missing a value, or a value is censored due to rescue therapy use or an adverse event of myasthenic crisis, missing data at Week 12 will be treated as non-responders. A logistic regression will then be used with the same covariates as defined in Section 5.4.3.2 for each of these dichotomous secondary endpoints to provide Odd Ratios with 95% confidence intervals and p-values.

5.4.3.3.3 Sensitivity #3: weighted GEE model at Weeks 1, 2, 4, 8 and 12:

Participants who received rescue therapy or who had an adverse event of death or myasthenic crisis will be considered as non-responders from the time of the intercurrent event. Other missing data will be assumed to be missing at random (i.e. no further imputation will be done). Each dichotomous secondary endpoint at Week 1, 2, 4, 8 and 12 will be analyzed as repeated measures using weighted Generalized Estimating Equations (GEE) on the mITT population. A binomial distribution with logit link will be used.

For achieving MSE, the model will include baseline MG-ADL score as covariate, treatment and visit as fixed effects, baseline-by-visit and treatment-by-visit interactions.

For MG-ADL and QMG responder rates, the model will include baseline MG-ADL score, baseline QMG score and geographical region (North America, Europe and East Asia) as covariates, treatment and visit as fixed effects, baseline-by-visit and treatment-by-visit interactions. The GEE procedure in SAS will be used.

An unstructured covariance matrix will be used to model the within-participant variance-covariance errors. In case of non-convergence, covariance structures with fewer parameters will be considered. The estimated odds will be reported for each treatment group at each scheduled visit. For the comparisons of zilucoplan versus placebo, Odd Ratios (OR) with 95% CI and p-values will be reported at each scheduled visit.

5.4.3.3.4 Sensitivity #4: Logistic Regression on CFS

The logistic regression as described in Section 5.4.3.2 will be performed on the CFS.

5.4.3.4   Supplementary analyses

5.4.3.4.1   Supplementary #1: Logistic Regression on PPS

The logistic regression analysis as defined in Section 5.4.3.2 will be performed on the PPS.

5.5   Exploratory Endpoints Analysis

5.5.1   Achievement of Minimal Manifestation Status per MGFA-PIS at Week 12 Without Rescue Therapy

Minimal manifestation status is a dichotomous endpoint. This is defined by the participant having a response of "Minimal Manifestations" on the MGFA-PIS eCRF page at Week 12 without having taken rescue therapy during the 12-week treatment period. Minimal manifestation status will be summarized using descriptive statistics in the mITT by treatment group and at each scheduled visit. Change in Status will also be summarized by treatment group at each scheduled visit.

5.5.2   CFB to Week 12 in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)

The WPAI:SHP endpoints will be summarized using descriptive statistics by treatment group at each scheduled visit. These endpoints are described in Section 6.1.5.7.

Each CFB to Week 12 WPAI endpoint will be analyzed in the mITT using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA). The same imputation approach will be used as for the main analysis of the primary endpoint for ICE1 and ICE2 (Section 5.3.2.2).

For each WPAI endpoint, MMRM ANCOVA will include treatment, baseline WPAI score, baseline MG-ADL Score, baseline QMG Score, geographical region (North America, Europe and East Asia), treatment-by-visit (interaction term), baseline WPAI score-by-visit (interaction term) as fixed effects and participant as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12. An "unstructured" covariance structure will be used. In the event the "unstructured" covariance structure model fails to converge, an AR (1) covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo will be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs and p-values. The least squares mean (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo at Weeks 1, 2, 4, and 8 will also be reported with the corresponding 2-sided 95% CIs. Statistical outputs such as LSMs and 95% CIs will be plotted from Week 1 to Week 12.

5.5.3   CFB to Week 12 in 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). These endpoints are described in Section 6.1.5.8.

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 in the mITT. The observed values of EQ VAS scores and change from Baseline will be summarized by treatment group 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.

5.5.4   CFB to Week 12 in Neuro-QOL Short Form Fatigue Scale

CFB to Week 12 in total score in Neuro-QOL Short Form Fatigue Scale will be analyzed in the mITT using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA). The same imputation approach will be used as for the main analysis of the primary endpoint for ICE1 and ICE2 (Section 5.3.2.2).

MMRM ANCOVA will include treatment, baseline total score in Neuro-QOL, baseline MG-ADL Score, baseline QMG Score, geographical region (North America, Europe and East Asia), treatment-by-visit (interaction term), baseline Neuro-QOL score-by-visit (interaction term) as fixed effects and participant as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12. An "unstructured" covariance structure will be used. In the event the "unstructured" covariance structure model fails to converge, an AR (1) covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo will be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs and p-values. The least square means (LSMs) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo at Weeks 1, 2, 4, and 8 will also be reported with the corresponding 2-sided 95% CIs. Statistical outputs such as LSMs and 95% CIs will be plotted from Week 1 to Week 12.

The CFB to Week 12 in Neuro-QOL Short Form Fatigue Scale will also be summarized in the mITT using descriptive statistics at each scheduled visit and by treatment group. A by-participant listing will be provided. Derivation rules for this endpoint are described in Section 6.1.5.9.

5.5.5   Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MG Composite Scores from baseline without rescue therapy

For each assessment, at each post-baseline assessment week (Weeks 1, 2, 4, 8, and 12) the number and percentage of participants who have a reduction (i.e., improvement) of $\geq$ X will be summarized by treatment group in the mITT. The improvement values will start at the maximum level of worsening and will continue to the maximum level of improvement seen in the study. Note this is an extension of the "Achieving a $\geq$3-point reduction in MG-ADL Score at Week 12 without rescue therapy" and "Achieving a $\geq$5-point reduction in QMG Score at Week 12 without rescue therapy" secondary endpoints. Additionally, the number and percentage of participants who have an increase (i.e., worsening) of $\leq$ X will be summarized. The worsening values will start at $\leq$ 1 and will continue to the maximum level of worsening seen in the study.

For each assessment, these results from maximum level of worsening to maximum level of improvement will be plotted on a cumulative frequency plot: right part of the bar plot will represent cumulative proportion of participants with the improvement/worsening for zilucoplan and left part will be for placebo. A reference line of 2 points improvements for MG-ADL, 3 points for QMG and 5 points for MGC will be provided. Maximum level of worsening and improvement may be redefined to increase the clarity of the graph.

MG-ADL response (defined as $\geq$ 2 points improvement from baseline) will be analyzed using the logistic Regression defined in Section 5.4.3.2. Similarly, QMG response (defined as $\geq$ 3 points improvement from baseline) will be analyzed using the logistic Regression defined in

Section 5.4.3.2. Odd Ratios, 95% Confidence interval and associated p-value will be provided as exploratory. Additionally, time to first MG-ADL response (≥ 2 points improvement from baseline) will be analyzed as exploratory over the 12-week treatment period. It will be defined (in days) as: Date of first MG-ADL response – date of first IMP + 1.

Participants who used rescue therapy prior to Week 12 or who are withdrawn from the treatment/study before achieving first MG-ADL response will be censored at time of event, whichever occurs first. Participants who never achieved a response at Week 12 will be censored at the date of their last MG-ADL assessment.

Time to first MG-ADL response over the 12-week treatment period will be analyzed as time-to-event, using Kaplan-Meier plots. Median time to MG-ADL response over the treatment period will also be calculated with 95% CIs. Treatment difference will be evaluated using a Log Rank test.

The same analysis will be done on:

- MG-ADL response, defined as ≥ 3 points improvement from baseline;
- QMG response, defined as ≥ 3 points improvement from baseline;
- QMG response, defined as ≥ 5 points improvement from baseline.

5.5.6   Sub-scores of the QMG, MG-ADL, MG-QOL15r, and MG-Composite scores

Items for the functional scales are defined in Table 5–2. The functional sub-score for a participant is defined as the total score of the corresponding items (or the value of the item if it is a single score).

Table 5–2:   Functional Sub-scores

Function	Scales			
	QMG	**MG ADL**	**MG-QOL15r**	**MGC**
Ocular	1-3	7-8	2	1-3
Bulbar	4-5	1-3	3,9	4-6
Respiratory	8	4	-	7
Limb/Axial	6-7, 9-13	5-6	12,15	8-10

If an item response has a missing value, the methods defined in Section 6.1.5.1, Section 6.1.5.2, Section 6.1.5.3, Section 6.1.5.3 for imputing missing values will be used.

The 4 sub-scores on QMG, MG-ADL, MG-QOL15r, MGC will be summarized using descriptive statistics by treatment group and by scheduled visit in the mITT. A by-participant listing will be provided.

The individual items for each total score (i.e. QMG, MG-ADL, MG-QOL15r, MGC) will also be summarized by treatment group in a shift table from Baseline to Week 12 visit.

5.6   Safety Analyses

Safety analyses will be presented on the Safety Set (SS) by dose group and overall. Listings for all safety analyses will be presented.

5.6.1   Extent of Exposure

IMP duration will be summarized by treatment group. The number of days on IMP will be calculated as follows:

IMP duration = [(Date of Last Dose Received) -(Date of First Dose Received)] +1

The exposure duration (i.e. total time at risk that incorporates 5 half-lives of zilucoplan) is defined as:

Exposure duration (in days) = [min (Last dose + 40 days, Last Visit/Contact) - (Date of First Dose Received)] +1

Patient-years exposure (PEY) for a treatment group will be calculated as the as the sum of the exposure durations of all study participants in the group divided by 365.25.

The number of study participants in each treatment group and overall extent of exposure in the SS will be summarized.

Note that temporary drug discontinuations and missed doses will not be incorporated into the calculations of the extent of study drug exposure analyses.

The number of doses missed (from the eCRF Study drug administration page after Day 1) will be summarized cumulatively treatment group.

In addition to the assessment of study medication duration as a continuous variable, the number and percent of study participants with treatment duration meeting the following criteria will also be summarized:
≥ 1 day
≥ 8 day
≥ 15 day
≥ 29 day
≥ 57 days
≥ 84 days

All drug administration details will be listed.

5.6.2   Adverse Events

5.6.2.1   Data considerations

Pre-existing conditions that are detected prior to administration of the first dose of study drug will be recorded as part of the medical history. For all subjects, the AE reporting period will start with the first administration of study drug on Day 1 and will end with the last study visit (i.e., End of Study Visit, Week 12 Visit), after which no new non-serious AEs are to be reported.

During the screening period and the safety follow-up period for the subjects who did not roll over into MG0011, only serious adverse events will be reported.

In addition, AEs will be classified for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 or later. 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.

A TEAE is defined as an AE starting on or after the time of first administration of IMP and up to and including 40 days after the final dose (or last contact depending on which occurs first). Adverse events starting before the date of the first administration of IMP will not be considered TEAEs.

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 5.1.1.10.

All TEAE summaries will be performed during the overall study and by study period of the COVID-19 pandemic period as defined in Section 5.1.1.3.2 . 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.

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

5.6.2.2   AE summaries

1. A TEAE overview table will be provided by treatment group, including the number, percentage of participants and frequency of the following TEAEs:

    - Any TEAEs

    - Serious TEAEs

    - TEAEs leading to permanent withdrawal from IMP

    - Treatment-related TEAEs

    - Severe TEAEs

    - TEAEs leading to death

−   All deaths (AEs leading to death)

2. The number, percentage of participants and frequency of the following TEAEs will be summarized by SOC, HLT, PT, and by treatment group:

    −   Any TEAEs

    −   Serious TEAEs

    −   Severe TEAEs

    −   Treatment-related TEAEs

    −   TEAEs leading to permanent withdrawal from IMP

    −   Treatment-related TEAEs leading to permanent withdrawal from IMP

    −   TEAEs leading to death

3. The number, percentage of participants and frequency of the following TEAEs will be summarized by SOC, PT, and by treatment group:

    −   Any TEAEs above threshold of 5% of participants (in any treatment group)

    −   Non-serious TEAEs above reporting threshold of 5% of participants (in any treatment group)

    −   Treatment-related TEAEs above reporting threshold > 5% of participants (in any treatment group)

4. The number, percentage of participants with TEAEs will be summarized by maximum intensity (mild, moderate and severe), SOC, PT, and by treatment group.

5. The number, percentage of participants and frequency of the following TEAEs will be summarized by relationship, SOC, PT, and by treatment group:

    −   Any TEAEs

    −   Serious TEAEs

    −   Fatal TEAEs

    −   Non-serious TEAEs above threshold of 5% of participants

For these summaries, the number and percentage of participants who experienced at least one TEAE as well as the number and percentage of participants who experienced each specific SOC and PT will be presented by treatment group. The corresponding number of TEAEs will also be presented for the Overall Summary of TEAEs table. For the presentation of TEAE incidences, the SOCs will be sorted alphabetically, and HLT within SOC – (if HLT is presented), and within HLT, the PT will be used and presented by decreasing total frequency based on the Zilucoplan treatment group.

The TEAE overview table and the number of percentage of participants of any TEAEs by SOC, HLT and PT will also be produced on the SS by treatment group on the subgroups defined in Section 5.8. Listings of all AEs, permanent withdrawal of IMP due to AEs, participant discontinuation from study due to AEs, AEs leading to death will be presented by treatment group and participants.

To assess the impact of the COVID-19 pandemic on safety, additional summaries and listings will be presented. For reporting purposes, AEs will be assigned to either pre-COVID-19, COVID-19 or post COVID-19 pandemic period by comparing the AE start date (based on imputed date) to the COVID-19 pandemic period start and end dates (Section 5.1.1.1.3.2). AE will be allocated to a period if it starts during the period. The following categories of TEAE will be summarized by MedDRA SOC, HLT and PT:

   − All TEAEs by time of onset relative to COVID-19 pandemic period (prior/during/post) by region and overall

   − All serious TEAEs by time of onset relative to COVID-19 pandemic period (prior/during/post) by region and overall

   − All TEAEs leading to study discontinuation by time of onset relative to COVID-19 pandemic period (prior/during/post) by region and overall

   − All TEAEs leading to permanent withdrawal of study medication by time of onset relative to COVID-19 pandemic period (prior/during/post) by region and overall

   − All COVID-19 related TEAEs by treatment group, region and overall

COVID-19 related TEAEs will be identified by searching for selected MedDRA terms as defined in Section 6.1.8 .

A separate listing of all COVID-19 related AEs will be presented.

In addition, all listing of AEs will include a column for COVID-19 relatedness (as defined above) and the time of onset of each AE relative to the COVID-19 pandemic.

A listing of all TEAE during the COVID-19 infection will be provided for participants infected by COVID-19. A TEAE during the COVID-19 infection is a TEAE that started from 5 days prior to the start date/ onset of a COVID-19 infection until the end date of the infection. If the COVID-19 infection is ongoing or the end date is missing at the time of database lock, TEAEs will be included up to 3 months (91 days) after the start of the infection or until the end of study date, which occurs first.

COVID-19 vaccination follows a specific mass vaccination program in a short time frame and the novelty of a vaccine is likely to increase the reporting of AEs. Vaccination might have an impact on the safety reporting in the non-COVID-19 vaccine clinical trials. Due to this, the potential impact of concomitant COVID-19 vaccination on the current trial may be different from other types of concomitant drugs and established vaccination, due to the frequency of potential events related to the COVID-19 vaccination and the evolving safety profile of these new vaccines. To control the potential bias arising when an important proportion of the vaccinated participants reported AEs to vaccination in the active group (which inappropriately may be captured as adverse reactions in the product information) additional safety outputs within the frame of sensitivity analysis will be created.

Additional sensitivity safety analysis with outputs presenting the TEAEs occurred when participants were considered as not at risk of TEAEs related to COVID-19 vaccination is proposed. The approach of interval censoring will be employed: interval censoring between

COVID-19 vaccination date and a pre-specified period in which participants are considered as at risk for COVID-19 vaccination related AEs. A 7-day period may allow the removal of the potentially most frequently reported AEs related to COVID-19 vaccines.
In such outputs, all TEAE data will be included, with the exception of the events occurred within for the defined window of 7 days post COVID-19 vaccination(s) for those participants vaccinated during the study and all TEAE data for those participants not vaccinated during the study.

The number, percentage of participants and frequency of the following TEAEs will be summarized by SOC, HLT, PT, and by treatment group:

– Any TEAE during the study but excluding TEAEs occurred within the 7-day period post each covid-19 vaccination (period including the day of vaccination)

– Any TEAE during the study occurring within the 7-day period post each COVID-19 vaccination (period including the day of vaccination)

– Any non-serious TEAE above threshold of 5% of participants (in any treatment group) censoring for AEs within the 7-day period post each COVID-19 vaccination (period including the day of vaccination).

– Any non- serious TEAE above reporting threshold of 5% of participants (in any treatment group), by relationship to study drug.

All AEs after the first COVID-19 vaccination will be listed for all vaccinated participants. Two separate listings will display the AEs after adjustment of the interval censoring (within the ES) and the concomitant COVID-19 vaccination (within the RS).

At all the outputs referring to the interval vaccination censoring, the following footnote will be incorporated: "COVID-19 Vaccination Interval Censored (TE)AEs exclude those (TE)AEs occurred within the pre-specified time period of 7 days post COVID-19 vaccination(s) for each participant, if applicable."

5.6.3   Other Safety Assessments

Other safety assessments (AE of interest, Laboratory data, Vital Signs, ECG and Immunogenicity) will also be performed.

5.6.3.1   AE of Interest (AEIs)

The following are AEIs (as defined in Section 6.1.6) that require special statistical analyses:

– Infections

– Neisseria infections

– Hypersensitivity reactions

– Anaphylactic reactions

– Injection site reactions

– Drug related hepatic disorders

– Malignancies

– Malignancies or unspecified tumors

The number and percentage of participants who experience each AE of Interest will be summarized by treatment group separately for each AE of interest. The following summaries will be presented:

– Incidence of AEIs and serious AEIs by SOC and PT (serious and non-serious will appear in the same table)

– Incidence of AEIs by relationship, SOC and PT

– Incidence of AEIs by maximum intensity (mild, moderate and severe), SOC and PT

Duration of TEAE (as defined in Section 5.1.1.10) for Injection site reactions (as defined in Section 6.1.6) will be summarized by treatment group and overall.

5.6.3.2   Clinical laboratory evaluations

The following table (Table 5–3) lists hematology, chemistry and coagulation analytes that are collected throughout the study, using a central laboratory and following the schedule of assessments according to the protocol.

Table 5–3:   Laboratory

Chemistry	Hematology
Alanine aminotransferase (ALT)	Hematocrit
Albumin	Hemoglobin
Alkaline phosphatase (ALP)	Mean corpuscular hemoglobin (MCH)
Amylase	Mean corpuscular hemoglobin concentration (MCHC)
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)
Bilirubin (total)	Platelet count
Blood urea nitrogen (BUN)	Red blood cell (RBC) count
Calcium	White blood cell (WBC) count and differential (%)
Chloride	Basophils (% and absolute)
Creatinine	Eosinophils (% and absolute)
Gamma-glutamyl transferase (GGT)	Lymphocytes (% and absolute)
Glucose	Monocytes (% and absolute)
Lipase	Neutrophils (% and absolute)
Potassium	**Coagulation**
Sodium	International normalized ratio (INR)/prothrombin time (PT)
Total protein	Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)
	Urinalysis

Table 5–3:   Laboratory

Chemistry	Hematology
	pH, Specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), urobilinogen, occult blood, hemoglobin and cells, microscopic examination
	Other
	C-reactive protein (CRP) Thyroid Stimulating Hormone (TSH) – screening only

All laboratory samples are collected prior to IMP administration at applicable visits. Coagulation test should only be performed in participants receiving anticoagulant therapy.

5.6.3.2.1   Laboratory values over time

Chemistry, hematology, coagulation and quantitative urinalysis (observed value, absolute change from Baseline) will be summarized in standard unit using descriptive statistics by treatment group at each scheduled visit. Qualitative urinalysis results will be summarized in frequency tables for each visit by treatment group.

The central data will be used for the summary tables. 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.

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.

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. Additional lab test, including pregnancy testing, will also be listed.

5.6.3.2.2   Individual Participant Changes of Laboratory Values

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 each scheduled post-Baseline visit and any post-Baseline visit (including unscheduled visit) by treatment group.

5.6.3.2.3   Laboratory Marked abnormalities

Treatment-emergent marked abnormalities (TEMAs) in laboratory parameters will be summarized by treatment group at each scheduled visit and at any visit (including unscheduled visit). Thresholds for defining marked abnormalities for relevant laboratory parameters are available in Appendix 6.2.1. Treatment-emergent is defined as meeting the criteria at any post-Baseline visit.

Listings will include a flag for values identified as Treatment-emergent Marked abnormalities (TEMA).

5.6.3.2.4   Assessment of potential liver toxicity

To assess the potential for liver toxicities, the following criteria will be used to define levels of liver function tests (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

Drug Hepatic disorders TEAEs will be defined as:

− TEAEs with narrow SMQ of "Drug related hepatic disorders - comprehensive search (SMQ)". However, these 2 sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)".

The following laboratory criteria for potential drug induced liver injuries are defined as follows:

− AST or ALT >3xULN with TBL >1.5xULN

− AST or ALT >3xULN with TBL >2xULN

In addition, post-baseline potential Hy's Law cases will be identified using the following definition:

− either AST or ALT > 3×ULN with concurrent ALP < 2 × ULN and concurrent total bilirubin > 2×ULN

In order to meet the above criteria, a study participant must experience the elevation in Bilirubin and ALT and AST (and the absence of the ALP elevation) at the same date. For example, a study participant who experiences a > 2xULN elevation of bilirubin at one date and a > 3xULN elevation in ALT (or AST) at a subsequent visit date has not fulfilled the Hy's law criteria.

The number and percentage of study participants with elevated liver function tests will be presented by treatment group at any visit (including unscheduled visits) in the Safety Set. The number and percentage of study participants with potential drug induced liver injuries including those who potentially meet the Hy's law criteria and Drug related hepatic disorders TEAEs will be summarized by treatment group. The liver function results for study participants with elevated liver function results will be listed. Scatterplots for each liver function test will be presented to show the shifts from Baseline to the maximum post-Baseline result. The upper limit of normal (ULN) of concern (i.e. 3xULN for ALT or AST, and 2xULN for TBL or ALP) will also be presented as lines on the plots. In addition, a scatterplot of the maximum post-Baseline TBL (/ULN) versus the maximum post-Baseline ALT (/ULN) will be provided on a logscale. Reference lines of 3ULN for ALT and 2ULN for TBL will be presented on the graph. If any study participant meets the potential Hy's law criteria, a graph displaying each liver function test (expressed as X ULN on a logscale) by time will be presented for each identified case.

5.6.3.3   Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, and temperature) will be collected throughout the study.

5.6.3.3.1   Vital Sign Values Over Time

Observed values and changes from Baseline will be summarized by vital sign variables and by scheduled visit by treatment group.

The number and percentage of participants who meet each of the marked abnormality criteria outlined in Appendix 6.2.2 will be summarized by treatment group at each scheduled visit and at any visit (including unscheduled visit).

Repeated and unscheduled measurements will be handled as described in Section 5.1.1.8 .

5.6.3.3.2   Individual Participant Changes of Vital Sign Values

The Vital Signs that are categorized as normal, high or low based on the reference will be presented in shift tables from Baseline to each scheduled post-Baseline visit and any post-Baseline visit (including unscheduled visit) by treatment group.

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

5.6.3.4   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 ($QTcF = QT/RR^{1/3}$)

5.6.3.4.1   Electrocardiogram Values Over Time

Observed values and changes from Baseline will be summarized by treatment group at scheduled visit and by ECG variable. Baseline value will be based on the screening visit as ECG is not performed on Day 1.

The number and percentage of participants who meet each of the marked abnormality criteria outlined Section 6.2.3 will be summarized by treatment group at each scheduled visit and at any visit (including unscheduled visit).

5.6.3.4.2   Individual Participant Changes of Electrocardiograms Values

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

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

5.6.3.5   Physical examination

Results of clinically significant physical examination abnormalities were reported as adverse events. No additional listing will be provided.

5.6.3.6   Total serum IgG and IgG subclasses

Total serum IgG concentrations and IgG subclasses will be summarized by treatment group and time point for observed values, change from Baseline, and percentage change from Baseline.

The maximum decrease from Baseline in total serum IgG (absolute and percentage decrease) will be reported in the listing and summarized for each treatment. In the event that a decrease from Baseline in total serum IgG is not observed in a given participant, the maximum decrease will be reported as the smallest increase from Baseline.

Mean and mean percentage change from Baseline values in total serum IgG will be plotted over time by treatment with all treatments overlaid on the same plot.

5.6.3.7   Immunogenicity

The ADA status for both active and placebo 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 'positive screen' and 'negative immunodepletion' will be defined as ADA negative

–   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.

Sample neutralizing antibody (NAb) status (positive/negative/missing) will be determined for ADA positive samples only.

The same definitions will be used for anti-PEG antibodies except for the determination of the Nab status.

5.6.3.7.1   ADA and anti-PEG Classification

Day 1 will be the baseline value for ADA status. The following ADA classifications will be derived from the sample ADA status:

Table 5–4:   ADA Classification

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Participants who are ADA negative at Baseline and ADA negative at all sampling points post-Baseline

Table 5–4:   ADA Classification

Classification	Classification Label	Definition
2	Pre-ADA negative – treatment induced ADA positive	Participants who are ADA negative at Baseline and ADA positive at any sampling point post-Baseline. It also includes participants who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with one or more ADA positive post-Baseline samples.
3	Pre-ADA positive – treatment reduced ADA	Participants who are ADA positive at Baseline, and ADA negative at all sampling points post-Baseline
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who are ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Observation Period) 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).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who are ADA positive at Baseline and ADA positive at any sampling point post-Baseline (including Observation Period) 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).
6	Inconclusive	Participants who have an ADA positive Baseline sample and some post-Baseline samples are missing, while other post-Baseline samples are ADA negative.
7	Treatment emergent ADA positive	Combination of 2 and 5
8	Pre-ADA positive	Combination of 3, 4, and 5

MSR = minimum significant ratio

In addition to the ADA classifications above, for the purpose of evaluations of the impact of ADA on plasma concentrations, IgG, and efficacy and safety endpoints, the following definitions will be used:

• Cumulative ADA status (positive/negative): if a participant has had at least one positive sample at any time point up (including unscheduled visits) to and including the given time point, that participant will be counted as positive at that time point, regardless of any subsequent negative measurements. Thus, the number of participants included in the summary of positive and negative samples will vary by time point for each treatment group.

- Overall ADA status: a participant will be classified as overall ADA Positive if at least one post-Baseline measurement (including unscheduled visits) is Positive. A participant will be classified as overall ADA Negative if at all post-Baseline visits the ADA status is Negative.

The ADA classification in Table 5–4 will be repeated for NAb for classifications 2, 3, 4, 5, 7 and 8. In addition, cumulative and overall Nab status will be defined as described above for ADA.

Classification in Table 5–4 will be repeated only for anti-PEG antibodies, and no Nab status will be determined for the anti-PEG antibodies.

5.6.3.7.2   ADA summaries

The following outputs will be presented on the SS.

Tables:

- Number and percentage of participants with positive, negative or missing sample ADA status at the time of each visit will be summarized by treatment group.

- Number and percentage of participants in each of the ADA classifications presented will be summarized by treatment group.

- The prevalence of immunogenicity (Classification 2, 3, 4 and 5), defined as the (cumulative) proportion of participants having ADA positive samples (including pre-ADA positive) at any point up to and including that time point will be summarized by treatment group. Missing samples will not be included in the denominator. The same table will be repeated for NAb.

- The first occurrence of treatment-emergent ADA positive (Classification 2 and 5) will be summarized using frequency and percentage at each post-Baseline visit by treatment group. Participants will be counted only once in the numerator based on the earliest visit at which treatment-emergent ADA positivity is observed. At other visits, participants will be counted in the denominator (assuming a measurement is available). Missing measurements will not be included in the denominator.

- The time to achieving treatment-emergent ADA positivity, separated by treatment group, will be summarized and analyzed based on Kaplan-Meier methods. Participants will be considered to have an event at the time point at which treatment-emergent ADA positive is first achieved. Participants who never had a treatment-emergent ADA positivity will be censored at the date of their last visit. This will also be plotted graphically.

- The TEAE overview table will be presented by treatment group and by ADA status. Additionally, the number and percentage of participants who experience some AEIs (Hypersensitivity reactions, injection sites reactions as defined in Section 6.1.6 and autoimmune disorders) will be presented by SOC and PT, by treatment group and by ADA Status. Autoimmune disorders will be defined if HLT is in 'Autoimmune disorders. For these summaries, participants will be presented for TEAEs occurring prior to becoming treatment emergent ADA positive, TEAEs occurring after becoming treatment emergent ADA positive, and TEAEs for participants who remained TE ADA negative (classifications 1,3,4,6).

Figures:

- Individual plots per participant will be plotted representing total IgG, MG-specific autoantibodies, neutralizing antibody (NAb) titer, MG-ADL total score. The sub-title of the

graph will include the participant number, bodyweight, treatment group, treatment-emergent ADA status, and ADA classifications. The dosing will be represented in the x axis with bars/arrows at the time of dose.

- The mean change from Baseline with 95% CI in MG-ADL total score versus time, by cumulative ADA status (positive/negative) at each individual timepoint will be plotted for each treatment group. The cumulative ADA positive and negative will be overlaid for comparison. The same plot will be repeated with cumulative NAb status.

- A plot of geometric mean with 95% CI of plasma concentrations of zilucoplan data by cumulative ADA status (positive/negative) at each scheduled visit will be presented.

- A plot of geometric mean with 95% CI of total IgG (absolute) and arithmetic mean of percentage change from Baseline by cumulative ADA status will be presented by treatment group.

5.6.3.7.3 Anti-PEG antibody summaries

The same tables will be provided for anti-PEG antibodies only (no Nab status, results or classification) by treatment group.

All individual study participant-level ADA results will be listed including the results from the screening assay, confirmatory assay with anti-PEG antibodies results, the status (of both ADA and anti-PEG antibodies), classification (of both ADA and anti-PEG antibodies) with the NAb results, status and classification for ADA.

5.6.3.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

Results of the C-SSRS will be summarized in SS by treatment group and scheduled timepoint using the number of participants and percentage with (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:

- Wish to be dead
- Non-specific active suicidal thoughts
- Active suicidal ideation with any methods (not plan), without intent to act
- Active suicidal ideation with some intent to act, without specific plan
- Active suicidal ideation with specific plan and intent

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

- Actual attempt
- Interrupted attempt
- Aborted attempt
- Preparatory acts or behavior
- Completed suicide

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 participant engaged in Non-Suicidal Self-Injurious Behavior?" in questionnaire.

A separate summary on frequency of C-SSRS number of episodes will be provided by treatment group.

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

5.7 Other Analyses

5.7.1 Other Exploratory endpoints

5.7.1.1 Pharmacokinetics

The plasma concentrations of zilucoplan and its two major metabolites (⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛) will be summarized by scheduled sampling day for the PK-PPS using n, arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric coefficient of variation (geoCV) and 95% CI (assuming log-normally distributed data).

A spaghetti plot of combined individual concentration versus time profiles will be presented by analyte in linear and semi-logarithmic scale with all participants overlaid on the same plot.

Additionally, mean (+SD) plasma concentration versus time overlaid for both analytes will also be presented for all scheduled timepoints on a linear and semi-logarithmic scale. The SD will not be provided on the semi-logarithmic scale.

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

PK summaries will be based on observed value. No imputation will be done. 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 least 2/3 of the individual data points at a timepoint are above the LLOQ. Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance.

- 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 will be listed for the PK-PPS and will include the actual sampling time in days relative to the previous dose.

PK assessments in participants undergoing rescue therapy will be analyzed separately.

Plasma concentration data of Zilucoplan may be subjected to population pharmacokinetic analysis to derive population estimates of PK parameters and test the effect of various covariates such as anti-drug antibodies, age, weight, gender. Details of the analysis will be described in a separate Data Analysis Plan (DAP). This analysis may be performed by combining the data from the current study with data from other Zilucoplan studies if deemed appropriate. The results of

the population PK analysis will not be reported in the clinical study report (CSR) but in a separate modelling report.

5.7.1.2   Pharmacodynamics

Pharmacodynamic analyses will be performed on the PDS.

 The pharmacodynamic endpoints include:

–   sRBC lysis assay

–   C5 levels

Summary statistics will be provided for the values, change from baseline, and percent change from baseline at each of the scheduled assessment time points. The change from baseline for each of these endpoints will be assessed by an ANCOVA model with treatment as a factor and the corresponding baseline value as a covariate. The active dose will be compared to the placebo group based on the ANCOVA model.

PD assessments in participants undergoing rescue therapy will be analyzed separately.

Population PD or population PK/PD analyses may be conducted for the PD variables of interest. Details of such PD or PK/PD analyses will be described in a separate DAP. The results of the analyses will not be reported in the CSR but in a separate report.

5.7.1.3   Biomarkers and Autoantibodies

Blood samples for mechanistic biomarker testing [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), and inflammatory markers] will be obtained prior to administration of study drug (within 1 hour of dosing). The results of the biomarker analysis and autoantibodies will be summarized by treatment group on the SS. This data will be listed on the RS. Other biomarker testing may be done and will be reported separately.

5.7.1.4   Pharmacogenomic

Participation in the pharmacogenomic assessment is optional, and participants must provide additional consent for the pharmacogenomic analysis. For participants who choose to participate in pharmacogenomic studies, a blood sample will be obtained. All genomic analyses will be performed at an accredited laboratory.

Pharmacogenomic assessment may be analyzed in a separate report.

5.7.1.5   Additional Rescue Therapy analyses

Participants are expected to remain on stable doses of all medications unless medically indicated changes become necessary.

Participants requiring rescue therapy during Treatment Period are analyzed as time-to event in Section 5.4.2 as secondary efficacy endpoint. In addition, the frequency and type of rescue medication (Immunoglobulin or Plasma Exchange) a participant receives will be summarized. These summaries will be provided by treatment group for the mITT Population. The frequency of use of rescue therapy will be compared between both treatment groups using a Pearson's chi-square test. Rescue therapy use will also be summarized by subgroup as defined in Section 5.8.

5.7.2 Specific analyses for Japanese Participants

Study participant characteristics

Study participant characteristics will be summarized for participants in the mITT population from Japan only (as specified in Section 6.1):

- Analysis Population and Patient Disposition (Section 5.2)

- Demographics and other baseline characteristics (as specified in Section 6.1)

- Protocol deviations (as specified in Section 6.1)

- MG specific Prior and Concomitant Medications (as specified in Section 6.1)

- Study Treatment Duration (as specified in Section 5.6.1)

- Rescue medication (as specified in Section 5.7.1.5).

Efficacy endpoints

The following endpoints will be summarized using descriptive statistics for participants in the mITT population in Japan only by treatment:

- Primary efficacy endpoint

  - Change from Baseline (CFB) in Week 12 MG-ADL score. It will also be presented by visit.

- Secondary efficacy endpoints

  - CFB to Week 12 in the Quantitative Myasthenia Gravis (QMG) Score. It will also be presented by visit.

  - CFB to Week 12 in the Myasthenia Gravis Composite (MGC) Score. It will also be presented by visit.

  - CFB to Week 12 in the Myasthenia Gravis – Quality of Life revised (MG-QOL15r) Score. It will also be presented by visit.

  - Time to first administration of rescue therapy over the 12-week Treatment Period

  - Achieving Minimal Symptom Expression (MSE), defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy. It will also be presented by visit.

  - Achieving a ≥ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy. It will also be presented by visit.

  - Achieving a ≥5-point reduction in QMG Score without rescue therapy at Week 12. It will also be presented by visit.

The observed change from baseline with standard errors will be plotted by visit for MG-ADL and for QMG. In addition to the overall summary, the primary endpoint CFB in Week 12 MG-ADL scores will be analyzed in the mITT population using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment, baseline MG-ADL Score, baseline QMG Score, treatment-by-visit (interaction term), baseline MG-ADL Score-by-visit (interaction term), as fixed effects and participant as a random effect. The MMRM ANCOVA will include

Weeks 1, 2, 4, 8, and 12. An AR (1) correlation structure will be used to model the within participant covariance errors. The Kenward-Roger approximation will be used to estimate the degrees of freedom. Least squares mean (LSM) and standard errors (SE) will be provided by treatment group for each visit. LSM treatment difference and 95% confidence intervals will also be provided for all visits. The same imputation as the main analysis of the primary endpoint for ICE1 and ICE2 will be used. More details can be provided in Section 5.3.2.2.

- **Pharmacokinetics**

The plasma concentrations of zilucoplan and its two major metabolites (   ) will be summarized by treatment group and by scheduled sampling day for the PK-PPS for Japanese participants (as specified in Section 5.7.1.1)

- **Pharmacodynamics**

Pharmacodynamic parameters (as specified in Section 5.7.1.2) will be summarized on the PD-PPS in Japanese participants.

- **ADA summaries** (as mentioned in Section 5.6.3.7):

    – Number and percentage of participants with positive, negative or missing ADA status at the time of each visit and overall will be summarized by treatment group.

    – Number and percentage of participants in each of the ADA classifications will be summarized by treatment group.

    – Number and percentage of participants with first occurrence of treatment-emergent ADA positive at each visit will be summarized by treatment group.

    – The cumulative number of 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.

Safety endpoints

- An TEAE overview table will be provided.

- The number, percentage of participants and frequency of the following TEAEs will be summarized by SOC, HLT, PT, and by treatment group:

    – Any TEAEs

    – Serious TEAEs

    – Severe TEAEs

    – Treatment-related TEAEs

    – Permanent withdrawal of IMP due to TEAEs

    – Treatment-related TEAEs resulting in permanent withdrawal of IMP due to TEAEs

    – TEAEs leading to death

- The number, percentage of participants and frequency of any TEAEs will be summarized by maximum intensity (mild, moderate and severe), SOC, PT, and by treatment group.

- The number, percentage of participants and frequency of the following TEAEs will be summarized by relationship, SOC, PT, and by treatment group:

  – Any TEAEs

  – Serious TEAEs

- Incidence of AEIs by SOC and PT by treatment group (as defined in Section 5.6.3.1)

5.8 Subgroup analyses

Safety analyses on TEAEs and the primary and secondary efficacy endpoints will be analyzed on the following subgroups:

  – Race (Asian, Black or African American, White, Other/Mixed)

  – Age (<65 years / $\geq$ 65 years)

  – Gender (Male / Female)

  – Duration of disease at Baseline (<median, $\geq$ median)

  – MGFA disease class at Baseline (Class II (IIa, IIb), III (IIIa, IIIb), or IV (IVa or IVb))

  – Chronic Kidney Disease Stages: normal renal function (eGFR $\geq$ 90 mL/min/1.73m2) , mild (eGFR 60–89 mL/min/1.73m2 [CKD stage 2]), moderate (eGFR 30–59 mL/min/1.73m2 [CKD stage 3]), severe (eGFR 15–29 mL/min/1.73m2 [CKD stage 4]) renal insufficiency end stage renal disease : eGFR < 15 mL/min/1.73m²

  – MG Refractory (yes/no; defined in Section 6.1.4.4)

Additionally, the primary and secondary efficacy endpoints will also be analyzed on the following subgroups:

  – Baseline MG-ADL ($\leq$9 / $\geq$10)

  – Baseline QMG ($\leq$17 / $\geq$18)

  – Region (North America, Europe, and East Asia)

  – Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

  – Weight in Kg (<43, 43-56, 56-<77, 56-<150, $\geq$ 150)

  – BMI: <18.5, 18.5 - <25, $\geq$25 - <30, $\geq$30 - <40, $\geq$ 40 (kg/m2)

  – Ever had a crisis (dichotomous yes/no class variable)

  – Prior thymectomy (dichotomous yes/no class variable)

  – Prior steroid therapy (i.e., Group A from Table 6–2 dichotomous yes/no class variable)

  – Steroid therapy taken at baseline (i.e., Group A from Table 6–2; dichotomous yes/no class variable)

- Prior immunosuppressive therapy (nonsteroidal) (i.e., Group E from Table 6–2;dichotomous yes/no class variable)

- Immunosuppressive therapy (nonsteroidal) at baseline (i.e., Group E from Table 6–2; dichotomous yes/no class variable)

- Prior history of IVIG or SC immunoglobulin or PLEX (i.e., Group D from Table 6–2; dichotomous yes/no class variable)

- Diagnosed with Thymoma

- By timing of study participants enrollment relative to COVID-19 pandemic periods (prior/during/after) as defined in Section 5.1.1.1.3.2

- By timing of Week 12 visit relative to COVID-19 pandemic periods (prior/during/after) as defined in Section 5.1.1.1.3.2

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.

For refractory and non-refractory participants, the CFB at Week 12 in MG-ADL will be assessed in each stratum separately using a MMRM with treatment and visit (categorial) as fixed effects, baseline MG-ADL, baseline QMG, region as covariates and baseline-by-time, treatment-by-time interactions. An "unstructured" covariance structure will be used. In the event the "unstructured" covariance structure model fails to converge, an AR (1) covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The least square means (LSMs) and standard errors (SE) of each treatment group, and the least squares mean differences (LSMDs) between zilucoplan and placebo will be reported for the Week 12 Visit along with the corresponding 2-sided 95% CIs for each subgroup stratum.

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

5.9   Interim Analyses

Not Applicable

5.10   Data Monitoring Committee (DMC) or Other Review Board

Not Applicable

6   SUPPORTING DOCUMENTATION

6.1   Appendix 1 Non-key analysis specifications

6.1.1   Baseline characteristics and demographics

Participant demographics and baseline characteristics will be summarized by treatment group and overall, for the mITT, PPS and Safety Populations, using descriptive statistics. Additional subgroup summary will be presented based on the enrolled date relative to the cut-off date by prior and during/post COVID-19 pandemic period based on the mITT.

Descriptive statistics for continuous variables (including n, mean, SD, Median, Min and Max) will be provided for:

- Age (years), calculated as (year of informed consent date – year of birth

- Height (cm)

- Weight (kg)

- Body mass index (BMI) (kg/m^2) calculated as: $BMI = \frac{Weight\ (kg)}{(Height\ (m))^2}$ using the weight and height measurements obtained at screening.

- Baseline MG-ADL and QMG scores

Descriptive statistics for categorial variables (including counts and percentages) will be provided for:

- Gender (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)

- Age (<18, 19- <65 and ≥65 years).

- Geographic region (North America, Europe, and East Asia)

- Country

- BMI in kg/m^2 (<18.5, 18.5 - <25, ≥25 - <30, ≥30 - >40, ≥ 40)

- Weight in Kg (<56, 56-<77, ≥ 77 - <150, ≥ 150)

- MD-ADL scores (≤9/≥10)

- QMG scores (≤17 / ≥18)

- Chronic Kidney Disease Stages: normal renal function (eGFR ≥ 90 mL/min/1.73m2) , mild (eGFR 60–89 mL/min/1.73m2 [CKD stage 2]), moderate (eGFR 30–59 mL/min/1.73m2 [CKD stage 3]), severe (eGFR 15–29 mL/min/1.73m2 [CKD stage 4]) renal insufficiency end stage renal disease : eGFR < 15 mL/min/1.73m²A by-participant listing of Baseline characteristics will be provided.

6.1.2 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol which could potentially have a meaningful impact on the study conduct, on the primary analysis, key safety or PK/PD outcomes for an individual participant. IPDs will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

A summary of number and percentage of participants having important protocol deviation by relationship to COVID-19 will be provided for the RS population by treatment group

Relationship to COVID-19 will be programmed from the COVID-19 Impact eCRF page or when available, it will be assessed by the sites.

6.1.3 Medical history

6.1.3.1 Medical history (other than MG disease history)

Medical History will be summarized by treatment group and overall, by system organ class (SOC), high level term (HLT) and preferred term (PT) for the mITT population. A participant will be counted only once for each preferred term. The summary will present the results alphabetically by System Organ Class (SOC), HLT within SOC, and within HLT, by decreasing frequency for the PT in active treatment group. Additionally, the summary will be repeated by pre-, during the COVID-19 pandemic based on the medical history start date relative to the pandemic cut-off date.

Medical History will be listed on the RS population.

6.1.3.2 gMG disease history

The following gMG disease history data will be summarized by treatment group and overall, for the mITT Population.

- Age at onset (years)

- Duration of disease (years) = (Date of Study Day 1 – Date of Diagnosis)/365.25

Note: If the Date of Diagnosis day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Diagnosis date is later than the date of Study Day 1, impute Study Day 1.

- Symptoms at onset (Ocular/Generalized)

- MGFA Disease Class at Screening (Class II (IIa, IIb), III (IIIa, IIIb), or IV (IVa or IVb))

- Ever had a Crisis (Yes/No)

- Time since most recent crisis (months)

  ◦ Time since most recent crisis will be calculated as (Date of Study Day 1– Date of crisis)/ (365.25/12)

Note: If the Date of Crisis day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Crisis date is later than the date of Study Day 1, impute the date of Study Day 1.

- Crisis History (Number of crises: 1, 2, 3, more than 3)

- Family members have MG (Yes, No)

- Diagnosed with Thymoma (Yes, No)

- Prior Thymectomy (No: Yes [Total Thymectomy, Subtotal Thymectomy])

- Time since Thymectomy (months), calculated as (Date of Study Day 1 – Date of Thymectomy)/ (365.25/12)

Note: If the Date of Thymectomy day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Thymectomy date is later than the date of Study Day 1, impute the date of Study Day 1.

Baseline characteristics will be listed overall and by COVID-19 pandemic period.

6.1.4 Prior/concomitant medications

6.1.4.1 Prior/concomitant medications classification

Medications will be classified as follow based on imputed start and stop dates & times as outlined in Section 5.1.1.10.

- **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 Period.

- **Concomitant Only** medications will include any medication that started after the first administration of IMP and continues during the Treatment Period.

Table 6–1: Prior and Concomitant Medications

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

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or taken at baseline, it will be assumed that it is taken at baseline.

6.1.4.2 Prior and concomitant medications (non-MG therapy)

A non – MG related medication is defined by the "indication" value on the Prior and Concomitant Medication eCRF form not equal to "Therapy for MG".

Past, Prior, Baseline, Concomitant or Concomitant Only medications will be summarized by treatment group and overall, on the SS. Medications will be presented in alphabetical order by Anatomical Main Group (ATC Level 1), then by Pharmacological Subgroup (ATC level 3) and finally by decreasing frequency of PT within Zilucoplan group. In the case of ties, sort these

alphabetically within the Zilucoplan treatment group. Summaries will include the overall number and percentage of participants receiving at least one treatment of a PT.

A by-participant listing will be provided.

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

6.1.4.3   MG Specific Prior and Concomitant Medications

MG specific medication will be presented separately from the other prior and concomitant medications (for both tables and listings). A MG specific medication is defined by the "indication" value on the Prior and Concomitant Medication eCRF form = "Therapy for MG".

MG specific Past, Prior, Baseline, Concomitant and Concomitant only medications will be summarized by treatment group and overall on the SS as defined in Section 6.1.4.2.

A by-participant listing will be provided.

Additionally, the number and percentage of participants who are taking one or more of the sets of MG specific medications presented in Table 6–2 (i.e., Groups A-E) will be summarized using the same 2 sets of tables: MG specific prior medications and MG specific medications taken at baseline.

Table 6–2:	Concomitant Class	
Group	**Concomitant**	**Preferred Term**
A	Prednisone for MG	PREDNISONE
	Other corticosteroids for MG	DEXAMETHASONE METHYLPREDNISONE METHYLPREDNISONE SODIUM SUCCINATE TBD*
B	azathioprine	AZATHIOPRINE
	mycophenolate	MYCOPHENOLATE MOFETIL
C	IV Ig	IMMUNOGLOBULINS NOS
	SC Ig	IMMUNOGLOBULINS NOS
D	IVIg, SCIg, or plasma exchange*	IMMUNOGLOBULINS NOS PLEX
E	cyclosporine	CICLOSPORIN
	cyclophosphamide	CYCLOPHOSPHAMIDE
	methotrexate	METHOTREXATE
	tacrolimus	TACROLIMUS
	rituximab	RITUXIMAB
	Other third line immunosupressants	TBD**

*plasma exchange will be on the Procedures eCRF

**TBD: To be defined: a complete list of corresponding medications and preferred terms will be provided by UCB prior to DBL

6.1.4.4   Refractory criteria

A participant will be considered "MG Refractory" if they meet the following criteria (based on eCRF MG Treatment History page):

Treatment for at least one year with two or more of the following therapies:

- Prednisone
- Azathioprine
- Mycophenolate
- Cyclosporine
- Cyclophosphamide
- Methotrexate
- Tacrolimus
- Rituximab
- Eculizumab
- Other Corticosteroids for MG
- Other Immunosuppressive therapies (IST)

OR History of treatment with at least one of the above therapies for 1 year or more and required chronic plasma exchange or IVIG or Subcutaneous IG at least every 3 months for the 12 months prior to enrolment.

The MG Refractory status at baseline will be summarized by treatment group and overall, on the SS population. Additionally, the number and percentage of participants who have ever received one or more of the MG specific medications presented above will be summarized accordingly in the same table (eCRF form = "MG Treatment History")

6.1.5   Data derivation rules

6.1.5.1   MG Activities of Daily Life score (MG-ADL score)

The MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity. Higher scores are associated with more severe symptoms of MG. A 2-point change in MG-ADL Score is considered clinically meaningful [Wolfe et al. 1999; Muppidi et al. 2011].

Table 6–3 presents the 8 items with corresponding response scale, each scored on a 0 to 3-point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the 8 individual scores; range 0 to 24.

If a participant is missing a response for one of the 8 individual MG-ADL items, the participant's corresponding item score from the previous MG-ADL assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG-ADL, the

MG-ADL total score will be set to missing for that visit. If the participant is missing responses to more than one of the 8 items, the MG-ADL total score will be set to missing for that visit.

Table 6–3:   MG-ADL Score

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

6.1.5.2   Quantitative Myasthenia Gravis (QMG) Score

The QMG is a standardized and validated quantitative strength scoring system that was developed specifically for MG. Higher scores are representative of more severe impairment. A change in the QMG Score of 3 points or more may be considered clinically meaningful, in a typical clinical trial population of MG patients [Barohn, 1998; Katzberg, 2014].

Table 6–4 presents the scoring scale for the 13 individual assessments, each scored on a 0 to 3-point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the individual scores; range 0 to 39.

If a participant is missing a response for one of the 13 individual QMG items, the participant's corresponding item score from the previous QMG assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled QMG, the QMG total score will be set to missing for that visit. If the participant is missing responses to more than one of the 13 items, the QMG total score will be set to missing for that visit.

Table 6–4:   QMG Score

Item	None	Mild	Moderate	Severe
Grade	**0**	**1**	**2**	**3**
Double vision (lateral gaze) (seconds) Measured both to the right and to the left (take worst score between both eyes)	61	11-60	1-10	Spontaneous
Ptosis (upward gaze) (seconds)	61	11-60	1-10	Spontaneous
Facial muscle	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing (4 oz water, ½ cup)	Normal	Minimal coughing or throat clearing	Sever coughing. Choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech following counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9
Right arm outstretched (90° sitting) (seconds)	240	90-239	10-89	0-9
Left arm outstretched (90° sitting) (seconds)	240	90-239	10-89	0-9
Forced vital capacity	≥80%	65-79%	50-64%	<50%
Right hand grip (kg)	≥45 (M) ≥30 (F)	15-44 (M) 10-29 (F)	5-14 (M) 5-9 (F)	0-4 (M) 0-4 (F)
Left hand grip (kg)	≥35 (M) ≥25 (F)	15-34 (M) 10-24 (F)	5-14 (M) 5-9 (F)	0-4 (M) 0-4 (F)
Head, lifted (45% supine) (seconds)	120	30-119	1-29	0
Right leg outstretched (45-50%, supine) (seconds)	100	31-99	1-30	0
Left leg outstretched (45-50%, supine) (seconds)	100	31-99	1-30	0

F=female; M=male.

6.1.5.3   MG Composite (MGC) score

The MG Composite (MGC) is a 10-item scale that has been used to measure the clinical status of patients with MG, both in the practice setting and in clinical trials, in order to evaluate treatment response. Higher scores in the MGC indicate more severe impairment due to the disease. A 3-point change in this assessment is considered clinically meaningful [Benatar et al. 2012; Sadjadi 2012].

Table 6–5 presents the 10 items with corresponding response scale scores. The total score is the sum of the 10 individual scores; range 0 to 50.

If a participant is missing a response for one of the 10 individual MG Composite items, the participant's corresponding item score from the previous MG Composite assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG Composite assessment, the MG Composite total score will be set to missing for that visit. If the participant is missing responses to more than one of the 10 items, the MG Composite total score will be set to missing for that visit.

Table 6–5:   MG-C score items and scoring algorithm

	Item	Result/Grade	Result/Grade	Result/Grade	Result/Grade
Imputed from QMG	Ptosis, upward gaze (physician examination)	>45 seconds/0	11-45 seconds/1	1-10 seconds/2	Immediate/3
	Double vision on lateral gaze, left or right (physician examination)	>45 seconds/0	11-45 seconds/1	1-10 seconds/3	Immediate/4
	Eye closure (physician examination)	Normal/0	Mild weakness (can be forced open with effort)/0	Moderate weakness (can be forced open easily)/1	Severe weakness (unable to keep eyes closed)/2
Imputed from MG-ADL	Talking (patient history)	Normal/0	Intermittent slurring or nasal speech/2	Constant slurring or nasal but can be understood/4	Difficult to understand speech/6
	Chewing (patient history)	Normal/0	Fatigue with solid food/2	Fatigue with soft food/4	Gastric tube/6
	Swallowing (patient history)	Normal/0	Rare episode of choking or trouble swallowing/2	Frequent trouble swallowing eg, necessitating changes in diet/5	Gastric tube/6
	Breathing (thought to be caused by MG)	Normal/0	Shortness of breath with exertion/2	Shortness of breath at rest/4	Ventilator dependence/9

Table 6–5:   MG-C score items and scoring algorithm

	Item	Result/Grade	Result/Grade	Result/Grade	Result/Grade
	Neck flexion or extension (weakest) (physician examination) [1]	Normal/0	Mild weakness/1	Moderate weakness (ie, 50% weak, +/-15%)/3	Severe weakness/4
	Shoulder abduction (physician examination) [1]	Normal/0	Mild weakness/2	Moderate weakness (ie, 50% weak, +/-15%)/4	Severe weakness/5
	Hip flexion (physician examination) [1]	Normal/0	Mild weakness/2	Moderate weakness (ie, 50% weak, +/-15%)/4	Severe weakness/5

[1] 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

6.1.5.4   Myasthenia Gravis Quality of Life (MG-QoL 15r)

The Myasthenia Gravis-Quality of Life Revised (MG-QOL15r) is a 15-item survey that was designed to assess quality of life in patients with MG. Higher scores indicate more severe impact of the disease on aspects of the patient's life [Burns, 2010; Burns, 2016]. The following are the 15 questions and the corresponding response scales, each scored on a 0-2 point scale (0=Not much at all, 1=Somewhat, 2=Very Much).

1. I'm frustrated by my myasthenia gravis.

2. I have trouble using my eyes because of my MG (e.g. double vision).

3. I have trouble eating because of my myasthenia gravis.

4. I have limited my social activity because of my myasthenia gravis.

5. My myasthenia gravis limits my ability to enjoy hobbies and fun activities.

6. I have trouble meeting the needs of my family because of my myasthenia gravis.

7. I have to make plans around my myasthenia gravis.

8. I am bothered by limitations in performing my work (include work at home) because of my

9. I have difficulty speaking due to my myasthenia gravis.

10. I have lost some personal independence because of my myasthenia gravis (e.g. driving, shopping, running errands) 11. I am depressed about my myasthenia gravis

12. I have trouble walking due to my myasthenia gravis

13. I have trouble getting around public places because of my myasthenia gravis.

14. I feel overwhelmed by my myasthenia gravis.

15. I have trouble performing my personal grooming needs due to my myasthenia gravis.

The MG-QOL15r total score is the sum of the 15 individual item scores with a range of 0 to 30.

If a participant is missing a response for one of the 15 individual MG-QOL15r items, the participant's corresponding item score from the previous MG-QOL15r assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG-QOL15r, the MG-QOL15r total score will be set to missing for that visit. If the participant is missing responses to more than one of the 15 items, the MG-QOL15r total score will be set to missing for that visit.

6.1.5.5   Minimal Symptom Expression (MSE)

Minimal Symptom Expression (MSE) is designed to assess how many participants become free or virtually free of MG symptoms as measured by achieving an MG-ADL total score of 0 or 1 on therapy [Vissing et al. 2018].

6.1.5.6   MGFA Post-Intervention Status

The MGFA Post-Intervention Status (MGFA-PIS) is a physician-determined assessment of clinical symptoms of MG after initiation of MG specific therapy.

Pharmacologic Remission (PR) is defined as follows: The participant has no symptoms or signs of MG since baseline and continues to take therapy for MG. Participants taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.

Minimal manifestation is defined as follows: 'The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of Complete Stable Remission (CSR) or Pharmacologic Remission (PR) do have weakness that is only detectable by careful examination.' For the purpose of the current study, minimal manifestation will be determined at each timepoint after treatment initiation (rather than after 1 year).
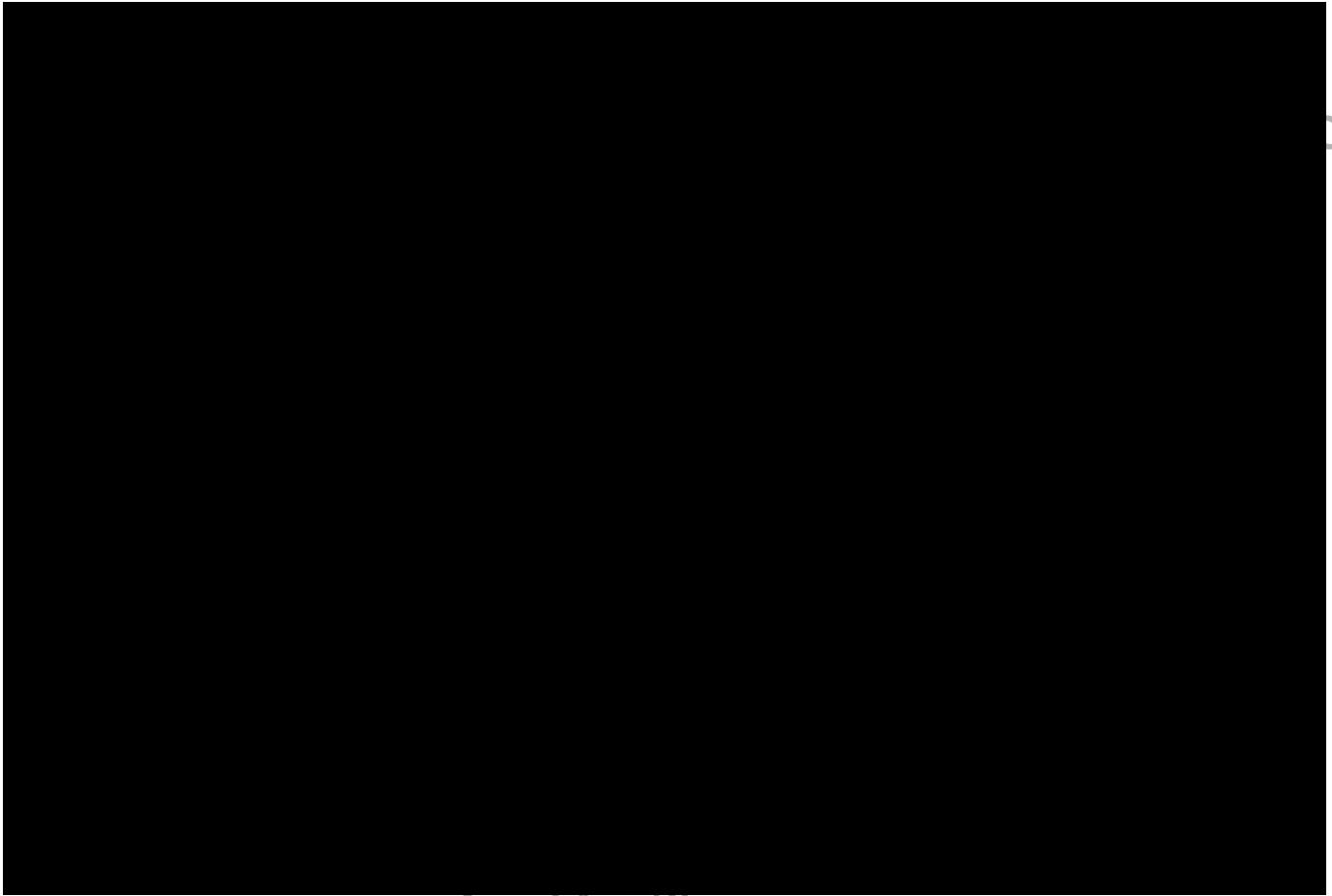
Change in status since baseline (improved, unchanged, worse, exacerbation, or died of MG) will also be determined.

6.1.5.7   Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) is a standardized 6-item questionnaire for assessing the amount of both absenteeism (work time missed) and presenteeism (reduced on-the-job effectiveness) due to health problems [Reilly et al. 1993]. All participants will be asked to complete the WPAI:SHP questionnaire at Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12. The questions and response scales are provided in Table 6–6.

WPAI:SHP endpoints are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (i.e., worse outcomes).

Table 6–6:   WPAI:SHP

The WPAI:SHP endpoints and endpoint algorithms are provided below. If a question's response is missing the endpoint which uses that response will be set to missing. Endpoint scores will be multiplied by 100 to express results as percentages.

6.1.5.8   EQ-5D-5L

The 5-level EuroQol-5D (EQ-5D-5L) version is a standardized instrument for measuring generic health status. The EQ-5D-5L is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems [EuroQOL Group 1990]. Participants answer questions based on symptoms and health status on the day the questionnaire is completed. There is also an overall good or bad health question on a 0-100-point

VAS (visual analog scale). All participants will be asked to complete the EQ-5D-5L at Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12.

6.1.5.9 Neuro-QOL Fatigue Short Form

The Neuro-QOL Fatigue Short Form is part of the Neuro-QOL battery of measures that quantify the physical, mental, and social effects experienced by patients with neurological conditions. The instrument consists of 8 questions each answered on a 1-5 integer ordinal scale (1: Never; 2: Rarely; 3: Sometimes; 4: Often; and 5: Always) with higher scores indicating greater level of fatigue. The total raw score will be calculated as the sum of the values of the response to each question. The total score ranges from 8 to 40. The total score can be approximated (i.e. prorated) if at least 4 of the questions are non-missing by summing the response scores from the items that were answered, multiply by 8 and divide by the number of items that were answered (if the prorated score is a fraction it will be rounded up to the nearest whole number). The raw score will not be transformed to a standardized T-score as this is only accurate when all questions on the short form have been answered.

All participants will be asked to complete the Neuro-QOL Fatigue Short Form at Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12.

6.1.6 AEs of Interest (AEIs)

Table 6–7: AEs of Interest selection criteria

No	Event (also included in Title of TFL output)	Selection criteria
1	Infections	TEAE with SOC "Infections and infestations"
2	Neisseria infections	TEAE with HLT "Neisseria infections"
3	Hypersensitivity reactions	SMQ='Hypersensitivity' (narrow scope)
4	Anaphylactic reactions	SMQ= 'Anaphylactic reaction' <u>and</u> TEAEs meeting at least one of the following criteria where the different terms (within each sub-category) occur on the same date or on 2 consecutive days, under the condition that the zilucoplan treatment is still ongoing at the first of these 2 days. 1. If a participant 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 participant 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 or on 2 consecutive days**, then both events will be flagged as anaphylactic reactions. If a participant 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 or on 2 consecutive days**, then both events will be flagged as anaphylactic reactions.
5	Injection site reactions	TEAE with HLT='Injection site reactions' or HLT='Administration site reactions NEC'
6	Drug related hepatic disorders	TEAEs in SMQ narrow scope='Drug related hepatic disorders - comprehensive search' but excluding these 2 sub-SMQs: "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)".
7	Malignancies	TEAEs in SMQ= "Malignant tumours (SMQ)"
8	Malignancies or unspecified tumours	TEAEs in SMQ= "Malignant or unspecified tumours (SMQ)" or "Malignant tumours (SMQ)" Note: the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" must be reviewed for potential malignancies.Table

Table 6–8: Anaphylactic Reactions Categories

Category	Preferred Term
A	ANAPHYLACTIC REACTION
	ANAPHYLACTIC SHOCK
	ANAPHYLACTIC TRANSFUSION REACTION
	ANAPHYLACTOID REACTION
	ANAPHYLACTOID SHOCK
	CIRCULATORY COLLAPSE
	DIALYSIS MEMBRANE REACTION
	KOUNIS SYNDROME
	SHOCK
	SHOCK SYMPTOM
	TYPE 1 HYPERSENSITIVITY
B	ACUTE RESPIRATORY FAILURE

Table 6–8: Anaphylactic Reactions Categories

Category	Preferred Term
	ASTHMA
	BRONCHIAL OEDEMA
	BRONCHOSPASM
	CARDIO-RESPIRATORY DISTRESS
	CHEST DISCOMFORT
	CHOKING
	CHOKING SENSATION
	CIRCUMORAL OEDEMIA
	COUGH
	CYANOSIS
	DYSPNOEA
	HYPERVENTILATION
	IRREGULAR BREATHING
	LARYNGEAL DYSPNOEA
	LARYNGEAL OEDEMA
	LARYNGOSPASM
	LARYNGOTRACHEAL OEDEMA
	MOUTH SWELLING
	NASAL OBSTRUCTION
	OEDEMA MOUTH
	OROPHARYNGEAL SPASM
	OROPHARYNGEAL SWELLING
	RESPIRATORY ARREST
	RESPIRATORY DISTRESS
	RESPIRATORY DYSKINESIA
	RESPIRATORY FAILURE
	REVERSIBLE AIRWAYS OBSTRUCTION
	SENSATION OF FOREIGN BODY
	SNEEZING
	STRIDOR

Table 6–8:   Anaphylactic Reactions Categories

Category	Preferred Term
	SWOLLEN TONGUE
	TACHYPNOEA
	THROAT TIGHTNESS
	TONGUE OEDEMA
	TRACHEAL OBSTRUCTION
	TRACHEAL OEDEMA
	UPPER AIRWAY OBSTRUCTION
	WHEEZING
C	ALLERGIC OEDEMA
	ANGIOEDEMA
	ERYTHEMA
	EYE OEDEMA
	EYE PRURITUS
	EYE SWELLING
	EYELID OEDEMA
	FACE OEDEMA
	FLUSHING
	GENERALISED ERYTHEMA
	INJECTION SITE URTICARIA
	LIP OEDEMA
	LIP SWELLING
	NODULAR RASH
	OCULAR HYPERAEMIA
	OEDEMA
	PERIORBITAL OEDEMA
	PRURITUS
	PRURITUS ALLERGIC
	PRURITUS GENERALIZED
	RASH
	RASH ERYTHEMATOUS

Table 6–8:   Anaphylactic Reactions Categories

Category	Preferred Term
	RASH GENERALIZED
	RASH PRURITIC
	SKIN SWELLING
	SWELLING FACE
	URTICARIA
	URTICARIA PAPULAR
D	BLOOD PRESSURE DECREASED
	BLOOD PRESSURE DIASTOLIC DECREASED
	BLOOD PRESSURE SYSTOLIC DECREASED
	CARDIAC ARREST
	CARDIO-RESPIRATORY ARREST
	CARDIOVASCULAR INSUFFICIENCY
	DIASTOLIC HYPOTENSION
	HYPOTENSION

6.1.7   Compliance

Not Applicable.

6.1.8   COVID-19 terms

Table 6.9:   Preferred Terms to define COVID-19 infection

Name	Scope
Asymptomatic COVID-19	Narrow
COVID-19	Narrow
COVID-19 pneumonia	Narrow
COVID-19 treatment	Narrow
Post-acute COVID-19 syndrome	Narrow
SARS-CoV-2 antibody test positive	Narrow
SARS-CoV-2 RNA increased	Narrow
SARS-CoV-2 sepsis	Narrow
SARS-CoV-2 test false negative	Narrow
SARS-CoV-2 test positive	Narrow
SARS-CoV-2 viraemia	Narrow
Suspected COVID-19	Narrow

6.2 Appendix 2: Abnormality criteria for Laboratory, Vital Sign and Electrocardiogram Parameters

6.2.1 Laboratory Assessments Marked Abnormality Criteria

The following criteria will be applied in the determination of marked abnormalities for laboratory parameters. 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 summaries.

Table 6–10: Laboratory Marked Abnormalities

Parameter	Unit (conventional)	Unit (Standard)	Marked Abnormality Criteria
Hematology			
Hemoglobin	g/dL	g/L	<8.0 g/dL; <80 g/L
WBC (Leukocytes)	10^9/L	10^9/L	Low: <2.0 x 10^9/L High: >100 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	10^9/L	10^9/L	<50.0 x 10^9/L
Other			
CRP[a]	mg/dL	mg/L	>10 mg/dL; >100 mg/L
Biochemistry			
AST	U/L	U/L	>5.0 x ULN if Baseline value is normal; >5.0 x Baseline value if Baseline is abnormal
ALT	U/L	U/L	>5.0 x ULN if Baseline value is normal; >5.0 x Baseline value if Baseline is abnormal
ALP	U/L	U/L	>5.0 x ULN if Baseline value is normal; >5.0 x Baseline value if Baseline is abnormal
Albumin	g/dL	g/L	< 2g/dL; < 20g/L
Bilirubin (total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal > 3.0 x Baseline value if Baseline is abnormal
Calcium	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
Creatinine	mg/dL	umol/L	>3.0 x ULN
GGT	U/L	U/L	>5.0 x ULN if Baseline value is normal; > 5.0 x Baseline value if Baseline is abnormal

Estimate glomerular filtrate rate (eGFR)[b]	mL/min/1.73 m²	mL/min/1.73 m²	<29 mL/min/1.73m²
Glucose[c]	mg/dL	mmol/L	Low: <40 mg/dL; < 2.2 mmol/L High: >250 mg/dL; >13.9 mmol/L
Potassium	mEq/L	mmol/L	Low: <3.0 mmol/L High: >6.0 mmol/L
Sodium	mEq/L	mmol/L	Low: <125 mmol/L High: >155 mmol/L
Amylase	U/L	U/L	>2.0 x ULN
Lipase	U/L	U/L	>2.0 x ULN

[a] 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/ ALT= alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; dL = deciliter; GGT: gamma-glutamyltransferase; L = liter; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal

[b] 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 $eGFR = 141 * min(Scr/\kappa,1)^{\alpha} * max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [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 61.9 for females and 79.6 for males. Subjects with missing race was considered as non-black for eGFR calculation.

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

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.

6.2.2   Marked Abnormalities Vital Signs

Abnormality criteria to be applied in the assessment of vital signs parameter values are given below:

Table 6–11: Marked Abnormalities Vital Signs

Parameter	Abnormality Criteria
Pulse rate (beats/min)	≤50 and a decrease from Baseline≥15 ≥120 and an increase from Baseline≥15
Systolic Blood Pressure (mmHg)	≤90 and a decrease from Baseline≥20 ≥160 and an increase from Baseline≥20
Diastolic Blood Pressure (mmHg)	≤50 and a decrease from Baseline≥15 ≥105 and an increase from Baseline≥15
Temperature	>101⁰F (38.3 ⁰C)

Table 6–11: Marked Abnormalities Vital Signs

Parameter	Abnormality Criteria
Body Weight	≥ 10% decrease from Baseline
	≥ 10% increase from Baseline

6.2.3   Marked Abnormalities Electrocardiogram (ECG)

Abnormality criteria to be applied in the assessment of ECG parameter values are given below:

Table 6–12: Marked Abnormalities ECG

Parameter	Abnormality Criteria
QT interval (ms)	≥500ms
	≥60ms increase from Baseline
QTcF (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 dose of IMP.

6.3   Appendix 3: Changes to Protocol-Planned Analyses

A modified ITT population (mITT) was added. PK-PPS and PD-PPS were added in Section 4 to analyze PK and PD data. Additionally, a COVID-19 Free Set (CFS) was added.

Following FDA review, the primary estimand was revised so that data after rescue therapy, after any death or myasthenic gravis are assumed to be treatment failure whereas any other missing data are assumed to be missing at random. Multiple imputation described in the protocol was updated accordingly where data after rescue therapy or any death or myasthenic crisis will be imputed baseline or the last efficacy score (including unscheduled visit), whichever is worst, based on FDA's feedback. The main analysis population was revised from ITT to mITT, including all randomized participants with at least 1 study drug and at least 1 post baseline efficacy assessment. The pattern-mixture model approach was proposed as a supplementary analysis.

Moreover, more extensive analysis on efficacy were added on the COVID-19 Free Set as sensitivity analysis to support the efficacy on the overall population. Some safety analyses were added to assess the impact of the COVID-19 pandemic.

The analysis of the secondary endpoint, received rescue therapy over the 12-week Treatment Period, was modified from a logistic regression (i.e., as specified in the protocol) to a time-to-event, log-rank test (Section 5.4.2).

Additionally, the set of covariates in the logistic regression model for the endpoint: Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy; was reduced (i.e., removing baseline QMG Score, and geographical region as covariates as described in Section 5.4.3). This change was made to ensure the number of covariates was appropriate for the number of events anticipated for this endpoint.

Moreover, the protocol initially planned to use a fixed-sequential testing procedure using a pre-defined order of all the seven secondary endpoints. However, considering the small number of events expected for the secondary endpoints in the lowest part of the hierarchy (last 4 secondary endpoints) and the fact that the study is not powered to detect a statistically significant effect on these endpoints, it was changed to test these 4 secondary endpoints using a Holm procedure within a gatekeeping framework. Therefore, the order of the key secondary endpoints in the first family based on clinical expertise is not changed.

7   REFERENCES

Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. Ann N Y Acad Sci. 1998;841:769-772.

Benatar M, Sanders DB, Burns TM, Cutter GR, Guptill JT, Baggi F, et al; Task Force on MG Study Design of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Recommendations for myasthenia gravis clinical trials. Muscle Nerve. 2012;45(6):909917.

Burns, TM, Grouse CK, Conway MR, Sanders DB, and MG Composite and MG-QOL 15 study group. Construct and concurrent validation of the MG-QOL 15 in the practice setting. Muscle Nerve. 2010;41(2):219-226.

Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. Muscle Nerve. 2016;54(6):1015-1022.

Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. Muscle Nerve. 2014;49(5):661-665.

Muppidi S, Wolfe GI, Conaway M, Burns TM; MG Composite and MG-QOL15 study group. MG ADL: still a relevant outcome measure. Muscle Nerve. 2011;44(5):727-731.

Nehring, S.M.; Goyal, A.; Patel, B.C. (2020). StatPearls Publishing, web link: https://www.ncbi.nlm.nih.gov/books/NBK441843/.

Sadjadi R, Conaway M, Cutter G, Sanders DB, Burns TM; MG Composite MG-QOL15 Study Group. Psychometric evaluation of the myasthenia gravis composite using Rasch analysis. Muscle Nerve. 2012;45(6):820-825.

United States Department of Health and Human Services, National Cancer Institute. Common Terminology for Adverse Events (CTCAE), Version 5.0, November 17, 2017.

Vissing J, J. S. (2018). 'Minimal Symptom Expression' with Eculizumab in Myasthenia Gravis. *AANEM*. Washington, DC.

Yuan, Y. Sensitivity Analysis in Multiple Imputation for Missing Data. Paper SAS270-2014. SAS Institute (2014).

Approval Signatures

Name: mg0010-sap-amendment 5.0

Version: 2.0

Document Number: CLIN-000181834

Title: MG0010 SAP Amendment 5.0

Approved Date: 29 Apr 2022

Document Approvals	
Approval Verdict: Approved	Name: ███████████ Capacity: Clinical Date of Signature: 27-Apr-2022 10:29:54 GMT+0000
Approval Verdict: Approved	Name: ███████████ Capacity: Clinical Date of Signature: 29-Apr-2022 01:51:37 GMT+0000