STATISTICAL ANALYSIS PLAN

AMENDMENT 4

Study: MG0017

Product: Zilucoplan

A PHASE 3B, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF ZILUCOPLAN IN PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS SWITCHING FROM INTRAVENOUS COMPLEMENT COMPONENT 5 INHIBITORS TO SUBCUTANEOUS ZILUCOPLAN

Sponsor Name: UCB Biopharma SRL

Legal Registered Address: Allée de la Recherche 60
1070 Brussels | BELGIUM

Regulatory Agency Identifier Number(s):

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VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
1.0	25th October 2022	Not Applicable	Original version
Amendment 1.0	19th January 2023	Described below	
Amendment 2.0	17th August 2023	Described below	
Amendment 3.0	11 March 2024	Described below	
Amendment 4.0	01 November 2024	Described below	

Amendment 1.0

The purpose of the SAP amendment 1.0 is to reflect the introduction of an optional Extension Treatment Period in the study design, as described in the protocol amendment 3 (dated 30 Nov 2022). The optional Extension Treatment Period allows access to zilucoplan for participants who wish to continue receiving it after completing the 12-week Main Treatment Period of the study. It allows for study participants to continue receiving zilucoplan treatment until the approval of the marketing application for the indication of generalized myasthenia gravis (gMG) in the US or until further notice from the Sponsor.

The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Introduction	Change protocol amendment 2.0 dated 24 October 2022 to protocol amendment 3.0 dated 30 November 2022.	Updates
Section 1.1 Objectives and Estimands/Endpoints Table 1.1: Objectives and estimands/endpoints Section 1.2 Study Design Section 5.1.1.1.2 End date of the Treatment Periods Section 5.1.1.1.3.1 Study periods for safety and efficacy data Section 5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit Section 5.1.1.1.5 Definition of Baseline values Section 5.2 Participant Dispositions Section 5.3.2 Other efficacy endpoint analyses Section 5.4.1 Extent of Exposure Section 5.7 Interim Analysis Section 6.1.2 Protocol deviations Section 6.1.4.1 Prior/concomitant medications classification Section 6.1.8 Extent of Exposure	Overall design of the study, treatment groups and duration updated to include the Extension Treatment Period. Endpoints updated to define the duration. End date of treatment periods defined to align with the different periods. Definitions of study periods.	To include an optional Extension Treatment Period in the study and allow eligible participants who have completed the 12-week Main Treatment Period to have continued access to zilucoplan.

Amendment 2.0

The purpose of the SAP amendment 2.0 is to make the changes as listed in the next table.

The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Section 4 Populations for Analysis	Deleted text: • ~~Screened Set (ScS): The ScS will include all screened participants including screen failures (see Section 6.3)~~ • Safety Set (SS): The SS will include all study participants who received at least 1 dose of study medication and will be used for the ~~demography and~~ safety analyses.	• Screened Set was redundant. • Section 6.1.1: "In case there is a difference of more than 5 study participants, those descriptive statistics will be duplicated in the SS."
Section 5.1.1.1.3.1 Study periods for safety and efficacy data	Added underlined text for the Safety Follow Up (SFU) Period during the Main Treatment Period: • SFU Period: 40 days (after the last dose for patients who do not enter the extension period <u>or do not transition to commercially available ZLP directly after the Week 12 visit</u>).	To define the rules for the participants to enter the period uniformly across the section.
Section 5.1.1.1.4 Mapping of assessments performed at (Early) Withdrawal Visit	Section title was updated from: • Mapping of assessments performed at Early Discontinuation Visit, to • Mapping of assessments performed at (Early) Withdrawal Visit	Early discontinuation visit is not defined based on the study protocol
Section 5.1.1.7.3 Missing data due to COVID-19	• Added clarification that the protocol deviations related to COVID-19 will be documented only in listings.	• COVID-19 related protocol deviations are mostly related to missed visits due to COVID-19 social restrictions or COVID-19 infections; currently the pandemic period is over and only limited such PD occurrences are expected;

		data can be documented only in listings.
	• Below text is deleted: ~~If the WHO declares an end to the pandemic prior to the end of the study, included additional summary analyses based on the COVID-19 pandemic period (during/post).~~	• By the time WHO declared the end of the pandemic period (05 May 2023) 5 out of the 20 patients had entered the study. During the end of the pandemic period COVID-19 social restrictions had been removed; summaries could not be affected by COVID-19 outbreak at the time being.
Section 5.2 Participant Dispositions	Deleted text: • **Reasons for screen failures** will be summarized using ~~the ScS for overall~~ ES • **Disposition of analysis sets** will be summarized ~~by treatment groups and~~ overall by analysis sets (ES, ITT, mITT, SS, PK-PPS, PD-PPS). Percentages will be based on the number of participants in the ES overall. • ~~Finally, if the WHO declares an end to the pandemic prior to the enrollment of the last study participant, the number of study participants enrolled during each COVID-19 pandemic (during/post) 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 ES. The table will be done overall.~~	• Screen Set is deleted from the SAP • MG0017 is a single arm trial • By the time WHO declared the end of the pandemic period (05 May 2023) 5 out of the 20 patients had entered the study. Towards the end of the pandemic period COVID-19 social restrictions had been removed; enrollment could not be affected by COVID-19 outbreak.
Section 5.3.1.1.2 Main analytical approach	Deleted text: CFB in MG-ADL score will be summarized by visit using descriptive statistics in the mITT. CFB MG-ADL will be listed for all participants of the mITT ~~with visit flagged if the visit was done prior to the COVID-19 pandemic cut-off date~~.	Any flag related to the COVID-19 pandemic cut-off date will not be issued. No output related to the COVID-19 pandemic period (during/post) will be created.

Section 5.3.2 Other efficacy endpoint analyses	• Deleted text: For the MG-ADL and QMG responder rate the number and percentage of participants who have a reduction (i.e., improvement) of ≥ X will be summarized ~~by treatment group~~ in the mITT at Week 12.	• MG0017 is a single arm trial
	• Added text as clarification regarding the definition of MG-ADL and QMG response: The MG-ADL score responder rate will be assessed based only on participants having an MG-ADL score ≥ 3 at Baseline, while the QMG score responder rate will be assessed based only on participants having an QMG score ≥ 5 at Baseline	• Response cannot be determined for participants with MG-ADL score < 3 with QMG score < 5 at Baseline
	Added text: Individual line plots with individual values of Total MG-ADL, QMG and MG-QoL15r scores will be created in mITT. For participants infected with COVID-19 as per the AE page, CFB in QMG and MG-QOL15r score will be listed by visit separately.	To illustrate individual time course of MG-ADL and QMG scores
Section 5.7 Interim Analysis	Added text: If further interim analysis will be considered during the Main Treatment Period, then this will be of exploratory nature and only descriptive statistics will be provided.	To clarify the descriptive nature of the interim cuts.
5.4.2 Data consideration	Added text: The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: – Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. – Grade 2 Moderate; minimal, local or noninvasive intervention indicated;	Data collected in the eCRF is not based on the CTCAE categories. Definitions needed to be added to map the AE intensity (mild, moderate, severe) to CTCAE grading.

	limiting age-appropriate instrumental activities of daily living. Note: instrumental activity of daily living refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. – Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living. Note: self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden – Grade 4 Life-threatening consequences; urgent intervention indicated. – Grade 5 Death related to AE. Programming mapping definitions are added.	
5.4.2.2 AE summaries	Added text: All AEs within a 7-day period post each COVID-19 vaccination will be summarized for all vaccinated participants. Two separate listings will display the AEs after adjustment of the interval censoring and the concomitant COVID-19 vaccination.	As per UCB guidance related to COVID-19 vaccination
Section 5.4.3.1	Title changed from "AEs of special interest" to "AEs of Special Interest and AEs of Interest". Definition of AEs of Interest is provided	Adverse Events (AEs) of hypertensitivity, anaphylactic reactions, drug related hepatic disorders and malignancies or unspecified tumors were added to the AE summaries in order to further assess the ZLP safety and be aligned within the ZLP program.
5.4.3.2.4 Assessment of potential liver toxicity	Added criterion: AST or ALT >3xULN with INR>1.5 (if INR is measured)	To define Hy's law according to the study protocol
5.5.1 Pharmacokinetics	Deleted text: ~~A spaghetti plot of combined individual concentration versus time profiles will be presented by analyte in linear and semi-~~	No figures to be created as based on the study protocol PK will be measured in only two timepoints.

	~~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 LLOQ on the semi-logarithmic plots.~~	
5.5.1.4 Participants' treatment satisfaction	Added text: • Bar charts illustrating the mean and standard error at each visit by domain will be provided. • Individual participant listings will be provided for all participants and for participants infected with COVID-19 as per the AE page.	• To facilitate the data results interpretation • To align with the efficacy questionnaire data
5.7 Interim Analyses	Added text: "If further interim analysis will be considered during the Main Treatment Period, then this will be of exploratory nature and only descriptive statistics will be provided."	Clarification on the analysis purposed of any interim cut during the main treatment period
6.1.1 Baseline characteristics and demographics	• Deleted text: ~~Additional subgroup summary will be presented based on the enrolled date relative to the cut-off date by during/post COVID-19 pandemic period based on the mITT.~~ • An additional cut off of BMI=35 m/kg^2 is added	• Any summaries based on the COVID-19 periods will not be considered. • As per UCB updated guidance
Section 6.1.2 Protocol deviations	• IPD summaries to be provided in the mITT Deleted text: ~~A summary of number and percentage of participants having important protocol deviation by relationship to COVID-19 will~~	• Randomized Set (RS) is not applicable to MG0017.

	~~be provided for the RS population by treatment group~~ • Added text: "A COVID-19 related flag will be present in IPD listings."	• Clarification
Section 6.1.2.3 gMG disease history	Text on summary statistics of the following parameters is deleted: • 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.	Information is not recorded in the eCRF
	Text added: "Note: Generalized symptoms at onset: participants with respiratory symptoms or symptoms in the limb, bulbar or any other location; participants at this category might also have ocular symptoms at onset as well."	Information was missing
	Text on summary statistics is added: • Reason for switching to study medication (Logistical challenges including travel and time spent at a hospital, Challenges with venous access, Lengthy intravenous infusion, Other)	Information was missing from the section
Section 6.1.4.3 MG Specific Prior and Concomitant Medications	Text is added in Table 6.2 Medication Class:	To update the table

	Group F: Pyridostigmine Bromide is added at the Group F therapies Footnote: *plasma exchange will be on the Procedures eCRF (if concomitant procedure).	
6.1.6 AEs of Interest	Algorithmic approach to derivation of AEs of Interest in added	To summarize the AEIs
Section 6.2.1 Laboratory Assessments Marked Abnormality Criteria	• Text labs from Table 6-6 Laboratory Abnormalities: • Calcium, Albumin, CRP and GGT labs are deleted	• According to the study protocol, albumin, CRP and GGT are not collected. • Calcium as parameter of abnormalities is checked via the Corrected Calcium which cannot be derived in the study.
6.3 Appendix 3: Changes to Protocol-Planned Analyses	Deleted text: ~~The Screened Set population has been added to ease the display of some descriptive statistics.~~	Screen Set has been deleted from the SAP Amendment 2

Amendment 3.0

The purpose of the SAP amendment 3.0 is to make the changes as listed in the table below.

The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Section 5.1.1.10 Handling of missing dates and times	The following crossed-out text is deleted: Discharge date refers to the date of the end of study visit for completed or ~~the date of discontinuation~~ for participants that were withdrawn.	To remove the redundant text, as the date of discontinuation for withdrawn participants is captured in the eCRF in the safety follow up visit.
Section 5.4.1 Extent of Exposure	• The following text is added: "The missed doses will be derived based on the expected number of daily doses the participant should receive within a defined period minus the total number of doses he/she has received during that period. For this derivation, the number of total syringes administered to a participant at each visit will be considered via the total number of kits administered at each visit, assuming that	• The number of missed doses are not collected in the eCRF and should be derived. Added text is to document that the number of missed daily doses will be derived based on the number of administered kits vs number of returned syringes. This derivation

	each kit contains 7 syringes to be used for 7 daily doses." • The following text is added: For the Main Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP dose + 1. Participants that did not early withdraw should be censored at the date of Main Treatment Period completion. For the Overall Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP in Main Treatment Period + 1. Participants that did not (early) withdraw should be censored at the date of their last contact. For the Extension Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP in Extension Treatment Period+ 1. Participants that did not withdraw should be censored at the date of their last contact. For all treatment periods, participants that switch to commercially available Zilucoplan are not considered as discontinuation events; for the time to event analysis exposure will be censored at the date of their last contact.	rule is to be incorporated in the summary tables. • To document the derivation of the time to IMP discontinuation in the Main, Extension and Overall Treatment period in order to create the Kaplan-Meier curves.
Section 5.3.1.1 Main analytical approach	• The underlined text is added: For the efficacy endpoint, the CFB to Week 12 in MG-ADL score will be modeled using a mixed model for repeated measures (MMRM) with baseline MG-ADL Score and Week 1, 2, 4, 8 and 12 <u>as fixed factors and baseline MG-ADL Score by visit as interaction term</u>. The Least square mean (LSM) <u>followed by the 95% Confidence Interval (CI)</u> and standard error of the <u>corresponding CFB at each visit</u> will be reported.	• To provide further clarity on the MMRM model constrains and on the analysis outputs.

	• The following text is added: The NI of Week 12 MG-ADL over the Baseline MG-ADL, will be shown if the upper limit of the one sided 97.5% CI (or the two sided 95% CI) of the LSM MG-ADL CFB at Week 12 does not cross the non inferiority margin of 2 points.	• To update the SAP text with the non-inferiority statistical rule as proposed by the authorities.
Section 5.4.2.2 AE summaries	• The following text is added for the AE summaries to be produced: -Any TEAEs above 5% of occurrence	• Table is part of the disclosure outputs.
	• The following underlined text is added: The number, percentage of participants with TEAEs will be summarized by maximum intensity (mild, moderate and severe), SOC, and PT <u>as well as by intensity (mild, moderate and severe), SOC, and PT.</u>	• TEAEs summary by intensity is added so that the total number of events per Adverse Event will be counted and presented.
	• The following text is deleted: A listing of all TEAEs 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.	• The impact of COVID-19 pandemic on safety, will be assessed by other outputs included but not limited to outputs reporting all COVID-19 related TEAEs.
	• The following text is deleted: "Two separate listings will display the AEs after adjustment of the interval censoring and the concomitant COVID-19 vaccination."	• To remove the duplicate sentence.
Section 5.4.3.1 AEs of Special Interest and AEs of Interest	• Injection site reactions are added as part of the AEs of Interest	• Injection site reactions are missed from the previous SAP version.

	• The following crossed out text is deleted: The number and percentage of participants who experience each AE of Interest will be summarized ~~treatment group~~ separately for each AE of interest.	• This is one arm study.
5.4.3.2.3 Laboratory Marked abnormalities	The underlined text is added: "Treatment-emergent is defined as meeting the criteria at any post-Baseline visit while criteria are not present before dosing."	To correct the TEMA definition
5.4.3.2.4 Assessment of potential liver toxicity	Liver Function Tests criteria changed from " LFT > * x ULN" to "LFT ≥ * x ULN"	Update is according to the UCB internal guidance for LFT standard shells issued on 18 January 2024.
5.4.3.4 Electrocardiograms	Units are added at the ECG assessments	To provide further clarity
5.4.3.6 Columbia-Suicide Severity Rating Scale (C-SSRS)	• The following text is added: C-SSRS instrument recorded at screening visit references the lifetime period and the past six months period. Baseline to end of study visit summaries reference the period prior to the visit assessed. • The following underlined text is added: "Results of the C-SSRS, as well as the treatment emergent item at Week 12 (or (early) withdrawal will be summarized in SS by scheduled timepoint using the number of participants and percentage with:" [redacted]	• C-SSRS has two versions: a. Screening/Baseline version b. Since last visit version Text has been added for further clarity. • C-SSRS is also recorded at the (early) withdrawal visit. Also the "complete suicide item" is not subject to the "C-SSRS Screening/Baseline version"
6.1 Baseline characteristics and demographics	Weight (kg) categories are changed from "<56, 56-<77, 77 - <150, ≥ 150" to "<43, 43 - <56, 56-<77, 77 - <150, ≥ 150"	To reflect the protocol defined categories.
6.1.4.3 MG Specific Prior and Concomitant Medications	• "IVIG, SCID and Immunoglobulins NOS" terms are removed from Group D. • Following treatments are added: Plasmapheresis is added in Group D:	• IVIG or SCIG were included in both Group B and Group C • For completeness in MG treatment therapies.

	Galantamine is added in Group F Rozanolixizumab is added in Group H	
6.1.6 AEs on Interest	Injection site reactions derivation is added at Table 6-5: AEs of Interest selection criteria: TEAE with HLT='Injection site reactions' or HLT='Administration site reactions NEC'	Injection site reactions derivation is missing from the previous SAP version.
6.1.8 Extent of Exposure	• The denomination for the calculation of the reference period with respect to treatment compliance is changed as follows: Compliance between 2 study visits: Day of the visit in clinic – Day of the previous visit in clinic +1) changed to: Date the syringes are returned in clinic – Date the syringes are dispensed in clinic. Overall Compliance in the Main Treatment Period: Day of the last visit in clinic in the Main Treatment Period – Day of the baseline visit + 1 changed to: Date the last syringes are returned in clinic in the Main Treatment Period – Date the first syringes are dispensed in clinic Compliance in the Overall Treatment Period: Day of the last visit in clinic in the Extension Treatment Period – Day of the baseline visit + 1 changed to: Date the last syringes are returned in clinic in the Extension Treatment Period – Date the first syringes are dispensed in clinic in the Main Treatment Period • The following text is added: Of note, the number of syringes dispensed at each visit will be derived based on the number of kits dispensed at	• To adjust the compliance definition so that injections administered in a clinic visit will be part of the compliance measures with respect of the next time interval. Example: injections performed on Week 2 will be considered for the compliance between week 2 and week 12.

	that visit, assuming that each kit contains 7 single dose syringes to be used for the daily dosing.	• To further clarify the derivation of treatment compliance.
6.2.3 Marked Abnormalities Electrocardiogram (ECG)	• The top label row of Table 6-10: has been updated to Treatment Emergent Markedly Abnormal Criteria. • The underlined text is added the footnote of Table 6-10: Marked Abnormalities (ECG) Note: Treatment-emergent Markedly Abnormal is defined as meeting the criteria at any post-Baseline visit after the first dose of IMP and not meeting the criteria at Baseline.	• To capture the table contents. • To update and correct the Treatment Emergent Markedly Abnormal (TEMA) definition.
Section 6.1.6 AEs of Interest	• The following terms are added/deleted in Table 6-6: Anaphylactic Reactions Categories *Added:* Group A: Procedural Shock Group B: Cough Variant Asthma, Enhanced Respiratory Disease, Oropharyngeal Oedema, Pharyngeal Spam, Pharyngeal Swelling Group C: Circumoral Swelling, Oedema Blister, Periorbital Swelling, Swelling, Swelling of Eyelid Group D: Hypotensive Crisis, Post Procedural Hypotension *Deleted:* Group B: Respiratory dyskinesia Group C: Generalized erythema, Pruritus Generalized, Rash Generalized	• To capture the updates in MedDRA v26.1 coding dictionary

Amendment 4.0

The purpose of the SAP amendment 4.0 is to update the calculation of compliance.

Section # and Name	Description of Change	Brief Rationale
6.1.8 Extent of Exposure	Compliance calculation in the Overall Study period has been amended as follows:	
	• For participants entering in the Extension Treatment Period, the overall compliance in the Overall Treatment Period will be calculated as: (total number of syringes dispensed – total number of unused syringes – total number of malfunctioned syringes +1)/(Date of last drug administration – Date the first syringes are dispensed in clinic in the Main Treatment Period +1)*100.	• The date the syringes are returned in clinic might differ from the date of last dose administration; thus, compliance should be measured up to the last dose and not up to the return date in clinic.
	The following text has been added:	
	• If the participant was (early) withdrawn, then the date to be considered in the calculation of compliance as the end of exposure period will be the date of last administration of Zilucoplan and not the date the participant returned the syringes in clinic. Then, the compliance will be calculated as follows: (number of syringes dispensed at the previous clinic visit – number of unused syringes returned in clinic – total number of malfunctioned syringes +1)/(Date of last drug administration – Date the syringes are dispensed in clinic + 1)*100.	• As above

LIST OF ABBREVIATIONS

List of Abbreviations

AE	Adverse Event
AEs	Adverse events
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ALP	Alkaline phosphatase
ALQ	Above the Limit of Quantification
AST	Aspartate aminotransferase
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C-SSRS	Columbia-Suicide Severity Rating Scale
C5	Complement component 5
CFB	Change from baseline
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
eCRF	electronic Case Report form
ECG	electrocardiogram
eGFR	Estimate glomerular filtrate rate
ES	Enrolled Set
EW	Early withdrawal
FDA	US Food and Drug Administration
geoCV	Geometric coefficient of variation
gMG	Generalized Myasthenia Gravis
HLT	High level term
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

List of Abbreviations

IMP	investigational medicinal product
IST	immunosuppressant therapy
IV	intravenous
IVIG	intravenous immunoglobulin G
ITT	Intention to treat
kg	kilogram
LLoQ	Lower Limit of Quantification
LFT	Liver function tests
MA	Marked Abnormality
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis -Activities of Daily Living
MG-QOL 15r	Myasthenia Gravis MG Quality of Life 15 Item scale revised
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post Intervention Status
mL	Milliliter
MI	Multiple imputation
mITT	Modified Intention to treat
mg	milligram
MSE	Minimal symptom expression
NI	Non inferiority
PD	Pharmacodynamic
PD-PPS	Pharmadynamic Per Protocol Set
PEY	Patient-years exposure
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PLEX	Plasma exchange
PPS	Per Protocol Set
PR	Pharmacologic Remission
PT	Preferred term
QMG	Quantitative Myasthenia Gravis
SAEs	Serious Adverse Events

List of Abbreviations

SAP	Statistical Analysis Plan
SC	subcutaneous
SD	Standard deviation
SFU	Safety follow up
SMQ	Standardized MedDRA Query
SoC	Standard of care
SOC	System Organ Class
sRBC	sheep red blood cell
SS	Safety Set
TBL	Total bilirubin
TEAE	Treatment-Emergent Adverse Event
TEMAs	Treatment-emergent marked abnormalities
TFL	Table, Figure and Listing
TSQM-9	9 item Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
WHO	World Health organization
WHODD	World Health Organization Drug Dictionary
ZLP	zilucoplan

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 MG0017. 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 safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) analyses. Changes to protocol-planned analysis are documented in Section 6.3. Table, Figure and Listing specifications are contained in a separate document.

This SAP is based upon and assumes familiarity with protocol amendment 3.0 dated 30 November 2022.

If a future protocol amendment necessitates a substantial change to the statistical analysis of 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 using SAS software version 9.4 or above. 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 safety analyses are described below. The estimands corresponding to the secondary objectives and secondary analyses are also described below.

Table 1.1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Primary	
To evaluate the safety and tolerability of switching from intravenous (IV) Complement component 5 (C5) inhibitors to subcutaneous (SC) Zilucoplan (ZLP) in study participants with generalized Myasthenia Gravis (gMG)	The primary safety endpoints are: • Incidence of Treatment Emergent Adverse Events (TEAEs) over the Main Treatment Period • Incidence of TEAEs leading to withdrawal of study medication over the Main Treatment Period
Secondary	
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors in study participants with gMG	The secondary efficacy estimand is:

Objectives	Estimands/endpoints
	• Treatment: ZLP administered by daily SC injections (0.3mg/kg/day) • Target population: Adult study participants with gMG currently receiving an IV C5 inhibitor approved for the treatment of gMG according to the protocol-specified inclusion/exclusion criteria • Endpoint: Change from Baseline (CFB) to Week 12 in Myasthenia Gravis -Activities of Daily Living (MG-ADL) score • Intercurrent event handling: The intercurrent events considered in this study are: – ICE1: Administration of rescue therapy or changes in Standard of Care (SoC) dose regimens. Data collected at and after the point of the intercurrent event will be used as collected to gain understanding of clinical practice. – ICE2: Participant discontinuation from the study. It will be assumed that the participant had remained on their treatment (regardless of rescue therapy administration) throughout the study (i.e., a "hypothetical strategy" assuming participants did not discontinue the study and remained on treatment). • Population level summary: The mean of the endpoint
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors on an additional efficacy endpoint in study participants with gMG	The secondary efficacy endpoint is: • CFB to Week 12 in the Quantitative Myasthenia Gravis (QMG) score This endpoint will be analyzed following the same estimand structure as defined for the MG-ADL score. The endpoint assessed will change accordingly.
To evaluate safety and tolerability of SC ZLP after switching from IV C5 inhibitors on additional safety measures in study participants with gMG	The secondary safety endpoints are: • Incidence of serious TEAEs over the Main Treatment Period • Incidence of study withdrawal over the Main Treatment Period
Other	
To further explore the efficacy of SC ZLP on additional efficacy endpoints after switching from IV C5 inhibitors in study participants with gMG	The other efficacy endpoints are: • Time to first receipt of rescue therapy over the Main Treatment Period • Change in SoC therapy medication dose regimen for gMG during the Main Treatment Period

Objectives	Estimands/endpoints
	• Achievement of Minimal Manifestation Status per Myasthenia Gravis Foundation of America Post Intervention Status (MGFA-PIS) at Week 12 without rescue therapy • Achieving minimal symptom expression (MSE), defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy • CFB to Week 12 in QMG subscores: ocular, bulbar, respiratory, limb • CFB to Week 12 in Myasthenia Gravis MG Quality of Life 15 Item scale revised (MG-QOL15r) score • MG-ADL score responder rate (responder is defined as achieving ≥ 3-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy) • QMG score responder rate (responder is defined as achieving ≥5-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy)
To explore the time needed for administration of SC ZLP	The other endpoint is: • Time needed for administration of SC ZLP
To explore study participants' treatment satisfaction following the use of SC ZLP	The other endpoint is: • CFB to Week 12 in 9 item Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores
To explore study participant preference following the use of SC ZLP	The other endpoint is: • Patient Preference assessment at Week 12
To further evaluate the safety and tolerability of SC ZLP after switching from IV C5 inhibitors on other safety measures in study participants with gMG	The other safety endpoints are: • CFB to Week 12 in clinical laboratory tests • CFB to Week 12 in physical examination • ECG • Columbia-Suicide Severity Rating Scale (C-SSRS) • Incidence of TEAEs
To evaluate the PK of SC ZLP after switching from IV C5 inhibitors	The other PK endpoint is: • Plasma concentrations of ZLP and its major metabolites over the Main Treatment Period ([redacted])
To evaluate the PD of SC ZLP after switching from IV C5 inhibitors	The other PD endpoint is: • sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation over the Main Treatment Period

C5=complement component 5; CFB=change from Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; gMG=generalized myasthenia gravis; IV=intravenous; MG-ADL=Myasthenia Gravis-Activities of Daily Living; MG-QOL15r=Myasthenia Gravis – Quality of Life revised; MGFA-PIS=Myasthenia Gravis

Objectives	Estimands/endpoints

Foundation of America Post-Intervention Status; MSE=Minimal Symptom Expression; PD=pharmacodynamic(s); PK=pharmacokinetic(s); QMG= Quantitative Myasthenia Gravis; SC=subcutaneous; SoC=standard of care; sRBC=sheep red blood cell; TEAE=treatment-emergent adverse event; TSQM-9=9-item Treatment Satisfaction Questionnaire for Medication; ZLP=zilucoplan

1.2 Study design

MG0017 is a Phase 3b, multicenter, open-label, single-arm study to evaluate the safety, tolerability, and efficacy of ZLP in study participants with gMG switching from their current IV C5 inhibitor to SC ZLP.

To be eligible to participate in this study, participants must be adults (≥18 years of age) with a documented diagnosis of gMG (Myasthenia Gravis Foundation of America (MGFA) Class II-IVa), currently receiving an IV C5 inhibitor approved for the treatment of gMG for at least 3 months (for eculizumab) or 4 months (for ravulizumab) prior to Screening (with the last dose being administered at the Screening Visit ±3 days), considered to have a clinically stable disease as per the Investigator's judgment prior to Screening, and willing to switch from their current IV C5 inhibitor to SC ZLP.

The planned enrollment is 20 study participants in the US.

The study includes a 2-week or 8-week Screening Period (for participants receiving eculizumab or ravulizumab, respectively), a 12-week Main Treatment Period, and an optional Extension Treatment Period. A Safety Follow Up (SFU) Visit should be performed 40 days (±7 days) after the last dose of study medication.

The Screening Visit should be scheduled to coincide with the regularly scheduled study participant's IV C5 inhibitor administration (±3 days). Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen. The last regularly scheduled IV C5 inhibitor administration cannot occur beyond Day -14 (±3 days) of the Screening Period for study participants receiving eculizumab or beyond Day -56 (±3 days) of the Screening Period for study participants receiving ravulizumab to ensure approximately a 2-week or 8-week interval between the last regularly scheduled IV C5 inhibitor administration and the first SC ZLP administration during the Main Treatment Period, respectively.

At the end of the Screening Period and in case of no more than a 2-point change in study participants' MG-ADL score compared to the Screening Visit, study participants will enter the Main Treatment Period and will switch to SC ZLP (IV C5 inhibitor should not be administered after the Screening Visit). On Day 1, study participants will receive ZLP 0.3mg/kilogram (kg) administered SC. Following in-clinic education and training, all study participants will self-inject daily SC doses of study medication for the subsequent 12-weeks. Single-use pre-filled syringes in injection devices will be provided for use during the study. Of note, there will be no washout period during the study where study participants are not receiving treatment for MG.

During the Main Treatment Period, study participants will be contacted via phone call at Week 1, Week 4, and Week 8 to assess safety and tolerability. During these phone call visits, the MG-ADL assessment will also be performed. Study participants will return to the clinic at Week 2 and Week 12 to evaluate safety, tolerability, and efficacy. Additional assessments will

include questionnaires, PK, and PD. Safety assessments will include adverse event (AE) monitoring, physical examination, clinical laboratory tests, and C-SSRS.

The time needed for preparation and administration of SC ZLP will also be measured during the Main Treatment Period in accordance with the Schedule of Activities.

Study participants are expected to remain on a stable dose regimen of all medications unless medically indicated changes become necessary. All SoC therapy medications for gMG should be kept at the same dose regimen throughout the study, including corticosteroids and immunosuppressant therapy (IST) drugs. If rescue therapy becomes necessary due to major deterioration of a study participant's clinical status, or risk of MG crisis as per the Investigator's judgment, the study participant may receive intravenous immunoglobulin G (IVIG) or plasma exchange (PLEX) treatment as rescue therapy.

Additionally, if deemed needed as per the Investigator's judgment, study participant may be readministered their previous IV C5 inhibitor after discontinuation of the study medication.

All study participants who complete the Main Treatment Period will have the option to continue ZLP treatment in the Extension Treatment Period after the Week 12 visit. If a study participant withdraws from the study during the Main Treatment Period, the participant will complete an Early Withdrawal (EW) Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medications. Participants who opt not to continue into the Extension Treatment Period will complete a SFU Visit 40 days (±7 days) after the last dose of study medication.

The Extension Treatment Period consists of in-clinic visits every 12 weeks (±7 days) and will continue until all participants are withdrawn, until ZLP is approved and available in the US, or until further notice from the Sponsor. During these visits, ZLP accountability and resupply will be performed, medications updated, and safety will be assessed. Participants who withdraw or discontinue ZLP during the Extension Treatment Period will complete a Withdrawal Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medication. Participants who transition to commercially available ZLP will complete a Withdrawal Visit but will not require a SFU Visit. If by the time a participant completes the Main Treatment Period ZLP is commercially available, the participant may transition to commercially available ZLP directly following the Week 12 visit at the end of the Main Treatment Period.

2 STATISTICAL HYPOTHESES

The null hypothesis for the secondary efficacy endpoint of the secondary efficacy estimand is that the ZLP CFB in Week 12 MG-ADL is greater than the non-inferiority (NI) margin of 2. The alternative hypothesis is that the ZLP CFB in Week 12 MG-ADL is lower than the NI of 2.

This secondary efficacy endpoint will be tested at the 1-sided alpha of 0.025.

No multiplicity adjustment is planned in this study.

3 SAMPLE SIZE DETERMINATION

The secondary efficacy estimand will investigate if the Week 12 MG-ADL score is noninferior to the Baseline MG-ADL score with an NI margin of 2. It is assumed that the Week 12 CFB has

a standard deviation (SD) of 3 and that the true CFB is 0. Given a sample size of 20 study participants, the study has approximately 80% power to detect this, based on a 1-sided alpha of 0.025.

4 POPULATIONS FOR ANALYSIS

- Enrolled Set (ES): The ES will include all study participants who signed the ICF.
- Intention-to-Treat (ITT) Population: The ITT Population will include all eligible study participants. Efficacy analyses will be performed on the ITT in case there is a difference of at least 5 participants as compared to the modified Intention-to-Treat (mITT) Population.
- Modified ITT Population (mITT): The mITT Population will include all eligible study participants who received at least 1 post-Baseline dose of study medication and had at least 1 post-Baseline assessment. The mITT Population will be used for all efficacy analyses.
- Safety Set (SS): The SS will include all study participants who received at least 1 dose of study medication and will be used for the safety analyses.
- Pharmacokinetic Per-Protocol Set (PK-PPS): The PK-PPS will include all study participants in the safety population who received at least 1 dose of study medication and had at least 1 quantifiable PK measurement post dose of study medication without important protocol deviations that would affect the PK. The PK-PPS will be used for all PK analyses.
- Pharmacodynamic Per-Protocol Set (PD-PPS): The PD-PPS will include all study participants in the safety population who received at least 1 dose of study medication and had at least 1 quantifiable PD measurement post dose of study medication without important protocol deviations that would affect the PD. The PD-PPS will be used for all PD analyses.

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 9.4 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 test of secondary efficacy variable will be presented as p-values rounded to four decimal places. P-value less than 0.001 will be presented as "<0.001" and p-value greater than 0.999 will be presented as ">0.999." Statistical comparison will be one-sided and will be performed at the 0.025 level of significance.

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. 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 SFU, or the last study participant has prematurely discontinued prior to reaching the SFU, the database will be locked. TFLs will be produced.

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 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 investigational medicinal product (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 investigational medicinal product (IMP) including a '+'to denote post treatment 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

5.1.1.1.2 End date of the Treatment Periods

Each of the study periods is constituted of a treatment period.

The end date of the treatment period of each study period will be either the date of the last planned visit (Week 12 for the Main Treatment Period or the every 12 Weeks visit for the Extension Treatment Period) or the date of the Withdrawal visit (Early Withdrawal during the Main Treatment Period or Withdrawal Visit during the Extension Treatment Period) for participants who discontinued. If a participant does not have the last planned visit or Withdrawal visit, then either the date of the last scheduled (on site or phone call visits) or unscheduled visit during the considered period or the date of the last known dose of study drug during the considered 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, one concept of the definition of periods need to be considered for the study, which will be defined in detail in the section below.

5.1.1.1.3.1 Study periods for safety and efficacy data

- Two study periods are included in this study, the Main Treatment Period and the Extension Treatment Period.

No efficacy data are collected during the Extension Treatment Period thus, for efficacy analyses, only the Main Treatment Period will be considered.

The safety analyses will be performed on the Main Treatment Period as well as on the Overall Treatment Period. The Overall Treatment Period is constituted of the Main Treatment Period and of the Extension Treatment Period. The following definitions for completing study periods will be applied:

- A participant is considered to have completed the Main Treatment Period if he/she completed the Week 12 visit and:
  - Decided to enter the Extension Treatment Period.

  OR

  - Transitioned to commercially available ZLP directly after the Week 12 visit (no Withdrawal or SFU visit required).

  OR

  - Decided not to enter the Extension Treatment Period and completed a SFU visit.
- A participant is considered to have completed the study if he/she completed the Main Treatment Period and:
  - Did not enter the Extension Treatment Period.

  OR

  - Entered the Extension Treatment Period and:
    - withdrew from the Extension Treatment Period, discontinued ZLP, and completed the Withdrawal and SFU Visits.

    OR

    - transitioned to commercially available ZLP and completed the Withdrawal Visit. No SFU Visit is required.

The total duration of study participation in the Main Treatment Period for all participants will be up to approximately 20 or 26 weeks, including the following periods:

- Screening Period: 2 to 8 weeks
- Treatment Period: 12-weeks
- SFU Period: 40 days (after the last dose for patients who do not enter the extension period or do not transition to commercially available ZLP directly after the Week 12 visit).

The Extension Treatment Period is constituted of the following periods:

- Treatment period
- SFU period: 40 days, for participants that withdrew from the Extension Treatment Period

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 periods will be applied:

- Treatment period starts with the first day of IMP and ends 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 of the Main Treatment Period.
- Follow-up period starts one day after the end of the Treatment period and ends after the final assessments on the SFU visit.

5.1.1.1.4 Mapping of assessments performed at (Early) Withdrawal Visit

If a participant prematurely discontinues study drug at any time prior to Week 12 during the Main Treatment Period, the participant should return to clinic for a stand-alone EW Visit. If a participant withdrew during the Extension Treatment Period, the participant should perform a Withdrawal Visit. These assessments will be mapped to the next scheduled visit where each assessment is evaluated as per protocol. This approach means that there is a chance that EW (or Withdrawal) data will be mapped to different visits according to the schedule of assessments.

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 Main 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

Treatment group will be shown as: Zilucoplan 0.3mg/kg.

5.1.1.4 Center pooling strategy

It is planned to recruit study participants in different sites in North America in this study. 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 Efficacy endpoints

For secondary efficacy analyses, missing data will be handled according to the secondary efficacy estimand definition:

- For missing data of participants that discontinue from the study, a missing at random assumption will be used for imputation. This is in relation to the assumption that the participant had remained on their treatment throughout the study.
- For other missing data, the same missing at random assumption as the one used for imputing missing data of participants that discontinue from the study will be applied.

5.1.1.7.2 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.

5.1.1.7.3 Missing data due to COVID-19

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

- Added an electronic Case Report form (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 (in listings only).

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.

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 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, 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.
- **Disposition of analysis sets** will be summarized overall, by analysis sets (ES, ITT, mITT, SS, PK-PPS, PD-PPS). Percentages will be based on the number of participants in the ES 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 mITT population will contain the number and percentage of study participants who started, completed, permanently discontinued the Main Treatment Period with primary reason of discontinuation, and entered, completed, permanently discontinued the Extension Treatment Period with primary reason of discontinuation. Percentages will be based on the number of participants in the mITT population. This summary will be performed for the Main Treatment Period as well as for the Overall Treatment Period. The disposition and discontinuation reasons will be duplicate in the ES in case there is a difference of strictly more than 5 patients between the ES and the ITT.
- **Discontinuation due to AEs** using mITT population will summarize the total number of study participants who discontinued the study due to AEs by the categories: AE, serious fatal, and AE, non-fatal. This summary will be performed for the Main Treatment Period as well as for the Overall Treatment Period. The discontinuation due to AEs will be duplicate in the ES in case there is a difference of strictly more than 5 patients between the ES and the ITT.
- **Impact of COVID-19** using the mITT will summarize number and percentage of participants in each impact category by visit. This table will be done overall. 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. This summary will be performed for the Main Treatment Period as well as for the Overall Treatment Period. The impact of COVID-19 will be duplicate in the ES in case there is a difference of strictly more than 5 patients between the ES and the mITT.

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.

5.3 Planned efficacy/outcome analyses

5.3.1 Secondary efficacy estimand/secondary endpoint analyses

5.3.1.1 Main secondary efficacy endpoint

5.3.1.1.1 Definition of endpoint

The secondary efficacy endpoint is the CFB in Week 12 in 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 collected at each post baseline visit will be used to calculate change from Baseline, in summaries and for efficacy analyses.

5.3.1.1.2 Main analytical approach

For the efficacy endpoint, the CFB to Week 12 in MG-ADL score will be modeled using a mixed model for repeated measures (MMRM) with baseline MG-ADL Score and Week 1, 2, 4, 8 and 12 as fixed factors and baseline MG-ADL Score by visit as interaction term. The Least square mean (LSM) followed by the 95% Confidence Interval (CI) and standard error of the corresponding CFB at each visit will be reported.

An one-sample t-test will be used to compare the LSM of the CFB to Week 12 in MG-ADL score to a NI margin. The NI margin being investigated is a clinically relevant 2-point increase (worsening) at Week 12. The Week 12 CFB will be compared to 2 at a 1-sided α=0.025 level for the mITT Population. The p-value associated to this test will be reported. The NI of Week 12 MG-ADL over the Baseline MG-ADL, will be shown if the upper limit of the one sided 97.5% CI (or the two sided 95% CI) of the LSM MG-ADL CFB at Week 12 does not cross the non inferiority margin of 2 points (Food and Drug Administration, 2016).

A separate one sample t-test for the CFB will be employed based on the observed data setting the Week 12 MG-ADL score as the worst score though all the study visits for participants experienced ICE1 or ICE2; this analysis will serve as sensitivity analysis.

CFB in MG-ADL score will be summarized by visit using descriptive statistics in the mITT. CFB MG-ADL will be listed for all participants of the mITT. For participants infected with COVID-19 as per the AE page, CFB in MG-ADL will be listed by visit separately.

A listing of all the intercurrent events will be provided.

5.3.1.1.3 Handling of missing data

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

For secondary efficacy analyses, missing data will be handled according to the secondary efficacy estimand definition:

- For missing data of participants that discontinue from the study, a missing at random assumption will be used for imputation.
- For other missing data, the same missing at random assumption as the one used for imputing missing data of participants that discontinue from the study will be applied.

The MMRM that will be used to model the CFB to Week 12 in MG-ADL score consider missing data with the missing at random assumption.

5.3.1.1.4 Sensitivity analysis

The one-sample t-test will be applied on the observed data at Week 12.

A one-sample Wilcoxon Signed Rank Test will also be applied on the observed data at Week 12, with Worst observation carried forward between baseline and all post baseline visits.

5.3.1.2 Additional secondary efficacy endpoint

5.3.1.2.1 Definition of endpoint

The additional secondary efficacy endpoint is the CFB in Week 12 in QMG Score. More details on how these scores are calculated can be found respectively in Section 6.1.5.2.

5.3.1.2.2 Main analytical approach

For the additional secondary efficacy endpoint, the same strategy (main analytical approach in Section 5.3.1.1.2 and handling of missing data in Section 5.3.1.1.3) will be applied.

No statistical test will be performed for the additional secondary efficacy endpoint.

5.3.2 Other efficacy endpoint analyses

The other efficacy endpoints are:

- Time to first receipt of rescue therapy over the Main Treatment Period
- Change in SoC therapy medication dose regimen for gMG during the Main Treatment Period
- Achievement of Minimal Manifestation Status per MGFA PIS at Week 12 without rescue therapy
- Achieving MSE, defined as an MG ADL of 0 or 1 at Week 12 without rescue therapy
- CFB to Week 12 in QMG subscores: ocular, bulbar, respiratory, limb
- CFB to Week 12 in MG-QOL15r score
- MG-ADL score responder rate (responder is defined as achieving ≥ 3-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy)
- QMG score responder rate (responder is defined as achieving ≥5-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy)

The MG-ADL score responder rate will be assessed based only on participants having an MG-ADL score ≥ 3 at Baseline, while the QMG score responder rate will be assessed based only on participants having an QMG score ≥ 5 at Baseline.

All those endpoints will be analyzed using descriptive statistics, as mentioned in the Section 5.1.

The time to first receipt of rescue therapy over the Main Treatment Period and over the Overall Treatment Period will be analyzed as time-to-event, using Kaplan-Meier plots.

For the MG-ADL and QMG responder rate the number and percentage of participants who have a reduction (i.e., improvement) of ≥ X will be summarized in the mITT at Week 12. 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 ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy" and "Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy" endpoints.

Individual line plots with individual values of Total MG-ADL, QMG and MG-QoL15r scores will be created in mITT.

For participants infected with COVID-19 as per the AE page, CFB in QMG and MG-QOL15r score will be listed by visit separately.

5.4 Planned safety and other analyses

Safety analyses will be presented on the SS. Listings for all safety analyses will be presented.

5.4.1 Extent of Exposure

IMP duration will be summarized. 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 ZLP) 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) will be calculated as the sum of the exposure durations of all study participants divided by 365.25.

The overall extent of exposure in the SS will be summarized during the Main Treatment Period and in the Overall Treatment Period.

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. The missed doses will be derived based on the expected number of daily doses the participant should receive within a defined period minus the total number of doses he/she has received during that period. For this derivation, the number of total syringes administered to a participant at each visit will be considered via the total number of kits administered at each visit, assuming that each kit contains 7 syringes to be used for 7 daily doses.

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 days
- ≥ 15 days
- ≥ 29 days
- ≥ 57 days
- ≥ 84 days

All drug administration details will be listed.

The compliance between two in-clinic visits, as well as the overall compliance will be described.

The study withdrawal will be summarized over the Main Treatment Period and over the Overall Treatment Period time-to-event, using Kaplan-Meier plot.

For the Main Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP dose + 1. Participants that did not early withdraw should be censored at the date of Main Treatment Period completion.

For the Overall Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP in Main Treatment Period + 1. Participants that did not (early) withdraw should be censored at the date of their last contact.

For the Extension Treatment Period, time to IMP discontinuation is defined as: Date of last IMP dose – date of first IMP in Extension Treatment Period+ 1. Participants that did not withdraw should be censored at the date of their last contact.

For all treatment periods, participants that switch to commercially available Zilucoplan are not considered as discontinuation events; for the time to event analysis exposure will be censored at the date of their last contact.

5.4.2 Adverse Events

5.4.2.1 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 and SAE reporting period will start with the signature of the ICF and will end with the last study visit (i.e., SFU, Week 12 Visit).

In addition, AEs will be classified for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 or later (United States Department of Health and Human Services, Version 5.0, November 17, 2017). 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). 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.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
  Note: instrumental activity of daily living refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
  Note: self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

For the purpose of the tabulations AE intensity categories will be mapped to CTCAE severity classifications grade 1 to 5 as described below:

- Mild – Grade 1
- Moderate – Grade 2
- Severe – Grade 3, 4, 5, where
  - Grade 4 will be derived from the SAE monitoring form, when SAE is life threatening.
  - Grade 5 will be derived from the SAE monitoring form when SAE is fatal.

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.

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.

5.4.2.2 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
   - Any TEAEs above 5% of occurrence
   - 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 System Organ Class (SOC), high level term (HLT), and PT:
   - Serious TEAEs

- Non-serious TEAEs
- TEAEs leading to death

In case of 5 or less of the following TEAEs, no summary table will be displayed, and the listing of AEs will be used. In case of 6 events or more the number, percentage of participants and frequency of the following TEAEs will be summarized by System Organ Class (SOC), high level term (HLT), and PT:

- Any TEAEs
- Severe TEAEs
- TEAEs leading to permanent withdrawal from IMP
- Treatment-related TEAEs leading to permanent withdrawal from IMP

3. The number, percentage of participants with TEAEs will be summarized by maximum intensity (mild, moderate and severe), SOC, and PT as well as by intensity (mild, moderate and severe), SOC, and PT.
4. The number, percentage of participants and frequency of the following TEAEs will be summarized by relationship, SOC, HLT, and PT:
   - Any TEAEs
   - Serious TEAEs
   - Fatal TEAEs

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, HLT (if HLT is presented) and PT will be presented. 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.

Listings of all AEs in (ES), permanent withdrawal of IMP due to AEs, participant discontinuation from study due to AEs, AEs leading to death will be presented by participants in SS.

To assess the impact of the COVID-19 pandemic on safety, additional summaries and listings will be presented. All COVID-19 related TEAEs will be summarized by MedDRA SOC, HLT and PT.

Study participants with a confirmed or suspected COVID-19 infection were identified by searching TEAEs for selected MedDRA terms as defined in Section 6.1.9 and described as "COVID-19 related TEAEs.

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

In addition, all listing of AEs will include a column for COVID-19 relatedness.

Since the beginning of the COVID-19 pandemic, the COVID-19 vaccination followed a specific mass vaccination program in a short time frame. Administration of doses of COVID-19 vaccination might be needed during this study and 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 (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 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.

All AEs within a 7-day period post each COVID-19 vaccination will be summarized for all vaccinated participants. Two separate listings will display the AEs after adjustment of the interval censoring and the concomitant COVID-19 vaccination.

All AEs after a 7-day period of each COVID-19 vaccination will be listed for all vaccinated participants. Two separate listings will display the AEs after adjustment of the interval censoring and the concomitant COVID-19 vaccination.

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.”

5.4.3 Other Safety Assessments

Other safety assessments (AE of special interest, Laboratory data and Vital Signs) will also be performed in the SS.

5.4.3.1 AEs of Special Interest and AEs of Interest

The AEs of Special Interest identified in this study are the Hy's Law that are described in Section 5.4.3.2.4.

The following are AEs of Interest (as defined in Section 6.1.6 that require special statistical analyses:

- Hypersensitivity reactions
- Anaphylactic reactions
- Injection site reactions
- Drug related hepatic disorders
- Malignancies or unspecified tumors

The number and percentage of participants who experience each AE of Interest will be summarized 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.

5.4.3.2 Clinical laboratory evaluations

The following table (Table 5.1) 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 5.1: Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count		RBC indices: MCV MCH %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC count			
	Hemoglobin			
	Hematocrit			
Clinical chemistry[a]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Glucose	Calcium	Alkaline phosphatase	Amylase
	Lipase			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum hCG pregnancy test (as needed for women of childbearing potential) [b] The results of each test must be entered into the eCRF.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report form; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; INR=international normalized ratio; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in the protocol. All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct

Table 5.1: Protocol-required safety laboratory assessments

Laboratory assessments	Parameters

bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine testing will be performed at visits subsequent to the Screening Visit.

All laboratory samples are collected prior to IMP administration at applicable visits.

5.4.3.2.1 Laboratory values over time

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

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 Below the Limit of Quantification (BLQ) will be imputed with half of the lower limit of quantification Lower Limit of Quantification (LLOQ), and measurements Above the Limit of Quantification (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.

5.4.3.2.2 Individual Subject 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 visits).

5.4.3.2.3 Laboratory Marked abnormalities

Treatment-emergent marked abnormalities (TEMAs) in laboratory parameters will be summarized 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.Treatment-emergent is defined as meeting the MA criteria at any post-Baseline visit while the MA criteria are not present before dosing.

Listings will include a flag for values identified as TEMA.

5.4.3.2.4 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:

- AST: ≥ 3 x ULN, ≥ 5 x ULN, ≥ 8 x ULN, ≥ 10 x ULN, ≥ 20 x ULN
- 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
- ALP: ≥ 1.5 x ULN

Hepatic events will be defined as:

- TEAEs with narrow Standardised MedDRA Queries (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
- AST or ALT ≥ 3xULN with INR>1.5 (if INR is measured)

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 at any visit (including unscheduled visits) in the SS. 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. 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 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.

5.4.3.2.5 Analysis of Lipase, Amylase, and Eosinophils

Laboratory values (including corresponding normal ranges) will be used for shift tables/figures, patient profiles and aggregated plots.

Tables summarizing shifts from baseline to maximum post-baseline CTCAE for increase in lipase and amylase will be presented. The grades to be used for amylase and lipase are defined by CTCAE Version 5.0 as follows:

- Grade 0: ≤ ULN
- Grade 1: > ULN – 1.5 x ULN
- Grade 2: > 1.5 – 2.0 x ULN
- Grade 3: > 2.0 – 5.0 x ULN
- Grade 4: ≥ 5.0 x ULN

Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available.

Tables summarizing shifts from baseline to maximum post-baseline result for increase in eosinophils will be described according to the categories low, normal, and high.

The summary of these laboratory parameters will also include a "Missing" and "Total" category.

The aggregated line plots will be presented for study participants with increase in lipase and amylase with Grade 1 and above (i.e., >ULN) and with high results in eosinophils. The line plots will be presented by laboratory parameter (amylase, lipase, eosinophils).

5.4.3.3 Vital Signs

Vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be collected throughout the study.

5.4.3.3.1 Vital Sign Values Over Time

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

The number and percentage of participants who meet each of the marked abnormality criteria outlined in Appendix 6.2 will be summarized 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.

5.4.3.3.2 Individual Subject 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).

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 markedly abnormal.

5.4.3.4 Electrocardiograms

The following variables will be reported:

- Heart rate (beats/min)
- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)

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

5.4.3.4.1 Electrocardiogram Values Over Time

Observed values and changes from Baseline will be summarized 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 met each of the marked abnormality criteria outlined Section 6.2.3 will be summarized at each scheduled visit and at any visit (including unscheduled visit).

5.4.3.4.2 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.

5.4.3.5 Physical examination

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

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

C-SSRS instrument recorded at screening visit references the lifetime period and the past six months period. Baseline to end of study visit summaries reference the period prior to the visit assessed.

Results of the C-SSRS, as well as the treatment emergent item at Week 12 (or (early) withdrawal will be summarized in SS by scheduled timepoint using the number of participants and percentage with:

1. suicidal ideation,
2. suicidal behavior,
3. suicidal ideation or behavior,
4. self-injurious behavior without suicidal intent.

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

[redacted]

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

[redacted]

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

Self-injurious behavior without suicidal intent is corresponding to the response to [redacted] in questionnaire.

The treatment emergent item at Week 12 is defined as any item that is present at Week 12 that was not present at Baseline.

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

5.5 Other Analyses

5.5.1 Other endpoints and/or parameters

5.5.1.1 Pharmacokinetics

The plasma concentrations of ZLP and its two major metabolites ([redacted]) 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% Confidence Interval (CI) (assuming log-normally distributed data).

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 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

$$\text{geoCV}(\%) = \sqrt{\exp\left(\text{SD}^2\right) - 1} \times 100.$$

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 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 CSR but may be in a separate modelling report.

5.5.1.2 Pharmacodynamics

Pharmacodynamic analyses will be performed on the PD-PPS. The pharmacodynamic endpoint is the sRBC lysis assay.

Summary statistics will be provided for the values, change from baseline, and percent change from baseline at each of the scheduled assessment time points.

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 may be in a separate report.

5.5.1.3 Time needed for administration of SC ZLP

The time needed for administration of SC ZLP will be analyzed using descriptive statistics as detailed in Section 5.1.

5.5.1.4 Participants' treatment satisfaction

The participants' treatment satisfaction is assessed via the TSQM-9 questionnaire. Descriptive analyses of the Effectiveness, Convenience and Global Satisfaction subscore will be displayed. Bar charts illustrating the mean and standard error at each visit by domain will be provided. Individual participant listings will be provided for all participants and for participants infected with COVID-19 as per the AE page. The details for the derivation of scores based on the TSQM-9 questionnaire are available in Section 6.1.5.6.

5.5.1.5 Participants' treatment preference

The participants' treatment preference is assessed via a single question where only one answer should be selected. If more than one answer is selected, the value will be set as Missing.

Descriptive analyses, as detailed in Section 5.1, will be used to analyze the participants' preference.

5.5.1.6 Genomics

No Genomics analysis is planned in this study.

5.6 Subgroup analyses

No subgroup analyses are planned in this study.

5.7 Interim Analyses

If ZLP is not commercially available in the US at the time of the last visit of the last participant in the Main Treatment Period, an interim analysis will be conducted. This interim analysis will include all data collected during the Main Treatment Period.

At the interim analysis, all TFLs concerning the Main Treatment Period only will be provided, unless otherwise stated.

If further interim analysis will be considered during the Main Treatment Period then this, will be of exploratory nature and only descriptive statistics will be provided.

At the final analysis, all the TFLs concerning the Main Treatment Period and the Overall Treatment Period will be provided, except:

- The by visits participant disposition and safety analyses will be displayed only on the Overall Treatment Period,
- The participant disposition and safety listings will be provided on the Overall Treatment Period.

5.8 Data Monitoring Committee (DMC) or Other Review Board

No DMC or Other review Board are planned in this study.

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 for the mITT, using descriptive statistics. In case there is a difference of more than 5 study participants, those descriptive statistics will be duplicated in the SS.

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: $BMI = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$ 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)
- Country

- BMI in kg/m^2 (<18.5, 18.5 - <25, 25 - <30, 30 – <35, 35- < 40, ≥ 40)
- Weight in Kg (<43, 43 - <56, 56-<77, 77 - <150, ≥ 150)
- MD-ADL scores (≤9/≥10)
- QMG scores (≤17 / ≥18)
- Chronic Kidney Disease Stages: normal renal function (Estimate glomerular filtrate rate (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/1.73m². A 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 data base lock to confirm exclusion from analysis sets.

The summary of the IPDs will be performed for the Main Treatment Period as well as for the Overall Treatment Period in mITT.

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

A listing of the important protocol deviations will be provided for the Main Treatment Period as well as for the Overall Treatment Period in mITT population; a COVID-19 related flag will be present.

6.1.3 Medical history

6.1.3.1 Medical history (other than MG disease history)

Medical History will be summarized by SOC, 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 SOC, HLT within SOC, and within HLT, by decreasing frequency for the PT.

Medical History will be listed on the ES population.

6.1.3.2 gMG disease history

The following gMG disease history data will be summarized 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)

Note: Generalized symptoms at onset: participants with respiratory symptoms or symptoms in the limb, bulbar or any other location; participants at this category might also have ocular symptoms at onset as well.

- 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) = (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)
- Reason for switching to study medication (Logistical challenges including travel and time spent at a hospital, Challenges with venous access, Lengthy intravenous infusion, Other)

gMG disease history characteristics will be listed overall.

6.1.4 Prior/concomitant/follow-up 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.
- **Concomitant Only** medications will include any medication that started after the first administration of IMP.

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 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. In the case of ties, sort these alphabetically. Summaries will include the overall number and percentage of participants receiving at least one treatment of a PT.

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.

A by participant listing of Neisseria Meningitidis Vaccination and Prophylaxis will be provided in the SS.

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 "Myasthenia Gravis" on the Prior and Concomitant Medication eCRF form. MG specific Past, Prior, Baseline, Concomitant and Concomitant only medications will be summarized on the SS as defined in Section 6.1.4.2.

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-H) will be summarized using the same 2 sets of tables: MG specific prior medications and MG specific medications taken at baseline.

Table 6.2: Medication class

Group	Medication	Preferred Term on Prior/Concomitant eCRF form	Reported Term on gMG Treatment History Form
A	Prednisone for gMG	PREDNISONE	PREDNISONE
	Other corticosteroids for gMG	DEXAMETHASONE METHYLPREDNISONE METHYLPREDNISONE SODIUM SUCCINATE PREDNISOLONE METHYLPREDNISOLONE HYDROCORTISONE TBD**	OTHER CORTICOSTEROIDS PREDNISOLONE METHYLPREDNISOLONE
B	Azathioprine	AZATHIOPRINE	AZATHIOPRINE
	Mycophenolate	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL

Table 6.2: Medication class

Group	Medication	Preferred Term on Prior/Concomitant eCRF form	Reported Term on gMG Treatment History Form
		MYCOPHENOLATE ACID	
C	IVIG	IMMUNOGLOBULINS	INTRAVENOUS IMMUNOGLOBULIN
	SCIG	IMMUNOGLOBULINS	SUBCUTANEOUS IMMUNOGLOBULIN
D	PLEX* or Plasmapheresis	PLASMA EXCHANGE PLASMAPHERESIS	PLASMA EXCHANGE PLASMAPHERESIS
E	Cyclosporine	CICLOSPORIN	CYCLOSPORINE
	Cyclophosphamide	CYCLOPHOSPHAMIDE	CYCLOPHOSPHAMIDE
	Methotrexate	METHOTREXATE	METHOTREXATE
	Tacrolimus	TACROLIMUS	TACROLIMUS
	Rituximab	RITUXIMAB	RITUXIMAB
		TBD**	
F	Cholinesterase inhibitors	GALANTAMINE	GALANTAMINE
		PYRIDOSTIGMINE PYRIDOSTIGMINE BROMIDE	PYRIDOSTIGMINE
		AMBENONIUM	AMBENONIUM CHLORIDE AMBENOMIUM CHLORURE MYTELASE
		NEOSTIGMINE	NEOSTIGMINE METHYLSULFATE NEOSTIGMINE BROMIDE
		DISTIGMINE	DISTIGMINE BROMIDE
G	C5 inhibitors	ECULIZUMAB	ECULIZUMAB
		RAVULIZUMAB	RAVULIZUMAB
H	FcRn	EFGARTIGIMOD ROZANOLIXIZUMAB	EFGARTIGIMOD ROZANOLIXIZUMAB

eCRF=electronic Case Report Form; gMG=generalized myasthenia gravis; IVIG=intravenous immunoglobulin; NOS=not otherwise specified; PLEX=plasma exchange; SCIG=subcutaneous immunoglobulin
*plasma exchange will be on the Procedures eCRF (if concomitant procedure).
**TBD: To be defined: a complete list of corresponding medications and preferred terms will be provided by UCB prior to DBL

6.1.5 Data derivation rules

6.1.5.1 MG Activities of Daily Living 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, Herbelin, Nations, Bryan, & Barohn, 1999); (Muppidi, Wolfe, Conaway, & Burns, 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). [redacted]

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

[redacted]

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, et al., 1998); (Katzberg, Barnett, Merkies, & Bril, 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). [redacted]

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

[redacted]

Table 6.4: QMG Score

[redacted]

F=female; M=male.

The functional sub-scores for a participant are defined as the total score of the corresponding items (or the value of the item if it is a single score):

[redacted]

If an item response has a missing value, the same method as for the QMG total score for imputing missing values will be used.

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

The 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, et al., 2010), (Burns, et al., 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 myasthenia gravis

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.

6.1.5.4 Minimal Symptom Expression (MSE)

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., 2020).

6.1.5.5 MGFA Post-Intervention Status (MGFA-PIS)

The 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 or 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.

6.1.5.6 TSQM-9 questionnaire

The TSQM-9 is a self-administered PRO with Likert type response options that assesses satisfaction with medication use over 3 domains: Effectiveness (items 1 through 3), Convenience (items 4 through 6), and Global Satisfaction (items 7 through 9). Each domain score ranges from 0 to 100, with higher scores indicating increased satisfaction. The instrument is not disease specific. The TSQM 9 and previous versions have undergone qualitative and psychometric testing and were found to be valid and reliable.

- The Global Satisfaction subscore is based on Item 7, Item 8 and Item 9 and is calculated as follow:

[(Item 7 + Item 8 + Item 9 – 3)/14]*100

If either Item 7 or Item 8 is missing: [(sum of the 2 completed items – 2)/10]*100

If Item 9 is missing: [(Item 7 + Item 8 – 2)/8]*100

- The Effectiveness subscore is based on Item 1, Item 2 and Item 3 and is calculated as follow:

[(Item 1 + Item 2 + Item 3 – 3)/18]*100

If one Item is missing: [(sum of the 2 completed items – 2)/12]*100

- The Convenience subscore is based on Item 4, Item 5 and Item 6 and is calculated as follow:

[(Item 4 + Item 5 + Item 6 – 3)/18]*100

If one Item is missing: [(sum of the 2 completed items – 2)/12]*100

6.1.6 AEs of Interest

Table 6–5: AEs of Interest selection criteria

No	Event (also included in Title of TFL output)	Selection criteria
1	Hypersensitivity reactions	SMQ='Hypersensitivity' (narrow scope)
2	Anaphylactic reactions	SMQ= 'Anaphylactic reaction' and 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.
3	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)".

4	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
5	Injection site reactions	TEAE with HLT = ’Injection site reactions’ or HLT = Administration site reactions NEC’

Table 6–6: 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
	PROCEDURALSHOCK
	SHOCK
	SHOCK SYMPTOM
	TYPE 1 HYPERSENSITIVITY
B	ACUTE RESPIRATORY FAILURE
	ASTHMA
	BRONCHIAL OEDEMA
	BRONCHOSPASM
	CARDIO-RESPIRATORY DISTRESS
	CHEST DISCOMFORT
	CHOKING
	CHOKING SENSATION
	CIRCUMORAL OEDEMA
	COUGH
	COUGH VARIANT ASTHMA
	CYANOSIS
	DYSPNOEA
	ENHANCED RESPIRATORY DISEASE
	HYPERVENTILATION

Table 6–6: Anaphylactic Reactions Categories

Category	Preferred Term
	IRREGULAR BREATHING
	LARYNGEAL DYSPNOEA
	LARYNGEAL OEDEMA
	LARYNGOSPASM
	LARYNGOTRACHEAL OEDEMA
	MOUTH SWELLING
	NASAL OBSTRUCTION
	OEDEMA MOUTH
	OROPHARYNGEAL OEDEMA
	OROPHARYNGEAL SPASM
	OROPHARYNGEAL SWELLING
	PHARYNGEAL SPASM
	PHARYNGEAL SWELLING
	RESPIRATORY ARREST
	RESPIRATORY DISTRESS
	RESPIRATORY FAILURE
	REVERSIBLE AIRWAYS OBSTRUCTION
	SENSATION OF FOREIGN BODY
	SNEEZING
	STRIDOR
	SWOLLEN TONGUE
	TACHYPNOEA
	THROAT TIGHTNESS
	TONGUE OEDEMA
	TRACHEAL OBSTRUCTION
	TRACHEAL OEDEMA
	UPPER AIRWAY OBSTRUCTION
	WHEEZING
C	ALLERGIC OEDEMA
	ANGIOEDEMA
	CIRCUMORAL SWELLING
	ERYTHEMA
	EYE OEDEMA
	EYE PRURITUS
	EYE SWELLING
	EYELID OEDEMA
	FACE OEDEMA
	FLUSHING

Table 6–6: Anaphylactic Reactions Categories

Category	Preferred Term
	INJECTION SITE URTICARIA
	LIP OEDEMA
	LIP SWELLING
	NODULAR RASH
	OCULAR HYPERAEMIA
	OEDEMA
	OEDEMA BLISTER
	PERIORBITAL OEDEMA
	PERIORBITAL SWELLING
	PRURITUS
	PRURITUS ALLERGIC
	RASH
	RASH ERYTHEMATOUS
	RASH PRURITIC
	SKIN SWELLING
	SWELLING
	SWELLING FACE
	SWELLING OF EYELID
	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
	HYPOTENSIVE CRISIS
	POST PROCEDURAL HYPOTENSION

6.1.7 Potentially Clinically Significant Criteria for Safety Endpoints

No additional information.

6.1.8 Extent of Exposure

The time to study withdrawal is defined as Date of study withdrawal – date of first IMP + 1.

The compliance between 2 clinic visits will be calculated as: (number of syringes dispensed at the previous clinic visit – number of unused syringes returned in clinic – total number of malfunctioned syringes)/(Date the syringes are returned in clinic – Date the syringes are dispensed in clinic)*100.

The overall compliance in the Main Treatment Period will be calculated as: (total number of syringes dispensed – total number of unused syringes – total number of malfunctioned syringes) / (Date the last syringes are returned in clinic in the Main Treatment Period – Date the first syringes are dispensed in clinic)*100.

For participants entering in the Extension Treatment Period, the overall compliance in the Overall Treatment Period will be calculated as: (total number of syringes dispensed – total number of unused syringes – total number of malfunctioned syringes+1)/(Date of last drug administration – Date the first syringes are dispensed in clinic in the Main Treatment Period+1)*100.

If the participant was (early) withdrawn, then the date to be considered in the calculation of compliance as the end of exposure period will be the date of last administration of Zilucoplan and not the date the participant returned the syringes in clinic. Then, the compliance will be calculated as follows: (number of syringes dispensed at the previous clinic visit – number of unused syringes returned in clinic – total number of malfunctioned syringes+1)/(Date of last drug administration – Date the syringes are dispensed in clinic + 1)*100.

Of note, the number of syringes dispensed at each visit will be derived based on the number of kits dispensed at that visit, assuming that each kit contains 7 single dose syringes to be used for the daily dosing.

6.1.9 COVID-19 terms

Table 6.7: 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 6–8: 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
Eosinophils	10^9/L	10^9/L	≥1.5 x 10^9/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
Bilirubin (total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal > 3.0 x Baseline value if Baseline is abnormal
Creatinine	mg/dL	umol/L	>3.0 x ULN
Estimate glomerular filtrate rate (eGFR)[a]	mL/min/1.73 m^2	mL/min/1.73 m^2	<29 mL/min/1.73m^2

Parameter	Unit (conventional)	Unit (Standard)	Marked Abnormality Criteria
Glucose[b]	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

ALT= alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; dL = deciliter; L = liter; mg = milligram; mmol = millimoles; µg = microgram; U = unit;
ULN = upper limit of normal

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

[a] eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration or CKD-EPI formula (https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi) which is eGFR = 141 * min(Scr/κ,1)$^{\alpha}$ * max(Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 [if female] * 1.159 [if black]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. For derivation from values in standard units (umol/L) the κ values are 61.9 for females and 79.6 for males. Subjects with missing race should be considered as non-black for eGFR calculation.

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

6.2.2 Marked Abnormalities Vital Signs

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

Table 6–9: 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	>101^{0}F (38.3 ^{0}C)
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 6–10: Marked Abnormalities (ECG)

Parameter	Treatment Emergent Markedly Abnormal 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 MA criteria at any post-Baseline visit after the first dose of IMP and not meeting the MA criteria at Baseline.

6.3 Appendix 3: Changes to Protocol-Planned Analyses

The description of compliance has been added.

More precision on the model used for the main secondary endpoint strategy (MMRM followed by a One-Sample t-test on the LS Means) were given.

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