STATISTICAL ANALYSIS PLAN

Study: MG0020

Product: Rozanolixizumab

AN OPEN-LABEL, CROSSOVER STUDY TO EVALUATE ROZANOLIXIZUMAB SELF-ADMINISTRATION BY STUDY PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

A Phase 3, open-label, crossover study to evaluate self-administration of rozanolixizumab by study participants with gMG

Sponsor Name: UCB Biopharma SRL

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

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VERSION HISTORY

SAP Version	Date	Change	Rationale
1.0	03 Apr 2023	Not Applicable	Original version
Amendment 1.0	03 May 2024	Described below	

Amendment 1.0

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, consistency, formatting and typographical changes have been made.	Updated to provide clarity and be consistent with the remainder of the SAP.
1 Introduction	Added Protocol Amendment 4, 07 Sep 2023 and Protocol Amendment 5, 30 Nov 2023.	New protocol amendments were developed after the first version of the SAP.
1.2 Study Design	Defined that the Safety Follow-up Period may be up to 7 weeks, as participants may move to commercially available rozanolixizumab at the discretion of the investigator, shortening the duration of this period.	The option for participants to access commercially available rozanolixizumab was introduced in Protocol Amendment 5. Moving to a post-trial access program or commercially available rozanolixizumab may reduce the length of the Safety Follow-up Period.
3 Populations for Analysis	Full Analysis Set (FAS): All participants who are included in SS, were randomized and completed both Self-administration Periods. Both Self-administration Periods will be considered as complete if self-administration occurred on Visits 13 and 19 in accordance with the randomization scheme.	Specified the definition of FAS accepting only treatment assignments in accordance with randomization scheme.

Section # and Name	Description of Change	Brief Rationale
4.1 General considerations	Removed: The primary analysis will be performed at database lock after Last Participant Last Visit. In the case of missing visit information for MG-ADL or SIAQ, visit windowing will be applied based on the Protocol SOA. Else, visit windows will not be used.	All analysis, not limited to primary analysis, will be performed at database lock after Last Participant Last Visit. Ensures that data performed within the window of a visit will be assigned to the related visit appropriately.
4.1.1.2 Analysis Periods	Self-administration Period 2: Starts one day after the end of Self-administration Period 1 and ends at the end of Visit 20 assessments (EOT date).	By the Protocol, all end of treatment (EOT) assessments at Visit 20 (Week 19) belong to treatment phase.
4.1.3 Mapping of assessments performed at Early Withdrawal Visit	Added: If the mapped visit is the first visit in the next period, the visit will be assigned to the previous period.	To ensure that mapped data is assigned to the correct period.
4.1.4 Treatment assignment and treatment groups	Added: In the case that all [redacted] in each period were performed using the alternate method to the one randomized, the actual treatment sequence will reflect this.	To ensure that data is assigned to the correct self-administration method.
Table 1–1: Calculation rules for duration of AEs	Added footnote: Note: '--' represents a missing value	Footnote added to clarify missing onset/outcome dates.
4.2.2 Main analytical approach	Updated the analyses to specify the mean proportion of success would be presented with its 90% CI calculated using the Wilson method (without continuity correction), rather than a generalized linear mixed model. Specified that the Wilson method would be used rather than Clopper-Pearson exact method.	Specified the method of the calculation of CI for the mean proportion of success. Wilson method was selected rather than Clopper-Pearson exact method due to a larger number of participants able to perform self-administration using both methods, than planned in Sample Size Section 5. Therefore, a method considering Normal approximation was deemed sufficient.

Section # and Name	Description of Change	Brief Rationale
4.2.2 Main analytical approach	In case at least one of the three questions related to the administration is missing (correct infusion site, subcutaneous, intended dose), the self-administration is considered unsuccessful. Imputation will not be performed.	Specified that a missing response will not be imputed.
4.2.3 Sensitivity analyses	Sensitivity analyses by imputing a self-administration failure at Visit 13 or Visit 19 will not be performed. Any references to model fitting have been removed.	Specified that a missing response will not be imputed
4.2.4 Supplementary analyses	Specified supplementary analysis will be performed on the FAS only.	As a 2x2 contingency table is produced, the analysis should be performed on the FAS as these participants completed both self-administration periods and successful self-administration was assessed at Visit 13 and Visit 19.
4.3.1 Secondary endpoints	Defined a TEAE. Updated the definitions of assignment of TEAEs to a Self-administration period.	Assignment of TEAEs to a Self-administration period updated since the 8 weeks from final dose are now covered in the TEAE main definition text. Assignment to Self-administration period 2 updated to match definition of analysis periods.

Section # and Name	Description of Change	Brief Rationale
4.4.2 MG-ADL	Specified worsening in MG-ADL score will be a ≥2 point increase from Baseline at any timepoint during the treatment period. Added that MG-ADL worsening at the last available measurement of MG-ADL before the EOS Visit (Visit 21) would be presented in this table and a 90% CI estimated using the Wilson method. Stated that if time of collection is missing for MG-ADL at Visit 2, this will be considered as the Baseline assessment. Specified MG-ADL will be summarized at each visit by sequence only, not also split by self-administration method. Line plots of mean MG-ADL total score and mean change from baseline over time added. Spaghetti plots of MG-ADL total score and change from baseline over time also presented.	Aligns with the definition of MG-ADL worsening in the Protocol. MG-ADL worsening at the last available timepoint before EOS will be presented and a 90% CI calculated as specified in the Protocol. If time of collection for MG-ADL at Visit 2 is missing, this can be assumed as the Baseline assessment as MG-ADL is collected predose per Protocol. As the MG-ADL summary is split by sequence and visit, additionally splitting by self-administration method is not required. Plots added to visualize MG-ADL changes over time.

Section # and Name	Description of Change	Brief Rationale
4.4.3 Pharmacodynamic	For the RSS, observed values and percentage change from baseline will be summarized by sequence. Specified that if rescue therapy is taken, IgG values collected 8 weeks after the start of rescue medication will not be included in summary analysis. Line plots of median IgG concentrations and percentage change from baseline over time added. Spaghetti plots of IgG concentrations and percentage change from baseline over time will also be presented. A line plot presenting mean change from baseline in MG-ADL and median percentage change in IgG by sequence will be produced. Plots of individual percentage change from baseline in IgG concentrations and change from baseline in MG-ADL total score added. Specified IgG laboratory assessments are performed predose.	To provide a clearer picture of participants' IgG levels throughout the study. IgG values may be affected by rescue therapy use and influence analyses. Plots added to visualize IgG changes over time.
4.4.4 Immunogenicity	ADA summaries will be presented by sequence and overall	To provide a clearer picture of participants' ADA status throughout the study.

Section # and Name	Description of Change	Brief Rationale
4.4.5 SIAQ	Specified PRE-SIAQ is obtained predose at the Baseline Visit per Protocol. An additional table for POST-SIAQ individual item scores will be produced. A horizontal bar chart displaying individual domain scores for PRE-SIAQ and POST-SIAQ will be produced. Added that in the case of repeated measurements of PRE-SIAQ at the Baseline Visit, the earliest measurement will be considered.	Selecting the earliest PRE-SIAQ assessment ensures that the questionnaire was performed prior to administration of IMP at the Baseline Visit.
4.4.6 Self-administration at home	The number and proportion of participants deemed a treatment success at each of the self-administration visits will be tabulated. Proportion of success with 90% CI for self-administration of syringe driver and manual push at home will not be estimated using a generalized linear model.	Including all self-administration visits in the treatment success summary table. For 3 assessments of self-administration at home only descriptive statistics will be used.
4.4.7 TEAEs leading to permanent withdrawal	Summary table will be presented for SS and RSS, by SOC, HLT and PT. Removed the estimation of 90% CI with a generalized linear mixed model.	90% CI for occurrence of these TEAEs will not be calculated as explained in Section 4.8.

Section # and Name	Description of Change	Brief Rationale
4.5.1 Extent of exposure	Duration of infusion will be summarized for the RSS by method and timepoint. Defined the equation to calculate duration of infusion. The study medication duration will also be described by category: ≥1 day, ≥ 36 days, ≥ 78 days, and ≥ 120 days. Updated study medication duration category definitions from weeks to days.	Included an analysis to assess study medication duration of participant in the RSS. Specified how duration of infusion should be calculated. Duration categories updated to days since duration is calculated in days
4.5.2 Adverse events	Safety analysis will present TEAEs using SOC, HLT and PT. The following summaries were added: • Incidence of TEAEs by Intensity • Incidence of TEAEs by Relationship • Incidence of drug-related TEAEs • Incidence of severe TEAEs The following summary was removed: • Incidence of Treatment-Emergent Serious AEs – Participant Numbers Specified drug-related is based on the Investigator assessment. Incidence of TEAEs of Focus will also be presented for the RSS, in addition to the SS.	Added coding of AEs with HLT term. All MG studies use coding of AEs with SOC, HLT and PT terms. Included additional AE summaries. Participant Numbers summaries removed as individual participant AE data can be found in listings.

Section # and Name	Description of Change	Brief Rationale
4.5.3.1.1 Laboratory values over time	Updated the definitions of assignment of TE laboratory data to a period. Added: Central laboratory data will be used for the summary tables and figures. Local laboratory data will be listed only. Specified raw calcium values will be used in shift tables and corrected calcium values used for markedly abnormal assessments.	Updated assignment to a period to align with the Analysis Periods definition. Central and local laboratory data have differing reference ranges thus local laboratory data is to be listed only.
4.5.3.2 Vital signs	Added: In case of early withdrawal, the visit will be mapped to the pre-dose timepoint of the next scheduled visit. Added the assignment of TEMA assessments to a period.	Updated in order to present a timepoint for early withdrawal data. TEMA vital signs will be assigned to a period in outputs.
4.5.3.3 Electrocardiograms	Defined Treatment-emergent. Abnormal ECG findings will be listed.	Defined treatment-emergent and specified ECG abnormalities will be listed.
4.5.3.4.2 Suicidal risk monitoring	Actual attempts will be listed.	Specified that a listing will be provided for actual attempts.
4.6 Other analyses	Deleted "No other analysis is planned".	Updated since PMDA specific analyses have been introduced.
4.6.1 Subgroup analyses	No subgroup analyses are planned.	The proposed subgroup analyses were deemed inappropriate for the study design and would be challenging to interpret, due to the exposure (amount and time frame) not being comparable between the 2 subgroups.
4.6.2 Specific analyses for PMDA	Section added, including a list of summary tables to include Japanese participants only.	Specific analyses for the Japanese population are required by the PMDA.

Section # and Name	Description of Change	Brief Rationale
4.8 Changes to protocol-planned analyses	Removed: Demographics will be displayed overall for the SS as per Section 6.4 although in the Clinical Study Protocol (CSP) Section 9.2, it was specified by sequence and overall. Indeed, demographics will be reported for the Safety Set and not for the Randomized Safety Set. Added: The Full Analysis Set (FAS) is specified in the SAP Section 3 as all participants who are included in Safety Set, were randomized, and completed both self-administration periods. Both self-administration periods will be considered as complete if self-administration occurred on Visits 13 and 19 in accordance with the randomization scheme. In the CSP it was defined as all randomized study participants who received at least 1 dose of IMP (partial or full) and completed both self-administration periods. Added: Confidence intervals for the occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab will not be estimated as presented in the Protocol.	Text updated to specify demographics will be presented by sequence and overall, as per Protocol Section 9.2 for the RSS, however, will only be presented for overall for the SS. Rationale for changes added to this section are presented in Section 4.8.
Table 1–1: Expected 90% confidence intervals considering different success rates and 30 study participants completing both Treatment Periods	Success rate table added.	For consistency with the section in the Protocol.
6.1 Appendix 1: List of Abbreviations	HLT,INR and TEMA added to list of abbreviations.	Abbreviations used throughout the SAP.

Section # and Name	Description of Change	Brief Rationale
Appendix 3: Participant disposition	Reasons for screen failures will not be summarized by COVID-19 timepoint. Disposition of analysis sets will be summarized using the SS rather than ES. Added: Completed Study (A study participant is considered to have 'Completed Study' if 'Completed Study Participant' has been recorded in CRF form 'Study Termination Enrolled') Added listings for study participant disposition including participant analysis sets, re-screened participants, visit dates, self-administration training visits, and self-administration eligibility criteria.	Since no participant had a Baseline visit prior to the COVID-19 pandemic cut-off date of 05-May-2023, summaries split by timepoint of COVID-19 pandemic will not be presented. Disposition of analysis sets will be summarized using the SS as disposition of screen failures is presented in another table, and so presenting for the ES is not necessary. Specified the definition of Completed Study in accordance with Protocol Amendment 5. Added additional listings to display study participant disposition data.
6.4 Appendix 4: Baseline characteristics and demographics	COVID-19 pandemic cut-off end date of 05-May-2023 added. Myasthenic crisis in the past added to list of baseline characteristics. Specified demographics and baseline characteristics will also be presented by sequence and overall, for the RSS.	Update in COVID-19 pandemic end date since last SAP.
6.5 Appendix 5: Protocol deviations	Summary tables for IPDs by relationship to COVID-19 and IPDs by COVID-19 pandemic timepoint will not be presented.	Since no participant had a Baseline visit prior to the COVID-19 pandemic cut-off date of 05-May-2023, summaries split by relationship or timepoint of COVID-19 pandemic will not be presented.

Section # and Name	Description of Change	Brief Rationale
6.7.1 Categorization	Updated the definitions of assignment of prior/concomitant medications. Removed: The medications allocated to Self-administration Period 1 or Self-administration Period 2 will be included in the summary output. Other medications will only be listed.	Updated to align with the Analysis Periods definition. A summary table will also be produced for the SS included Training and Follow-up period.
6.7.2 Prior and concomitant medications summaries	Specified the list of rescue medications can be found in the Protocol and are identified in the CRF. A summary table will be presented for the SS.	Rescue medication will be analyzed for RLZ Total.
6.8.1 Handling of repeated and unscheduled measurements	The following general rules will apply to all repeated and unscheduled measurements, unless otherwise specified:	Repeated PRE-SIAQ measurements deviate from the general rules in this section. Handling of this data has been specified elsewhere in the SAP.
Table 6-2: Chemistry:	Creatinine: >3.0 x ULN or >3.0 x baseline Potassium Low: <3.0 mmol/L	Updated creatinine and potassium abnormality criteria.
Table 6-3: Vital Signs:	Removed "Body weight" from table.	Body weight is captured only at screening
Table 6-4: Electrocardiogram:	Removed "Treatment emergent value" from table.	The table specifies abnormality criteria, and all values are considered as treatment emergent.
6.12 Appendix 12: Impact of the coronavirus disease 2019 (COVID-19) on study data	Additional summary analyses based on COVID-19 timepoint will not be presented.	Since no participant had a Baseline visit prior to the COVID-19 pandemic cut-off date of 05-May-2023, summaries split by timepoint of COVID-19 pandemic will not be presented.
6.13 Appendix 13: AEs of focus for Rozanolixizumab program	Aseptic updated to Possible Aseptic, and removal of (Note: not applicable for MG0020)	Aligns with rozanolixizumab PSAP Amendment 2.

Section # and Name	Description of Change	Brief Rationale
7 References	[2] Brown, Lawrence D.; Cai, T. Tony; DasGupta, Anirban. Interval Estimation for a Binomial Proportion. Statist. Sci. 16 (2001), no. 2, 101–133. doi:10.1214/ss/1009213286.	Reference added for calculating of the Wilson confidence interval.

1 INTRODUCTION

The purpose of this SAP is to provide the information that is necessary to perform statistical analyses for the final analysis of study MG0020. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol. TFLs specifications are contained in a separate document.

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

- Protocol Amendment 3, 09 Dec 2022
- Protocol Amendment 4, 07 Sep 2023
- Protocol Amendment 5, 30 Nov 2023

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP may be amended accordingly. Changes to the analysis from the protocol are documented in Section 4.8. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

1.1 Objectives and endpoints

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Primary objective: • To evaluate the ability of study participants with gMG to successfully self-administer rozanolixizumab after training in the self-administration technique using the syringe driver and manual push methods	Primary endpoint: • Successful self-administration of rozanolixizumab (with correct use of syringe driver and manual push, respectively) during the Self-administration Period at Visit 13 ([redacted]; last dose of Self-administration Period 1) and Visit 19 ([redacted]; last dose of Self-administration Period 2). Successful self-administration is defined by the participant (i) choosing the correct infusion site, (ii) administering subcutaneous (SC), and (iii) delivering the intended dose.
Secondary	

Objectives	Endpoints
Secondary objective: • To evaluate the safety of SC self-administration of rozanolixizumab.	Secondary endpoints: • Occurrence of TEAEs after syringe driver or manual push self-administration from Visit 2 ([redacted] up to the End of Study Visit (Visit 21 [Week 26]). • Occurrence of local site reactions up to 24 hours after each administration during the Training Period and Self-administration Periods. • Occurrence of medication errors associated with adverse reactions during the 2 Self-administration Periods of the study.
Other	
Other objectives: • To evaluate the study participant's preferred method of rozanolixizumab administration	Other endpoints: • Participant's relative preference for: – Subcutaneous infusions performed by an health care provider (HCP) versus self-administration – The manual push method versus the use of a syringe driver for self-administration using the participant's preferred method of administration questions at Visit 19 ([redacted]).
• To evaluate symptom changes in study participants with gMG	• Myasthenia Gravis Activities of Daily Living score change from Baseline during the study.
• To assess the pharmacodynamics of rozanolixizumab	• Total IgG level over time during the Training Period and Self-administration Periods.
• To evaluate the immunogenicity of rozanolixizumab following SC self-administration	• Anti-rozanolixizumab antibodies (status and titer at trough during both Self-administration Periods).
• To assess the study participant's experience with self-administration of SC infusions at home	• [redacted]

Objectives	Endpoints
• To assess the ability of study participants with gMG to successfully self-administer rozanolixizumab at home after training in the self-administration technique using the syringe driver and manual push methods	• Successful self-administration of rozanolixizumab via manual push method or using a syringe driver at each of the 3 home self-administration visits during Self-administration Period 1 or 2, respectively. Successful self-administration via manual push or syringe driver is defined by the participant (i) choosing the correct infusion site, (ii) administering SC, and (iii) delivering the intended dose, as reported by the study participant to the site staff following each of the 3 home self-administrations.
• To assess the safety and tolerability of rozanolixizumab in study participants with gMG	• Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the study.

1.2 Study design

MG0020 is a Phase 3, open-label, randomized, 2-period, 2-sequence crossover study planned to be conducted at multiple sites in Europe, Japan, and North America. In MG0020, the safe and effective self-administration of rozanolixizumab using the syringe driver and manual push administration methods by study participants with gMG will be evaluated using a crossover design over [redacted] (Figure 1–1).

Study participants in Europe and North America are proposed to receive [redacted] fixed doses of rozanolixizumab for [redacted] as described below:

- Body weight ≥35kg to <50kg: dose to be administered [redacted]
- Body weight ≥50kg: dose to be administered [redacted]

Study participants in Japan are proposed to receive [redacted] fixed unit doses of [redacted] rozanolixizumab across body weight tiers for [redacted] as described below:

- Body weight ≥35kg to <50kg: dose to be administered [redacted]
- Body weight ≥50kg to <70kg: dose to be administered [redacted]
- Body weight ≥70kg to <100kg: dose to be administered [redacted]
- Body weight ≥100kg: dose to be administered [redacted]

Rozanolixizumab-naïve study participants and study participants previously exposed to rozanolixizumab will be included in the study.

Approximately 40 participants will be screened to achieve approximately 30 randomly assigned and evaluable participants for an estimated total of 15 evaluable participants per sequence. See Section 5 for the determination of sample size.

The total duration for each study participant is up to 29 weeks, including a Screening Period of up to 4 weeks, an [redacted] Treatment Period, and an up to 7-week Safety Follow-up Period (ie, End of Study Visit is 8 weeks after the last dose of rozanolixizumab in the Treatment Period, or earlier, if the study participant moves on to a post-trial access program or to commercially available rozanolixizumab during the Safety Follow-up Period).

The [redacted] Treatment Period of MG0020 starts with standardized [redacted] trainings over the course of a [redacted] Training Period when the study participant is trained on both the manual push and the syringe driver administration methods. During the Training Period, the study participant will receive [redacted] doses of rozanolixizumab SC and should practice both methods of administration at the study site. To act as a reference for the preference question (HCP vs self-administration) and to demonstrate subcutaneous infusions of rozanolixizumab, the first administration will be imperatively performed by the HCP. For all remaining training visits, the study participant should perform as many self-administrations as possible (under HCP supervision) depending on their training status. Self-administration under HCP supervision or administration by HCP will be documented in the case report form (CRF). At Visit 8 ([redacted]), after the completion of the Training Period and following the investigator's confirmation of the eligibility to perform self-administration, the study participant will be randomized 1:1 to either the syringe driver or to the manual push administration method. After completing Self-administration Period 1 (at Visit 13 [[redacted]]), the study participant will crossover to the alternative administration method, entering Self-administration Period 2 (Visit 14 [[redacted]]). A final release of the study participant for home self-administration will be based on a successful demonstration of self-administration using the assigned mode of administration (manual push or syringe driver use) at Visit 9 ([redacted] and Visit 15 ([redacted]), respectively. Study participants who cannot be confirmed eligible for self-administration will not perform self-administration and can continue to be treated on-site per protocol based on investigator decision. Additionally, if a study participant becomes no longer eligible for self-administration during the Self-administration Periods, he/she can continue to be treated on-site per protocol based on investigator decision. Adverse events, concomitant medication, vital signs, ECG, suicidality, blood and urine samples for safety laboratory tests, pregnancy tests and IgG will continue to be collected from these study participants until End of Study Visit/Early Withdrawal Visit.

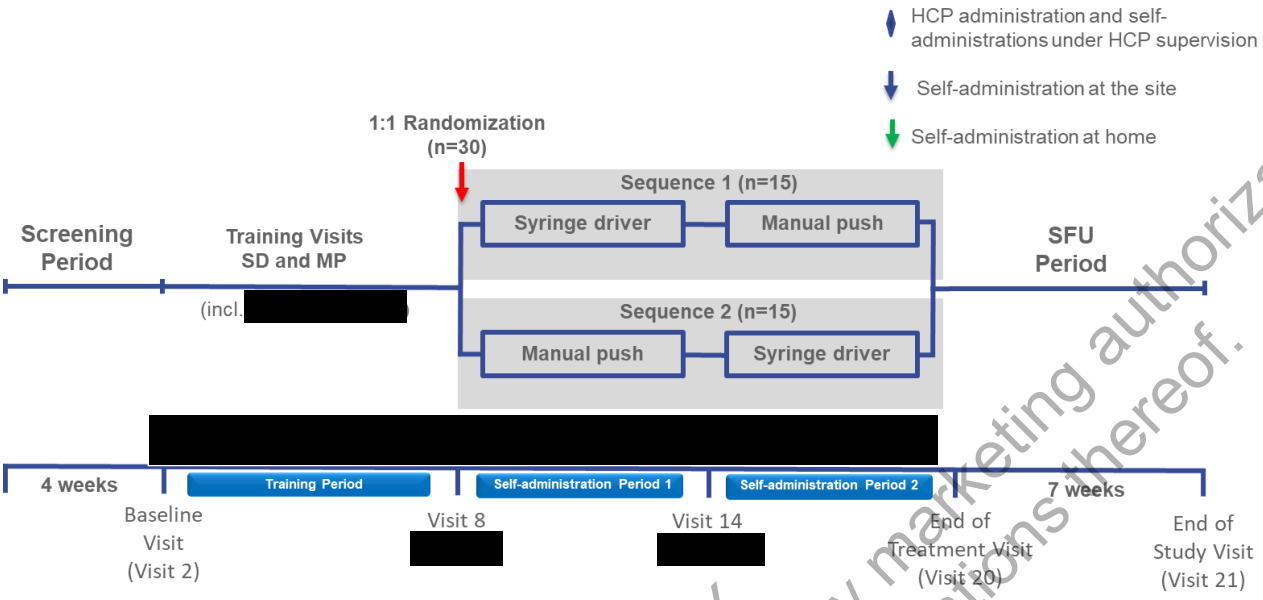
During both Self-administration Period 1 and Self-administration Period 2, self-administration will be performed at the site for 3 visits and at home (ie, unsupervised/not in the presence of an HCP) for 3 consecutive visits.

After the Self-administration Periods, study participants will enter the 7-week Safety Follow-up Period.

Following participation in MG0020, study participants who have completed the study (End of Study Visit performed) will have the option of a post-trial access to rozanolixizumab, if available according to local guidance, or to commercially available rozanolixizumab, at the discretion of the investigator.

The schedule of activities can be found in the protocol. The infusions are planned [redacted] from Visit 2 ([redacted] to Visit 7 ([redacted] for the Training Period, from Visit 8 ([redacted] to Visit 13 ([redacted]) for the Self-administration Period 1 and from Visit 14 [redacted] to Visit 19 ([redacted]) for the Self-administration Period 2.

Figure 1–1: Study Schema



HCP=health care professional; MP=manual push; SD=syringe driver; SFU=safety follow-up

2 STATISTICAL HYPOTHESES

This is an estimation study design with no formal statistical hypothesis testing.

2.1 Multiplicity adjustment

As there is no statistical hypothesis testing in this study, there will be no account for multiplicity.

3 POPULATIONS FOR ANALYSIS

- Enrolled Set (ES): All study participants who have signed the informed consent form.
- Safety Set (SS): All study participants who received at least 1 dose of investigational medicinal product (IMP) (partial or full). Analysis of this set will be according to the administration method the participants actually used and will be used for analyses of safety and demography outcomes as required.
- Randomized Safety Set (RSS): All participants who are included in SS and were randomized. Analysis of this set will be according to the administration method the participants actually used and will be used for analyses of safety, demography, and efficacy/outcomes.
- Full Analysis Set (FAS): All participants who are included in SS, were randomized and completed both Self-administration Periods. Both Self-administration Periods will be considered as complete if self-administration occurred on Visits 13 and 19 in accordance with the randomization scheme.

4 STATISTICAL ANALYSES

4.1 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.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of participants in each category will be presented. The denominator for percentages will be based on the number of participants appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous parameters, descriptive statistics will include number of participants with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum. If not otherwise specified, summary statistics will be displayed by sequence and overall for demographics, and by period and by self-administration method for period-specific assessments.

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

- "n" will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

The Baseline value is defined as the last nonmissing measurement before the first administration (prior to the Training Visits) at Visit 2 ([redacted] if not otherwise specified. Scheduled or unscheduled measurements can be used as the Baseline value.

In case of missing visit information for Myasthenia Gravis Activities of Daily Living (MG-ADL) and Self-Injection Assessment Questionnaire (SIAQ) data, visit windowing will be applied based on the Protocol Schedule of Activities (Section 1.3). Otherwise, visit windows will not be used.

A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) will be generated. They will be ordered by sequence, participant number, period, and timepoints as applicable.

4.1.1 Analysis time points

4.1.1.1 Relative day for listings

Relative day will be calculated depending on the position of the day compared to first and last doses of study drug:

- For days on or after the day of first dose of study drug and prior to or on the day of last study drug dose:

  Relative Day = [(Event Date – Date of First Dose)+1]

  The day of first dose will be Day 1.

- For days prior to the first dose of study drug:

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

The day prior to first dose will be Day -1.

- For days after the last dose of study drug:

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

  The day after the last dose will be Day +1.

Relative day will not be calculated for partial dates.

4.1.1.2 Analysis periods

The following study periods are defined for the classification by study period:

- Screening Phase: Prior to the date of first dose of study drug
- Treatment Phase:
  - Training Period: From the first dose (Visit 2) of study drug to the first dose in Self-administration Period 1 (Visit 8) minus one day
  - Self-administration Period 1: Starts one day after the end of Training Period and ends with the first dose in Self-administration Period 2 (Visit 14) minus one day
  - Self-administration Period 2: Starts one day after the end of Self-administration Period 1 and ends at the end of Visit 20 assessments (EOT date).
- Follow-up Phase: Starts one day after the end of Self-administration Period 2 and ends after the safety follow up assessments of Visit 21.

4.1.2 Definition of baseline values

The Baseline value is defined as the last nonmissing measurement before the first administration of IMP (prior to the Training Visits) at Visit 2 ([redacted] if not otherwise specified.

4.1.3 Mapping of assessments performed at Early Withdrawal Visit

Efficacy and safety assessments at Early Withdrawal (EW) will be assigned to the next scheduled visit (following the last scheduled visit that the study participant completed prior to withdrawal) where each assessment is evaluated as per protocol. This approach means that there is a chance that EW data will be mapped to different visits according to the schedule of assessments. If the mapped visit is the first visit in the next period, the visit will be assigned to the previous period.

4.1.4 Treatment assignment and treatment groups

For the analyses using SS, Rozanolixizumab (RLZ) Total will be displayed.

For some analyses using RSS, the actual sequence of treatment will be reported. Two sequences will be displayed: RLZ syringe driver – RLZ manual push and RLZ manual push – RLZ syringe driver as well as the column RLZ Total. In the case that all [redacted] in each period were performed using the alternate method to the one randomized, the actual treatment sequence will reflect this.

For other analyses using RSS and focusing on period specific assessments, each self-administration period and overall (Self-administration Period 1 and Period 2) will be split into two columns: RLZ syringe driver and RLZ manual push. For the AEs reporting, an RLZ Total

column will be added within the overall column to report the AEs occurring at least once in the self-administration period.

4.1.5 Multicenter studies

Individual center results will not be displayed.

4.1.6 Center pooling strategy

The data from all sites will be pooled for analyses purposes.

4.1.7 Intercurrent event handling

As per protocol, if a study participant becomes no longer eligible for self-administration during the Self-administration Periods, he/she can continue to be treated on-site per protocol based on investigator decision. Adverse events, concomitant medication, vital signs, ECG, suicidality, blood and urine samples for safety laboratory tests, pregnancy tests, and IgG will continue to be collected from these study participants until End of Study Visit/Early Withdrawal Visit.

Stopping self-administration during the Self-administration Periods will be considered as an intercurrent event in the analysis.

For the primary and secondary endpoints focusing on the self-administration, all data collected after stopping the self-administration will not be included in the analysis of the primary and secondary endpoint.

For the safety analysis, all data collected after stopping the self-administration will be included in the analysis (treatment policy strategy). It will be assumed that the planned use of manual push or syringe driver will follow the initial schedule. The following endpoints will also be analysed including the data collected after stopping Self-administration:

- Total IgG level over time during the Training Period and Self-administration Periods.
- Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the study.

4.1.8 Handling of missing or partially missing dates

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

- Classification of AEs as TEAEs;
- Classification of TEAEs into the study periods.
- Classification of medications as prior, or concomitant medications;
- Durations of AEs.

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

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

- If year, month and day are all missing then assign the date of first dose of IMP. If an imputed start date is after the specified end date, then assign January 01 of the year of the end date, or

the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).

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

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

- If only the month and year are specified, then use the last day of the month. If an imputed stop date is after last contact date and last contact date is before the data cut-off date, then assign last contact date as the stop date. If an imputed stop date is after last contact date and last contact date is after the data cutoff date, then assign data cutoff date as the stop date.
- If only the year is specified, then use December 31 of the known year. If an imputed stop date is after last contact date and last contact date is before the data cutoff date, then assign last contact date as the stop date. If an imputed stop date is after last contact date and last contact date is after the data cutoff date, then assign data cut-off date as the stop date.
- If the stop date is completely unknown, then use discharge date or data cut-off date. Discharge date refers to the date of the end of study visit for completed participants or the date of discontinuation for participants that were withdrawn. For any AEs with known start date after the date of discontinuation, the date of last contact will be used as the discharge date. For participants still ongoing in the study at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

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

Each TEAE should be classified into exactly one study period for the classification of TEAEs into study periods except if doubt remains after imputing the dates. In that case, an AE will be considered as TEAE in each study period.

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

Table 4–1: Calculation rules for duration of AEs

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

Note: '--' represents a missing value

4.2 Primary endpoint analysis

4.2.1 Definition of endpoint(s)

The primary outcome variable is the proportion of study participants able to successfully self-administer rozanolixizumab using both syringe driver and the manual push method, respectively, during the Self-administration Periods. Successful self-administration includes a correct SC infusion with the intended dose at the correct infusion site by the participant. Treatment success will be defined as a successful self-administration at the last dose of self-administration using the syringe driver (Visit 13 [redacted] for Sequence 1 and Visit 19 [redacted] for Sequence 2) or via manual push (Visit 19 [redacted] for Sequence 1 and Visit 13 [redacted] for Sequence 2).

4.2.2 Main analytical approach

The number and proportion of participants deemed a treatment success will be tabulated separately by period and overall for each self-administration method for the FAS.

The proportion of success together with its 90% CI will be estimated for each self-administration with syringe driver and manual push overall using the Wilson method (without continuity correction) [2]. The Wilson method was selected rather than the Clopper Pearson exact method due to a larger number of participants able to perform self-administration using both methods than planned in Section 5.

In case at least one of the three questions related to the administration is missing (correct infusion site, subcutaneous, intended dose), the self-administration is considered unsuccessful.

The self-administration data will be listed for the SS including the training information.

4.2.3 Sensitivity analyses

A sensitivity analysis will be performed using the same analytical approach as for the primary endpoint, but reporting the data collected for RSS.

4.2.4 Supplementary analysis

A within-participant assessment of treatment success (Y/N) with self-administration with the syringe driver or manual push will be tabulated through the use of a 2x2 contingency table presenting the number and proportion of participants in each category for the FAS. Successful self-administration includes a correct SC infusion with the intended dose at the correct infusion site. The last administered dose in each of the Self-administration Periods will be considered. The tabulation will be presented by sequence and overall.

4.3 Secondary endpoints analysis

4.3.1 Secondary endpoints

4.3.1.1 Definition of endpoint(s)

The secondary endpoints are:

- Occurrence of TEAEs after syringe driver or manual push self-administration from Visit 2 ([redacted] up to the End of Study Visit (Visit 21 [Week 26]).
- Occurrence of local site reactions up to 24 hours after each administration during the Training Period and Self-administration Periods.
- Occurrence of medication errors associated with adverse reactions during the 2 Self-administration Periods of the study.

A TEAE is defined as an AE starting on or after the date of first administration of rozanolixizumab in the study, up to and including 8 weeks (56 days) after the final dose.

A TEAE will be assigned to the Training period if the start date of the event is on or after the date of the first administration of rozanolixizumab during the Training Period and before the date of first administration of rozanolixizumab in Self-administration Period 1.

A TEAE will be assigned to the Self-administration Period 1 if the start date of the event is on or after the date of the first administration of rozanolixizumab in Self-administration Period 1 and before the date of the first administration of rozanolixizumab in Self-administration Period 2.

A TEAE will be assigned to the Self-administration Period 2 if the start date of the event is on or after the date of the first administration of rozanolixizumab in Self-administration Period 2 and up to the end of Visit 20 assessments (EOT date).

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless evidence exists that does not allow the AE to be treatment-emergent. Handling of missing dates for classification of AEs as TEAEs is described in Section 4.1.8.

The local site reactions up to 24 hours after each administration are defined as AEs reported as local site reactions as per CRF within one day after rozanolixizumab administration.

Medication errors associated with adverse reactions are defined as the AEs whose preferred terms belong to the Standardised MedDRA Queries (SMQ) "Medication errors" and leading to adverse reactions.

4.3.2 Main analytical approach

The number and proportion of participants experiencing TEAEs during the Training Period will be summarized overall for the SS. The number and proportion of participants experiencing TEAEs during the Self-administration Periods will be summarized by period and overall for each self-administration method for the RSS. The number and proportion of participants experiencing TEAEs during the Self-administration Periods whatever the self-administration method will also be reported.

The number and proportion of participants experiencing local site reactions up to 24 hours after IMP administration will be summarized:

- overall for the SS
- for the Training period for the SS
- during the Self-administration Periods by period and overall for each self-administration - method for the RSS
- during the Self-administration Periods whatever the self-administration method.

The number and proportion of participants experiencing medication errors associated with adverse reactions during the Self-administration Periods will be summarized by period and overall for each self-administration method for the RSS. The number and proportion of participants experiencing medication errors associated with adverse reactions during the Self-administration Periods whatever the self-administration method will also be reported.

A by-participant listing will also be produced including the medications errors together with the related adverse reactions for the RSS. As per the guidance on medication related adverse events (Pharmacovigilance Risk Assessment Committee. Good practice guide on recording, coding, reporting and assessment of medication errors (EMA/762563/2014). http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196979.pdf (2015). Accessed 30 Jan 2023.), a medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. An adverse reaction is a response to a medicinal product which is noxious and unintended (Directive 2001/83/EC, Article 1 (11)). An adverse event which is reported as a consequence of a medication error is considered as an adverse reaction.

4.4 Exploratory endpoints analysis

4.4.1 Participant's relative preference

The participants' relative preference for subcutaneous infusions performed by an HCP versus self-administration and the manual push method versus the use of a syringe driver for self-administration will be evaluated at Visit 19 ([redacted]) by sequence and overall for the RSS. Participants' preference will also be listed for the RSS.

4.4.2 MG-ADL

The symptom changes in study participants with gMG will be evaluated. The complete list of MG-ADL items and scores are provided in Table 6–5. The total score will be calculated according to the rules set down in Section 6.11.

The MG-ADL total score and change from Baseline will be summarized at each visit for the RSS by sequence using descriptive statistics.

Worsening in MG-ADL score will be defined by a ≥2 points increase from Baseline at any timepoint during the treatment period. The number and proportion of study participants experiencing a worsening of their MG-ADL symptoms during the study will be summarized overall for the RSS. This table will also include the number, proportion and 90% CI of study participants experiencing MG-ADL worsening, considering the last available measurement in the study before the End of Study Visit (Visit 21). The 90% CI will be estimated using the Wilson method (without continuity correction) [2].

Since MG-ADL is completed predose, if time of collection is missing for Visit 2, this will be considered as the Baseline assessment.

Line plots of mean MG-ADL total score and mean change from baseline over time by sequence will be presented for the RSS. Spaghetti plots of MG-ADL total score and change from baseline over time will be presented for the RSS.

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

4.4.3 Pharmacodynamic

The pharmacodynamics of rozanolixizumab will be assessed considering the total IgG level over time. Total serum IgG concentrations including observed values and percentage change from baseline will be summarized overall for the Training period for the SS and by sequence for the RSS. For the analysis of the IgG data, in case rescue therapies are taken, the data up to (not including) the start date of rescue therapy and the data 8 weeks after the start date of rescue therapy will be utilized for the summary tables, ie the data from (including) start date of rescue therapy, to 8 weeks after start date of rescue therapy will be excluded from summary analysis. In cases where a study participant drops out, no missing value imputation will be performed for the IgG.

Line plots of median IgG concentrations and percentage change from baseline over time by sequence will be presented for the RSS. Spaghetti plots of IgG concentrations and percentage change from baseline over time will also be presented for the RSS.

A line plot presenting mean change from baseline in MG-ADL total score and median percentage change from baseline in IgG concentrations will be produced by sequence for the RSS.

In addition, a plot displaying individual percentage change from baseline in IgG concentrations, change from baseline in MG-ADL total score and duration of infusion will be produced for the RSS.

Total serum IgG concentrations will be listed by participant for the SS.

IgG laboratory assessments are performed predose.

4.4.4 Immunogenicity

The immunogenicity of rozanolixizumab will be assessed following subcutaneous self-administration.

Evaluation of rozanolixizumab immunogenicity will be performed using data from all evaluable study participants in the SS, defined as all study participants who have an evaluable pretreatment (baseline) sample (negative or positive ADA sample status), and at least 1 evaluable post-baseline value. Study participants with an evaluable pretreatment (baseline) sample but without a single evaluable sample taken post-baseline will be included in the reporting of pre-existing ADA but excluded from all other immunogenicity analyses.

ADA Sample Status

- The ADA sample status will be determined for the pre-treatment (Baseline) and post-treatment (post-Baseline) visits where samples are taken for ADA analysis. The classifications below are made under the assumption that the rozanolixizumab concentrations (which are not measured in this study) are equal or below the validated drug tolerance limit of the ADA assay (200µg/mL rozanolixizumab) allowing detection of 100ng/mL ADA
- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**
- Samples that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc, will be defined as **Missing**.

ADA Participant Status

The ADA participant status will be classified on study participant and group level as outlined below (Shankar et al. 2014; Rup et al, 2015). A description of how study participants will be categorized for the immunogenicity assessment is provided in Table 4–2

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

Study participants who are identified as being treatment-induced or treatment-boosted ADA-positive will be grouped as treatment-emergent (TE)-ADA positive participants. Study participants who are identified as being treatment-reduced or treatment-unaffected ADA-positive will be grouped as non-TE-ADA positive participants.

The individual and combined ADA participant categories will be derived and summarized through each scheduled assessment visit unless specified otherwise. Post-baseline time points where no ADA sample was collected, will be ignored for the categorization.

Table 4–2: Terms and Definitions for ADA Status Evaluation in Study Participant

Classification	Classification Label	Definition
Individual participant categories		
1	Pre-ADA negative – treatment induced ADA negative (ADA-NEG)	Study participants who have an ADA negative sample at Baseline and at all sampling points post-Baseline up to the timepoint of interest.
2	Inconclusive	Study participants who have an ADA positive or negative Baseline sample and some post-Baseline samples are missing, while other post-Baseline samples are ADA negative up to the timepoint of interest.
3	Pre-ADA negative – treatment induced ADA positive (TI-POS)	Study participants who have an ADA negative sample at Baseline and have at least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest.
4	Pre-ADA positive – treatment boosted ADA positive (TB-POS)	Study participants who have an ADA positive sample at Baseline and at least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest, with increased titer values compared to Baseline (greater than a predefined fold difference increase from Baseline value which will be defined within the validation of the assay i.e. MSR of the assay).
5	Pre-ADA positive – treatment reduced ADA positive (TR-POS)	Study participants with an ADA positive sample at Baseline, and ADA negative samples at all sampling points post-Baseline up to the timepoint of interest.
6	Pre-ADA positive – treatment unaffected ADA positive (TU-POS)	Study participants with an ADA positive sample at Baseline and an ADA positive sample at any sampling point post-Baseline up to the timepoint of interest, with titer values of the same magnitude as Baseline (less than a predefined fold difference from the Baseline value which will be defined within the validation of the assay, i.e. MSR of the assay[1]).
Combined participant categories		
7	Treatment emergent ADA positive (TE-POS)	Includes study participants who are treatment induced ADA positive (category 3) or treatment boosted ADA positive (category 4).
8	Non-treatment emergent ADA positive (Non-TE-POS)	Includes study participants who are treatment reduced ADA positive (category 5) or treatment unaffected ADA positive (category 6).
Note: if a participant has no baseline ADA, then she/he can't be treated as "Inconclusive".		

Classification	Classification Label	Definition
[1] The fold difference increase from baseline value, i.e. the minimum significant ratio (MSR=1.36) determined during assay validation, will be reported in the relevant tables, listings and figures. It reflects the fold difference in titer level that considered higher than the assay variation in titer determination.		

The following tables will be produced:

- Number and percentage of study participants with ADA (positive, negative, missing sample) status at the time of each visit will be summarized by self-administration sequence and overall for the RSS. Denominator is the number of study participants having a non-missing result at that visit.
- Number and percentage of study participants in each of the individual and combined ADA participant status categories presented in Table 4–2 will be summarized by self-administration sequence and overall for the RSS.
- Total prevalence of pre-existing ADA, defined as number and percentage of participants having an ADA positive sample status at baseline, with the denominator being the total number of study participants having an evaluable sample result at baseline will be summarized by self-administration sequence and overall for the RSS. Missing samples will not be included in the denominator.

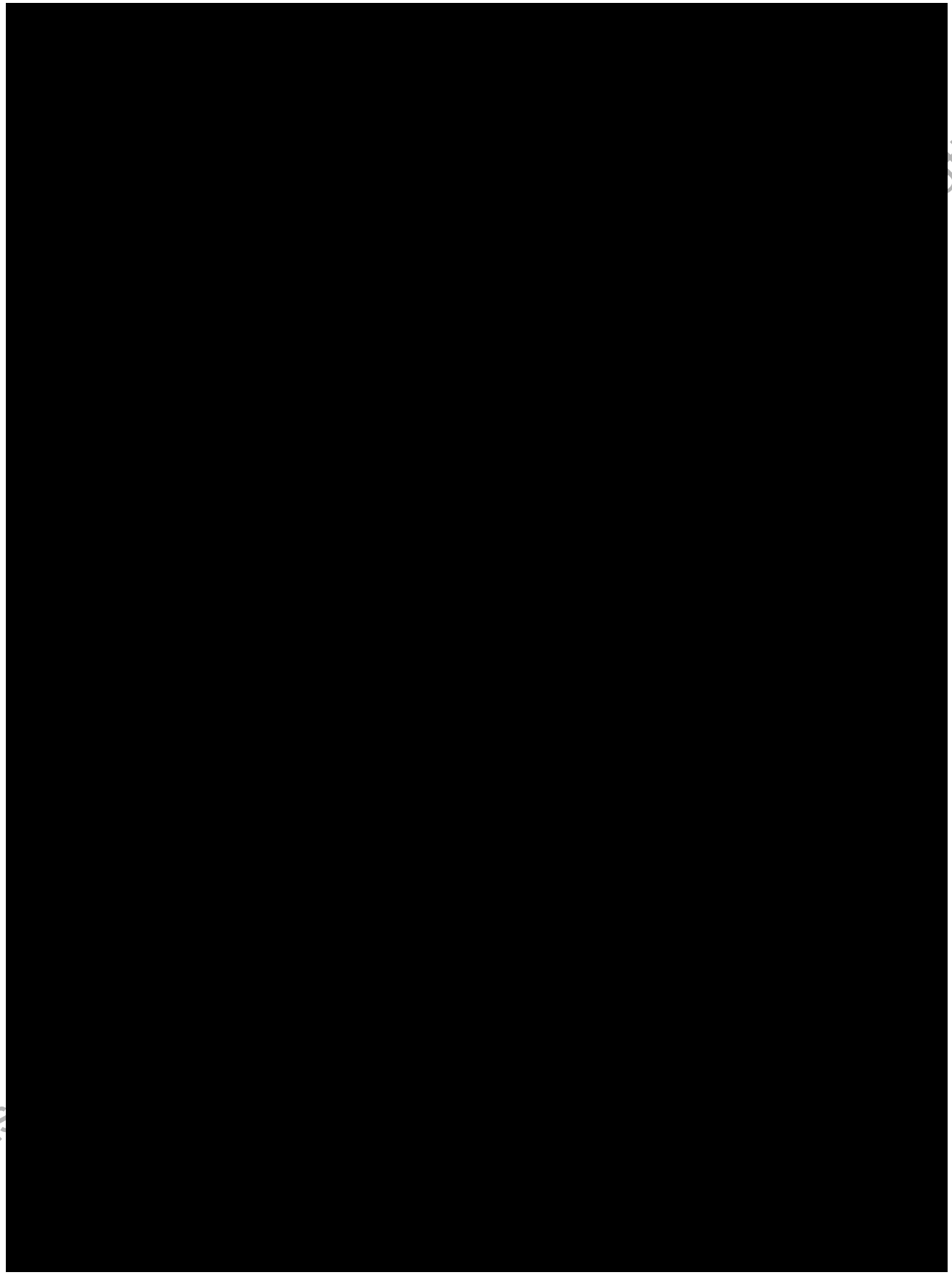
The following figures will be produced and will be based on the RSS:

- Individual time course plots for ADA positive study participants with at least one ADA positive sample, representing ADA titers (on log-scale), and the percentage CFB for total IgG. The sub-title of the graph will include the study participant number, bodyweight category, and individual ADA participant category (3, 4, 5, 6). The dosing will be represented in the x-axis with bars/arrows at the time of dose.

A by-participant listing by period, self-administration method and timepoint, of ADA sample status and titer will be produced.

4.4.5 SIAQ

[redacted]



[redacted]

4.4.6 Self-administration at home

The ability of study participants with gMG to successfully self-administer rozanolixizumab at home after training in the self-administration technique using the syringe driver and manual push methods will be assessed after each administration at home (Visits 10, 11, 12 [redacted] for Self-administration Period 1 and Visits 16, 17, 18 [redacted] for Self-administration Period 2). Successful self-administration includes a correct SC infusion with the intended dose at the correct infusion site by the participant and will be assessed by the site via a mandatory direct contact with the study participant via telephone or video call as soon as possible after each home self-administration.

The number and proportion of participants deemed a treatment success at each of the 3 home self-administration visits will be tabulated by period and overall for each self-administration method for the RSS.

The missing data will not be imputed.

The self-administration data will be listed for the SS.

4.4.7 TEAEs leading to permanent withdrawal

The safety and tolerability of rozanolixizumab in study participants with gMG will be assessed considering the occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the study in the SS.

The occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab will be summarized during the Self-administration Periods by the number and proportion of participants separately by period and overall for each self-administration method. This will be included in the AEs overview table. TEAEs leading to permanent withdrawal of rozanolixizumab will also be summarized for SS and RSS by System Organ Class (SOC) , High Level Term (HLT) and Preferred Term (PT).

Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the Training Period will also be summarized overall.

4.5 Other safety analysis

4.5.1 Extent of exposure

Study medication duration (days) will be summarized overall for the SS for Training Period and overall. For the RSS, study medication duration will be summarized also by Treatment Periods and overall. It will be calculated as:

- Date of last study medication infusion - Date of first study medication dosing + 1

The study medication duration will also be described by category: ≥1 day, ≥ 36 days, ≥ 78 days, and ≥ 120 days.

The number of administrations done by an HCP will be summarized overall from the date of first infusion to the last infusion.

Study medication duration (days) will also be reported overall for each period separately (Training period/Self-administration Period 1/ Self-administration Period 2). It will be calculated as:

- Date of last study medication infusion within the period - Date of first study medication dosing within the period + 1

The duration of infusion (in minutes) using self-administration treatment will be summarized for the RSS by method and timepoint. It will be derived as:

Duration of infusion (minutes) = Infusion stop time – Infusion start time.

All study medication administration details will be listed.

4.5.2 Adverse events

All AEs and SAEs will be collected from the signing of the informed consent form until the End of Study Visit (Visit 21) and will be coded (Section 6.2). TEAE definition is available in Section 4.3.1.1.

The following summaries will be provided overall for the SS and by period and overall for each self-administration method and overall for the RSS. Adverse events will be presented by SOC, HLT and PT:

- Incidence of AEs overview including any TEAEs, serious TEAEs, participant study discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, AEs leading to death, TEAEs leading to death. AEs leading to death will be reported for all screened participants in the table produced for SS.
- Incidence of TEAEs
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs by Intensity
- Incidence of TEAEs by Maximum Relationship
- Incidence of TEAEs by Relationship
- Incidence of Treatment-Emergent Serious AEs
- Incidence of TEAEs Leading to Study Discontinuation
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants
- Incidence of drug-related TEAEs
- Incidence of severe TEAEs
- Incidence of TEAEs leading to death
- Incidence of treatment emergent adverse event of special interest (AESI)
- Incidence of treatment emergent adverse event of special monitoring (AESM) by type of AESM

Drug-related is based on the Investigator assessment.

AESIs are the cases of potential Hy's Law (*cf.* Section 4.5.3.1.2).

AESMs include severe and/or serious headache, suspected aseptic meningitis and medication error associated with adverse reaction(s).

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

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

Listings of all AEs, all non-serious TEAEs, serious TEAEs, permanent withdrawal of IMP due to TEAEs, study participant discontinuation from study due to AEs, AEs leading to death, AESIs, and AESMs will be presented by sequence (if applicable), period (if applicable) and participant for the SS. AE duration will be included in the listings. Hospitalization data will be listed.

Rozanolixizumab treatment-emergent adverse events of focus (TEAEOF) will also be analysed for the SS. TEAEOF are defined in Section 6.13. The number and percentage of study participants who experience each category of the TEAEOF will be summarized. The following summaries will be presented by SOC, HLT and PT:

- TEAEOF (presented also for RSS)
- Serious TEAEOF
- TEAEOF by maximum intensity (mild, moderate and severe)

A by-subject listing of all TEAEOF by category (as listed above) will be provided. Further details related to the statistical analysis of the above mentioned treatment-emergent AEOFs are provided in Section 6.13.

4.5.3 Additional safety assessments

4.5.3.1 Clinical laboratory evaluations

The following table (Table 4–4) lists safety laboratory assessments that are collected throughout the study. Laboratory assessments are performed predose.

Table 4–4: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell (WBC) Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) count	
	Hemoglobin	
	Hematocrit	

Laboratory Assessments	Parameters			
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose (fasting state preferred)[b]	Calcium	Alkaline phosphatase	C-reactive protein (CRP)
	Lactate dehydrogenase (LDH)	Triglycerides	Low-density lipoprotein (LDL) High-density lipoprotein (HDL)	Total Cholesterol
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, albumin, 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 or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c] • Serology testing (for human immunodeficiency virus, Hepatitis B, and Hepatitis C) All study-required laboratory assessments will be performed by a central laboratory. The results of each test must be entered into the CRF.			

NOTES :

For additional assessments that may be required in case of AESM of severe and/or serious headache or suspected aseptic meningitis, see protocol Table 1-3.

[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 Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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] To be done at Screening only

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

4.5.3.1.1 Laboratory values over time

Hematology, clinical chemistry and quantitative urinalysis (observed value, absolute change from Baseline) will be summarized in standard units using descriptive statistics for the Training

period overall for the SS, for the Self-administration period by period and overall for each self-administration method for the RSS and for the Follow-up period overall for the RSS.

Central laboratory data will be used for the summary tables and figures. Local laboratory data will be listed only.

Measurements below the lower limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ), and measurements above the upper limit of quantification (ALQ) will be imputed to the upper quantification limit for the purpose of quantitative summaries. Handling of repeated measurements is described in Section 6.8.1.

An assessment is markedly abnormal (MA) if it meets the MA criteria outlined in Section 6.9.

Treatment-emergent (TE) is defined as meeting the criteria at any post-Baseline visit after the first infusion of study medication and within 56-days of the last infusion and not meeting the same criteria at Baseline (see SAP section 4.1.2).

A TE assessment will be assigned to the Training period if the start date of the assessment is on or after the date of the first administration of rozanolixizumab during the Training Period and before the first administration of rozanolixizumab in Self-administration Period 1.

A TE assessment will be assigned to the Self-administration Period 1 if the start date of the assessment is on or after the date of the first administration of rozanolixizumab in Self-administration Period 1 and before the first administration of rozanolixizumab in Self-administration Period 2.

A TE assessment will be assigned to the Self-administration Period 2 if the start date of the assessment is on or after the date of the first administration of rozanolixizumab in Self-administration Period 2 and up to the end of Visit 20 assessments (EOT date).

The number and percentage of participants who have TEMA clinical chemistry and hematology assessments at any visit (including unscheduled visit) will be summarized for the Training Period using the SS and by Treatment Period and follow-up for each self-administration method for the RSS.

The laboratory variables that are categorized as normal, high or low based on the reference range supplied by the analytical laboratory will be presented in shift tables from Baseline to any post-Baseline visit (including unscheduled visit) overall for the SS. Values of raw calcium will be used in shift tables, whereas corrected calcium is used for markedly abnormal assessments as outlined in Section 6.9.

Mean values in serum albumin, C-reactive protein, White Blood Cell Count with absolute count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelets will be plotted overall for the SS.

Unscheduled visits assessment will not be included in the summary statistics. 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 laboratory test, including pregnancy testing, will also be listed.

4.5.3.1.2 Potential drug-induced liver injury

The number and percentage of study participants who meet one or more of the following potential drug-induced liver injury (pDILI) criteria will be summarized overall for the SS:

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

In order to meet the above criteria, a study participant must experience the elevation in bilirubin and ALT or AST (and the absence of the ALP elevation) at the same visit. For example, a study participant who experiences a ≥2xULN elevation of bilirubin at one visit and a ≥3xULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. If participant meets part of one criterion but at least one parameter is unknown, then he/she should not be considered for meeting the criterion.

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

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

The number and percentage of study participants who meet one or more of the above LFT elevation criteria will be summarized overall for the SS.

A listing will also be provided for study participants who meet at least one of the above criteria. All results obtained at that visit for the specified parameters will be displayed.
Lifestyle , family medical history, symptoms of hepatitis and hypersensitivity, potential hepato-toxic medications inquiry and hepatic event supplemental medical history data, PK blood sampling will be listed for pDILI.

4.5.3.2 Vital signs

Vital signs will be taken at scheduled visits at the following timepoints:

- On Visit 2 ([redacted]), Visit 3 ([redacted] Visit 4 ([redacted] vital signs will be measured before rozanolixizumab administration, at the end of the infusion, 2 hours after the end of infusion, and 4 hours after the end of the infusion.
- On Visit 5 ([redacted] Visit 6 ([redacted] and Visit 7 ([redacted] vital signs will be measured before rozanolixizumab administration, at the end of the infusion, and 1 hour after the end of infusion.
- For site visits from Visit 8 ([redacted] vital signs will be measured before rozanolixizumab administration, at the end of the infusion, and 15 minutes after the end of infusion.

Observed values and changes from Baseline of vital signs variable (pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature) will be summarized at each timepoint for the Training period overall for the SS, for the Self-administration Period by period and overall for each self-administration method for the RSS and for the Follow-up period overall for the RSS. In case of early withdrawal, the visit will be mapped to the pre-dose timepoint of the next scheduled visit.

Treatment-emergent (TE) is defined as meeting the criteria at any post-Baseline visit after the first infusion of study medication and within 56-days of the last infusion and not meeting the same criteria at Baseline (see SAP section 4.1.2).

The number and percentage of participants who meet each of the TE markedly abnormal (MA) criteria outlined in Section 6.9 at any visit (including unscheduled visit) will be summarized for the Training Period using the SS and by Treatment Period and follow-up for each self-administration method for the RSS.

A TEMA assessment is assigned to the Treatment Period if the start date of the assessment is on or after the date of the first administration of RLZ during the Training Period and before the first administration of RLZ in Self-administration Period 1.

A TEMA assessment is assigned to the Self-administration Period 1 if the start date of the assessment is on or after the date of the first administration of RLZ in Self-administration Period 1 and before the first administration of RLZ in Self-administration Period 2.

A TEMA assessment is assigned to the Self-administration Period 2 if the start date of the assessment is on or after the date of the first administration of RLZ in Self-administration Period 2 and up to the end of Visit 20 assessments (EOT date).

All vital signs measurements and change from Baseline will be listed by participant. The listing will include a flag for values identified as MA. Unscheduled measurements will be presented in the listings.

4.5.3.3 Electrocardiograms

The following ECG variables will be reported:

- Heart rate
- PR interval
- RR interval
- QRS duration

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

Observed values and changes from Baseline will be summarized overall for the SS, at scheduled visit and by ECG variable. The number and percentage of participants with normal, abnormal not clinically significant and abnormal clinically significant ECG results will be provided in a shift table from Baseline to worst post-Baseline interpretation overall for the SS.

Treatment-emergent (TE) is defined as meeting the criteria at any post-Baseline visit after the first infusion of study medication and within 56-days of the last infusion and not meeting the same criteria at Baseline (see SAP section 4.1.2).

The number and percentage of study participants who meet each of the TEMA criteria outlined in Section 6.9 will be summarized overall for the SS at any visit (including unscheduled visit).

A listing of electrocardiogram data will be presented including unscheduled measurements. Abnormal ECG findings will be presented in a separate listing.

4.5.3.4 Other safety endpoint(s)

4.5.3.4.1 Physical examination

Physical and neurological examination abnormal results will be listed for the SS. Any clinically significant abnormal results will be recorded as AEs.

4.5.3.4.2 Suicidal risk monitoring

A by-participant listing of the C-SSRS questionnaire data will be provided for the SS. Any clinically significant abnormal results will be recorded as AEs. Actual attempts will be presented in a separate listing.

4.5.3.4.3 Assessment and management of Tuberculosis (TB)

By-participant listings of TB signs and symptoms questionnaire will be provided for the SS. Any clinically significant abnormal results will be recorded as AEs.

TB questionnaire is available in Section 6.15.

4.5.3.4.4 Hospitalization

Hospitalization information will be listed for the SS. Hospitalization will be systematically related to an SAE.

4.5.3.4.5 History of headache

The history of headache will be listed for study participants for whom data were collected using SS.

4.6 Other analyses

4.6.1 Subgroup analyses

No subgroup analyses are planned.

4.6.2 Specific analyses for PMDA

The following endpoints will be summarized for study participants in Japan only using SS unless otherwise specified:

- Study participant characteristics, including important PDs related to COVID-19 (if applicable):
  - Disposition and discontinuation reasons
  - Discontinuation due to AEs
  - Important PDs
- Demographics and other baseline characteristics:
  - Demographics
  - Baseline characteristics
- Extent of exposure:
  - Duration of study medication
- Evaluation of self-administration of study medication:
  - Study participants with successful self-administration of rozanolixizumab (using FAS)
  - Study participants experiencing any TEAEs and any local site reactions up to 24 hours after administration during the training period
  - Study participants experiencing any TEAEs and any local site reactions up to 24 hours after administration
  - Study participants experiencing any TEAEs, any local site reactions up to 24 hours after administration and any medication errors associated with adverse reactions (using RSS)
  - MG-ADL total score observed results and changes from baseline (using RSS)
  - Pre-SIAQ (infusion version) score obtained predose at baseline (using RSS)
  - Post-SIAQ (infusion version) score (using RSS)
  - Post-SIAQ (infusion version) individual item score (using RSS)
  - Participants' relative preference for subcutaneous infusions (using RSS)
  - Study participants with successful self-administration of rozanolixizumab by visit (using RSS)
  - Study participants with successful self-administration of rozanolixizumab at home (using RSS)
- TEAE summaries:
  - Incidence of TEAE – overview
  - Incidence of TEAEs by SOC, HLT and PT
  - Incidence of TEAEs by maximum intensity

- Incidence of TEAEs by intensity
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by relationship
- Incidence of serious TEAEs by SOC, HLT and PT
- Incidence of TEAEs leading to study discontinuation by SOC, HLT and PT
- Incidence of TEAEs leading to permanent withdrawal of study medication by SOC, HLT and PT
- Proportion of study participants with TEAEs leading to permanent withdrawal of study medication during the training period.

4.7 Interim analyses

No interim analysis is planned.

4.8 Changes to protocol-planned analyses

Demographics will be presented by sequence and overall as per Clinical Study Protocol (CSP) Section 9.2 for the RSS, however will only be presented for overall for the SS.

The Randomized Safety Set (RSS) is defined in the SAP Section 3 as all participants who are included in Safety Set and were randomized but in the CSP it was defined as all randomized study participants who received at least 1 dose of IMP (partial or full).

The Full Analysis Set (FAS) is specified in the SAP Section 3 as all participants who are included in Safety Set, were randomized, and completed both self-administration periods. Both self-administration periods will be considered as complete if self-administration occurred on Visits 13 and 19 in accordance with the randomization scheme. In the CSP it was defined as all randomized study participants who received at least 1 dose of IMP (partial or full) and completed both self-administration periods.

In this SAP, baseline assessment for the MG-ADL score follows the same definition as for other parameters and consists in the last non-missing measurement before the first administration (prior to the Training Visits) at Visit 2 although it was stated differently in the protocol Section 9.3.3. The reason is that there is no wash-out in this study and thus the first visit in Period 2 cannot be considered as baseline. Consequently, MG-ADL will be reported by sequence although it was mentioned by period and self-administration method in the protocol.

Confidence intervals for the occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab will not be estimated as presented in the Protocol. A simpler summary table was deemed appropriate for the team interpretation of the other safety endpoint.

4.9 Data Monitoring Committee (DMC) or other review board

A program Independent Data Monitoring Committee (pIDMC) has been established to provide a periodic review of safety data from studies across the rozanolixizumab program. Data emerging from this study will be included in the pIDMC periodic data reviews to assess the benefit-risk of rozanolixizumab. Analysis performed for the pIDMC is described in separate SAP and shells.

5 SAMPLE SIZE DETERMINATION

This study is not powered with respect to any endpoint and sample size is based on practical considerations. Confidence intervals expected to be observed under assumptions of the true success rate are provided in Table 5–1. It is planned to have approximately 30 participants in total (15 per sequence) who will perform self-administration using both the syringe driver and the manual push administration methods. In the protocol, it is specified that if study participants discontinue before the end of the Self-administration Period 2, replacement participants may be considered at the discretion of the sponsor, depending on how the discontinuation affects the study's ability to collect sufficient data to support the study objectives.

Table 5–1: Expected 90% confidence intervals considering different success rates and 30 study participants completing both Treatment Periods

Success Rate	Expected 90% confidence interval [a]
80%	64.3 to 90.9
90%	76.1 to 97.2
97%	85.1 to 99.8

[a] Exact Clopper Pearson confidence intervals

6 APPENDIX: SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

List of Abbreviations

AChR	Acetylcholine Receptor
ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AESM	Adverse Event of Special Monitoring
ALQ	Upper Limit of Quantification
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Lower Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CO	Self-confidence
CRF	Case Report Form
CSR	Clinical Study Report

List of Abbreviations

C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRM	Data Review Meeting
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
ES	Enrolled set
EW	Early Withdrawal
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FL	Feelings about injection
gMG	Generalized Myasthenia Gravis
HCP	Health Care Provider
HLT	High Level Term
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
LLOQ	Lower Limit of Quantification
LRP-4	Low-density lipoprotein Receptor-related Protein 4
MA	Markedly Abnormal
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MGFA	Myasthenia Gravis Foundation of America
MSR	Minimum Significant Ratio
MuSK	Muscle-specific Kinase
pDILI	Potential Drug-Induced Liver Injury
pIDMC	Program Independent Data Monitoring Committee
PK	Pharmacokinetic
PPS	Per Protocol Set

List of Abbreviations

PT	Preferred Term
RE	Injection site Reactions
RLZ	Rozanolixizumab
RSS	Randomized Safety set
SA	Satisfaction with self-injection
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SIAQ	Self-Injection Assessment Questionnaire
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SS	Safety Set
TB	Tuberculosis
TE	Treatment Emergent
TEAE	Treatment-Emergent Adverse Event
TEAEOF	Treatment-Emergent Adverse Events Of Focus
TEMA	Treatment-Emergent Markedly Abnormal
TFL	Table Figure Listing
ULN	Upper Limit of Normal

6.2 Appendix 2: Coding dictionaries

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

Medications will be coded according to B3 version Sep 2020 or later of the World Health Organization Drug Dictionary (WHODD).

6.3 Appendix 3: Participant disposition

The following outputs will be created:

- **Reasons for screen failures** (as collected on the Study Termination Screen Failure CRF page) will be tabulated using the ES for overall.
- **Disposition of study participants screened** will be tabulated using the ES for overall, by site. In this summary, the site number, principal investigator name, first participant in date, last participant out date will be reported together with the overall number of participants in SS, RSS and FAS and the number of participants by sequence for RSS and FAS.

- **Disposition of analysis sets** will be summarized by the randomized treatment groups, RLZ total and analysis sets (SS, RSS and FAS) using the SS. Participants included in the Training period will be displayed.
- **Disposition and discontinuation reasons** will be tabulated using the SS and RSS, and will contain the number and percentage of study participants by treatment group for the RSS, overall for the SS who:
  - Started Study
  - Completed Study (A study participant is considered to have 'Completed Study' if 'Completed Study Participant' has been recorded in CRF form 'Study Termination Enrolled')
  - Discontinued Study with primary reason for discontinuation (primary reason for premature study termination as collected in the Study Termination Enrolled CRF)
- **Discontinuation due to AEs** will be presented using SS to display the total number of study participants who discontinued the study due to AEs overall. The categories: AE serious fatal, AE non-fatal and other (AE non-serious fatal) will be detailed.
- **Impact of COVID-19** will be presented using SS to display the number and percentage of participants in each impact category overall and by visit.

Listings of study participant disposition including participant analysis sets, re-screened participants, visit dates, self-administration training visits, study discontinuation, impact of COVID-19 (if applicable) and study participants who did not meet study eligibility and self-administration eligibility criteria will be provided.

6.4 Appendix 4: Baseline characteristics and demographics

The following baseline variables will be summarized overall for the SS, and by sequence and overall for the RSS. Additional subgroup summary will be presented by, during, and post- the COVID-19 pandemic based on the enrolled date relative to the pandemic cut-off end date 05-May-2023, if applicable.

- Baseline MG-ADL (*cf.* Section 6.11)
- Baseline MGFA classification
- Myasthenic crisis in the past
- Age at MG diagnosis

  Notes: Age at MG diagnosis will be calculated as Year of Initial MG Diagnosis – Year of birth
- MG duration

  Notes: MG duration will be calculated as (Date of informed consent signed - Date of Initial MG Diagnosis+1)/365.25

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

- Historical AChR antibody status (positive, negative)
- Historical MuSK antibody status (positive, negative)
- Historical LRP-4 antibody status (positive, negative)
- Expected dose level ([redacted])

The following demographics variables will be summarized overall for the SS, and by sequence and overall for the RSS.

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

- Age (years)

  Notes: Missing age will be calculated as year of informed consent signed – year of birth.
- Height (cm)
- Weight (kg)
- Body mass index (BMI, kg/m^2), to be calculated as: BMI = Weight (kg) / (Height (m))^2

Categorical variables (using frequency counts and percentages):

- Age (18 - <65, 65 - < 85, >=85 years)
- Age (≤18,19-<65, ≥65 years)
- BMI (<30 kg/ m2, ≥30 kg/m2)
- Weight (35 - <50, 50-<70, 70-<100, ≥100kg)
- Gender (Male, Female, Undifferentiated, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino) and ethnic subgroup
- Country
- Rozanolixizumab status at study entry (Naïve, Non-Naïve). A participant will be considered as rozanolixizumab naïve if he did not receive it prior to study entry.

A by-participant listings of baseline characteristics and demographics will be provided using the SS. Childbearing potential data will be listed using the ES separately.

6.5 Appendix 5: Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary endpoint, or key safety, for an individual participant. The criteria for identifying important protocol deviations will be defined within the

appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation.

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

6.6 Appendix 6: Medical history

Previous and ongoing medical conditions will be summarized by primary system organ class and preferred term and listed for the SS.

6.7 Appendix 7: Prior / concomitant medications

6.7.1 Categorization

Medications will be classified as follows based on imputed start and stop dates & times as outlined in Section 4.1.8.

- **Prior** medications will include any medications that started before the first administration of IMP.
- **Concomitant** medications will include any medications that have been taken at least once after the first administration of IMP during the Training/Self-administration/Follow-up Periods.

Among concomitant medications, medications will also be classified as part of Self-administration Period 1 or Period 2.

The following rules will be used to assign a concomitant medication to Self-administration Period 1 or Period 2:

- Self-administration Period 1: a medication will be assigned to Self-administration Period 1 if it has been taken at least once between the first administration of IMP in Self-administration Period 1 (Visit 8) and 1 day before the first administration of IMP in Self-administration Period 2 (Visit 14). This includes medications that started prior to Self-administration Period 1 and those that continued into Self-administration Period 2.
- Self-administration Period 2: a medication will be assigned to Self-administration Period 2 if it has been taken at least once between the first administration of IMP in Self-administration Period 2 (Visit 14) and up to the end of Visit 20 assessments (EOT date).

6.7.2 Prior and concomitant medications summaries

The number and percentage of participants taking Prior or Concomitant medications will be summarized overall using the SS by Anatomical Therapeutic Chemical (ATC) class, presenting as Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), Preferred Term (PT).

Additionally, rescue medications are those that are mentioned in Protocol section 6.5.4 and identified if rescue medication is ticked as yes on the CRF Concomitant Medication page. The start date of rescue therapy should be on or after Baseline. All rescue therapies and procedures will be summarized using the SS.

The number and percentage of participants taking Concomitant medications will also be summarized using the RSS by Anatomical Therapeutic Chemical (ATC) class, presenting as

Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), Preferred Term (PT) by period and overall for each self-administration method.

Medications classified as Prior or Concomitant will be listed using the SS. The rescue therapy flag will be included. A by-participant listing of concomitant procedures will also be listed using the SS. Originally reported dates will be used for listings.

6.8 Appendix 8: Data derivation rules

6.8.1 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, unless otherwise specified:

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

6.9 Appendix 9: Markedly abnormal criteria for Rozanolixizumab program

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

Table 6–1: Hematology

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

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

Table 6–2: Chemistry

Parameter	Unit (conventional)	Unit (standard)	Marked Abnormality Criteria
AST (SGOT)	U/L	U/L	>5.0 x ULN
ALT (SGPT)	U/L	U/L	>5.0 x ULN
ALP (Alkaline Phosphatase)	U/L	U/L	>5.0 x ULN
GGT (Gamma Glutamyl Transferase)	U/L	U/L	>5.0 x ULN
Bilirubin (Total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal; >3.0 x Baseline value if Baseline is abnormal
Albumin	g/dL	g/L	<2 g/dL; <20 g/L
Creatinine	mg/dL	umol/L	>3.0 x ULN or >3.0 x baseline
Estimate glomerular filtrate rate (eGFR)[1]	mL/min/1.73 m^2	mL/min/1.73 m^2	eGFR <29 mL/min/1.73 m^2
C reactive protein (CRP)[2]	mg/L	mg/L	>100 mg/L
Calcium[3]	mg/dL	mmol/L	Low: Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L
			High: Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L
Immunoglobulin G[4]	(g/L)	(g/L)	≤1 g/L
Potassium	mmol/L	mmol/L	Low: <3.0 mmol/L
			High: >6.0 mmol/L
Sodium	mmol/L	mmol/L	Low: <125 mmol/L
			High: >155 mmol/L
Glucose[5]	mg/dL	mmol/L	Low: <40 mg/dL; <2.2 mmol/L
			High: > 250 mg/dL; >13.9 mmol/L
Total Cholesterol	mg/dL	mmol/L	>400 mg/dL; >10.34 mmol/L
Triglycerides	mg/dL	mmol/L	>500 mg/dL; >5.7 mmol/L

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

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

[1]The value of 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]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. For derivation from values in standard units (umol/L) the κ values are 61.88 for females and 79.56 for males.

[2]Includes CRP and High Sensitivity (HS) CRP. Reference for marked abnormality criteria: Nehring, S.M.; Goyal, A.; Patel, B.C. (2020). StatPearls Publishing, web link: https://www.ncbi.nlm.nih.gov/books/NBK441843/. A moderate elevation of CRP level per referred reference is used for the marked abnormality criteria for RLZ to ensure a change suggestive of inflammatory process is captured. Standard CRP test should be used. In case high sensitivity CRP (hs-CRP) test have been used in any ongoing studies apply same value (>100mg/L) as marked abnormality criteria.

[3]Corrected Calcium (mmol/L) =0.02 * (40 – Albumin (g/L)) + Calcium (mmol/L).
[4]Immunoglobulin G criterion based on immunodeficiency literature and noted in RLZ study protocols.
[5]Glucose high criterion defined by Grade 3 and higher events according to CTCAE, Version 4.03, June 14, 2010.

Table 6–3: Vital Signs

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

Table 6–4: Electrocardiogram

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

Abbreviations: bpm = beats per minute; ms = milliseconds; QTc(F) = Fridericia corrected QT interval;

Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit after the first infusion of study medication and within 56-days of the last infusion and not meeting the same criteria during Baseline.

6.10 Appendix 10: Compliance

Not applicable. The number of infusions will be recorded as detailed in Section 4.5.1.

6.11 Appendix 11: Myasthenia Gravis-Activities of Daily Living

The MG-ADL score comprises 8 items, each with a score of 0 to 3. The total score is obtained by summing the responses to each individual item. Thus, the score ranges from 0 to 24 with a higher score indicating more disability. The MG-ADL testing form is provided in Table 6–5.

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

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

Table 6–5: MG-Activities of Daily Living

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

6.12 Appendix 12: Impact of the coronavirus disease 2019 (COVID-19) on study data

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, impact categories and relationship to COVID-19;
- Additional fields were added in protocol deviation specification documents to record protocol deviations relationship to COVID-19.

6.13 Appendix 13: AEs of focus for Rozanolixizumab program

The AEOF selection criteria is specified in the Rozimab Safety AEs of Focus document developed by UCB. The purpose of this document is to detail the approach to identifying TEAEs

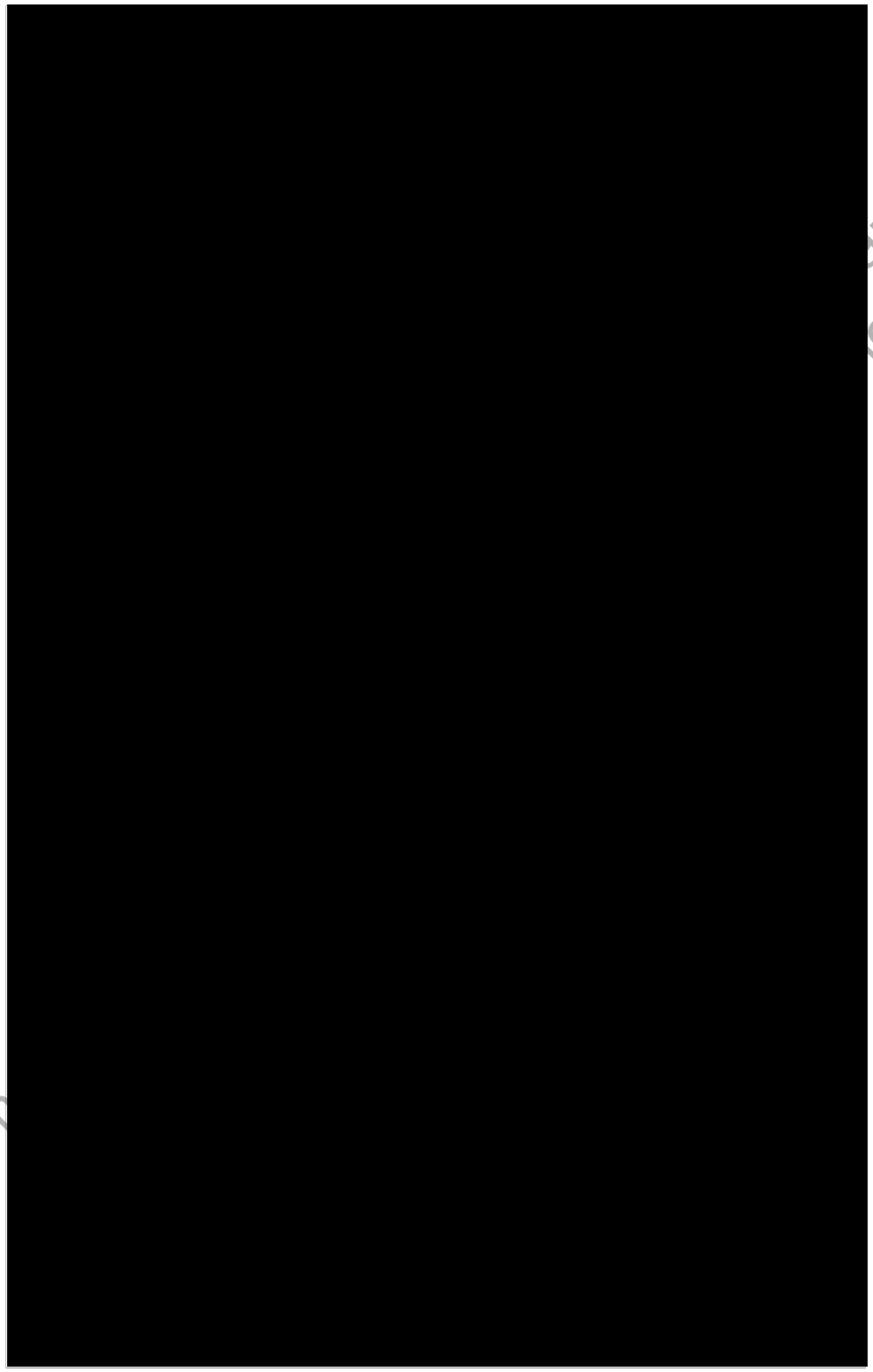
meeting criteria for AEOF for the Rozanolixizumab (also called RLZ) program.

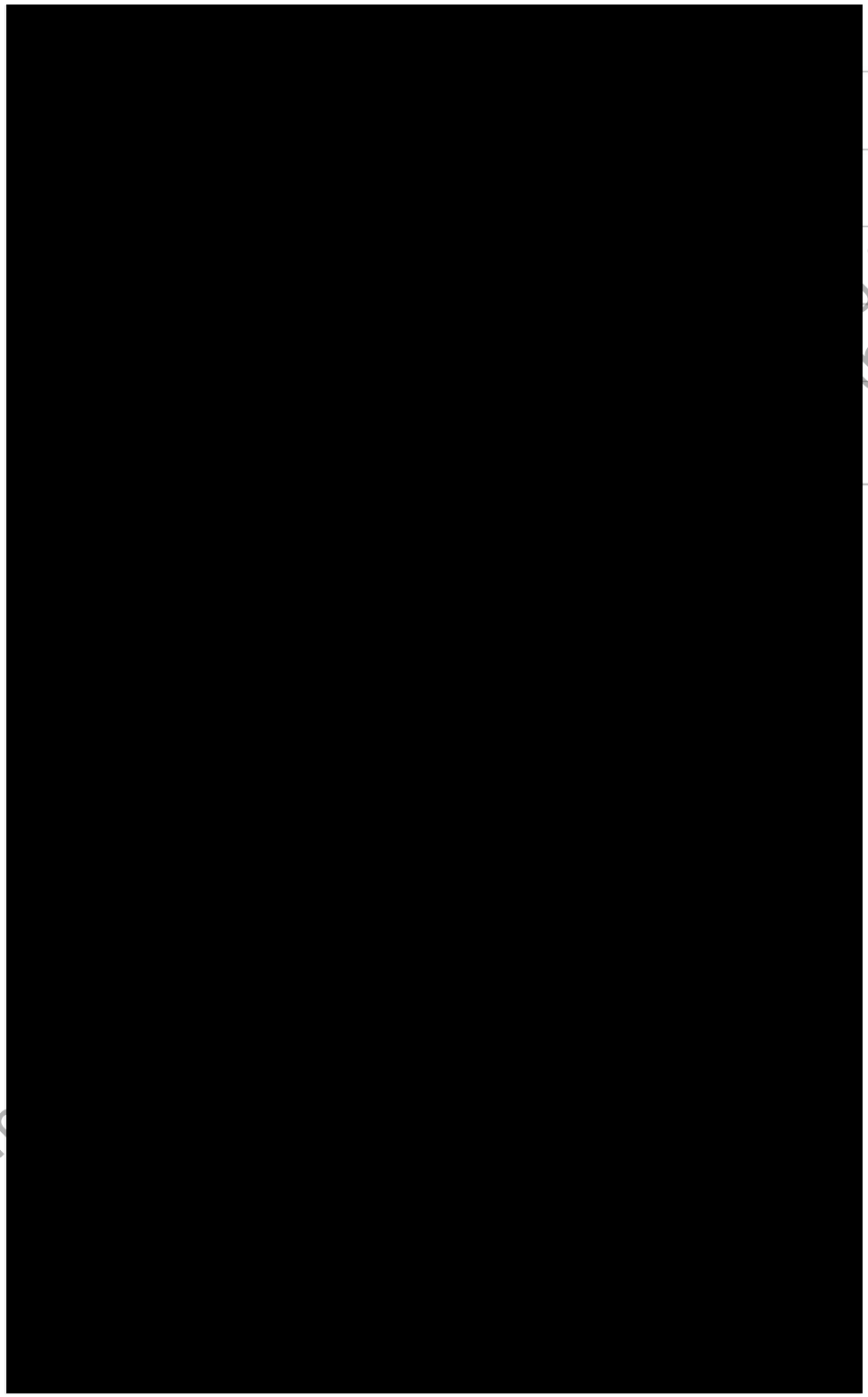
Following Events are AEOFs for Rozimab for MG studies:

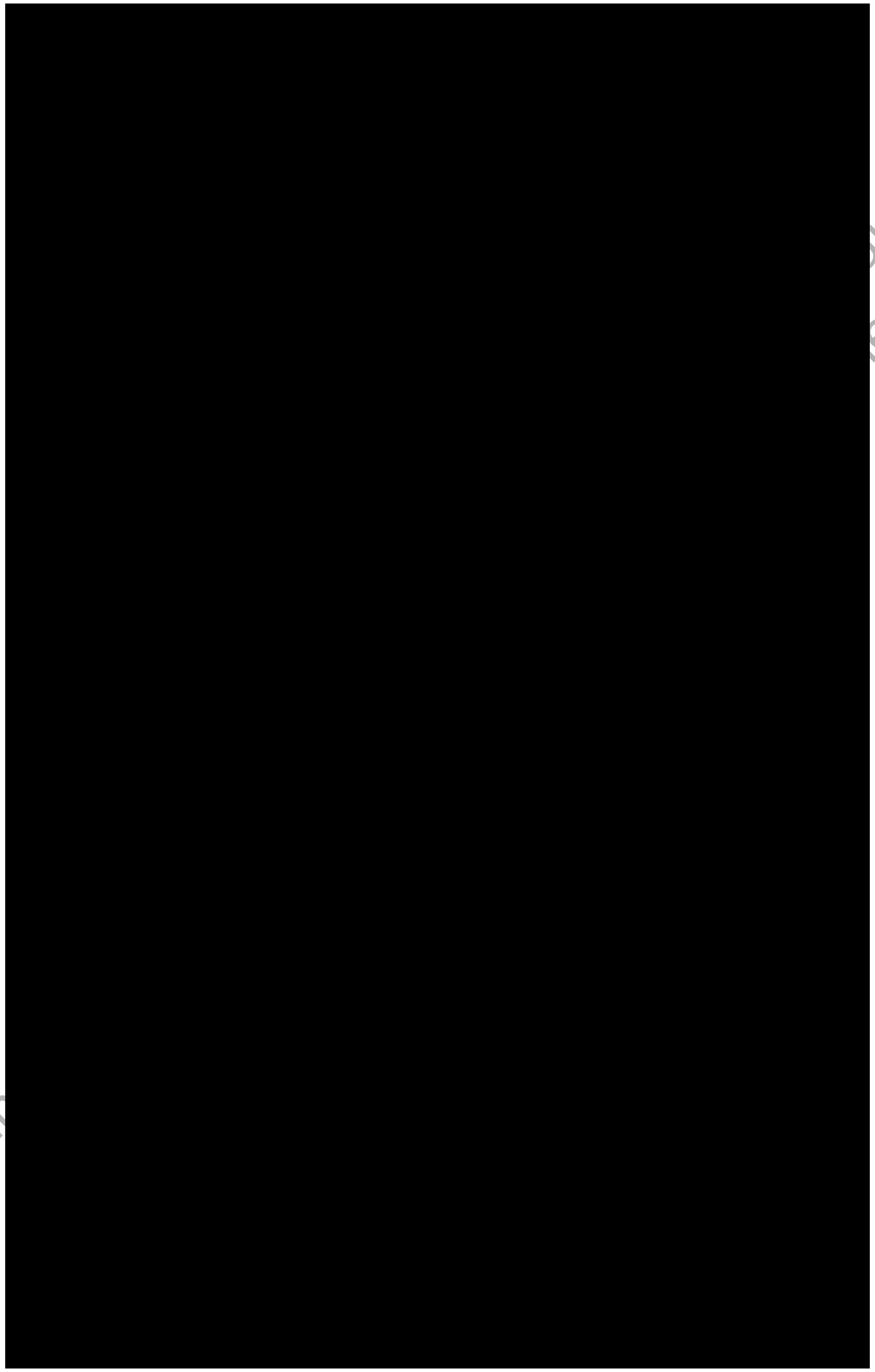
No	Event (also included in Title of TFL output)	Selection criteria
1	Headache (Note: also included in AESM if severe and/or serious)	TEAE with HLGT='Headaches'
2	Possible aseptic meningitis (Note: also included in AESM)	SMQ=' Noninfectious meningitis' narrow search
3	Gastrointestinal disturbances	TEAE with HLT='Gastrointestinal and abdominal pains (excl oral and throat)' or -HLT='Nausea and vomiting symptoms' or HLT='Diarrhoea (excl infective)' or HLT='Gastritis (excl infective)' or PT = 'Abdominal discomfort'
4	Hypersensitivity reactions	SMQ='Hypersensitivity' narrow search
5	Anaphylactic reactions	SMQ='Anaphylactic reaction' and TEAEs that either emerged on the **same day** as when a study medication injection reaction was received, or that emerged **one day after** a study medication injection was received, and which fulfill any of the following 3 criteria should be included in the summary table: 1. If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. 2. If a subject reports any TEAE which codes to a PT included in Category B **AND** reports any TEAE which codes to a PT included in Category C, **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions. 3. If a subject reports any TEAE which codes to a PT included in Category D **AND** reports (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.
6	Injection site reactions	TEAE with HLT='Injection site reactions' or HLT='Infusion site reactions' or HLT='Administration site reactions NEC'

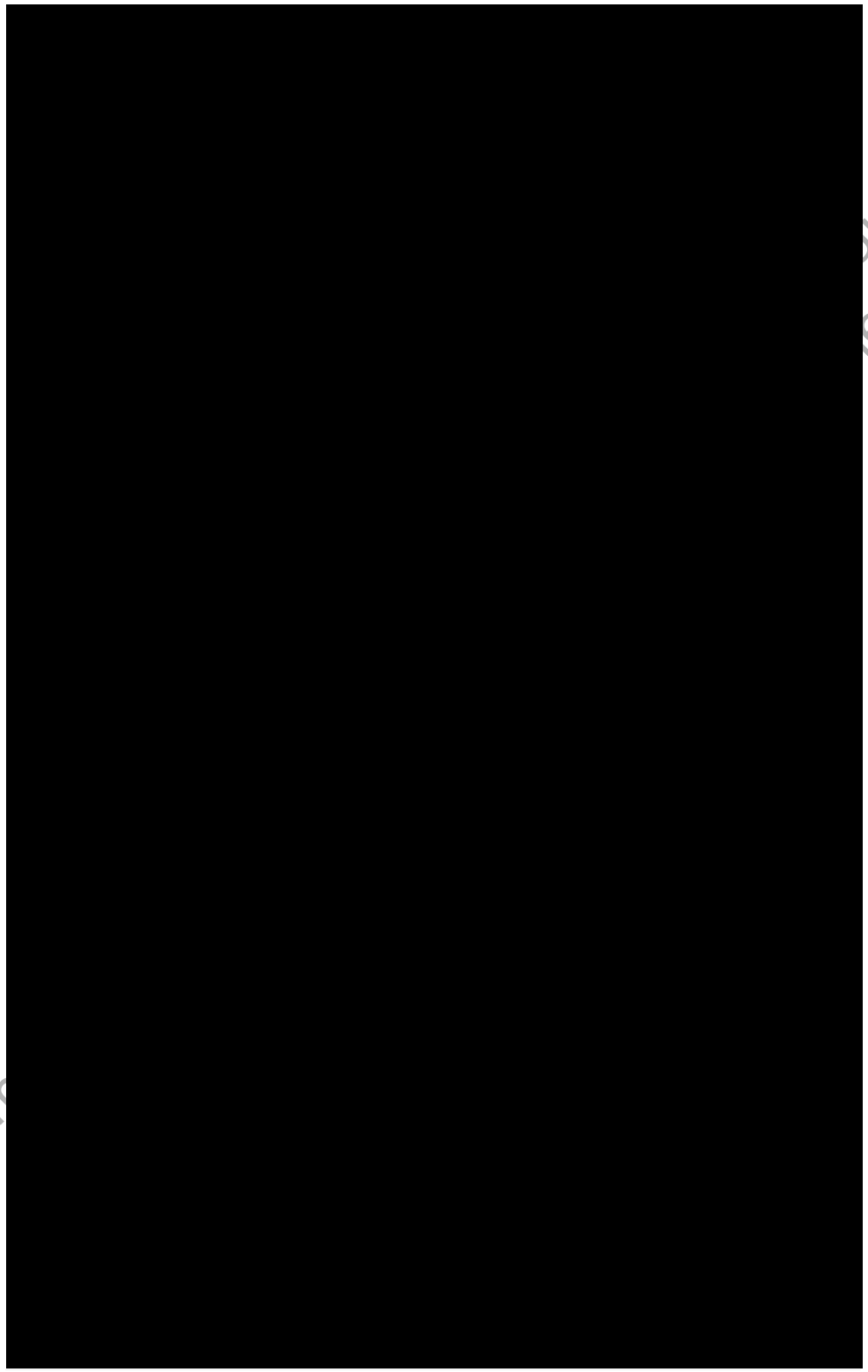
No	Event (also included in Title of TFL output)	Selection criteria
7	Infections	TEAE with SOC =”Infections and infestations” Note: This was added as a reminder for safety that infections are considered as AE of focus and require assessment. No programming of this topic is required as TEAEs can be found in general AE Tables.
8	Opportunistic infections	TEAEs in MedDRA SMQ = ‘Opportunistic infections’ narrow search
9	Reductions in albumin and plasma proteins	TEAEs with PT=’Blood albumin decreased’ or PT=’Protein albumin ratio’ or LLT=’Plasma protein abnormal’ or LLT=’Proteins serum plasma low’
10	Effects on the kidney	TEAEs in SMQ= ‘Acute renal failure’ narrow search
11	Drug related hepatic disorders	TEAEs in SMQ=’Drug related hepatic disorders - comprehensive search’ narrow and broad search
12	Effect on lipids	TEAEs with PT= ‘Blood cholesterol increased’ or PT= ‘Low density lipoprotein increased’ or PT= ‘Blood triglycerides increased’ or PT= ‘Hypercholesterolaemia’ or PT= ‘Hypertriglyceridaemia’ or PT= ‘Hyperlipidaemia’ or PT= ‘Dyslipidaemia’ or PT= ‘Lipids increased’

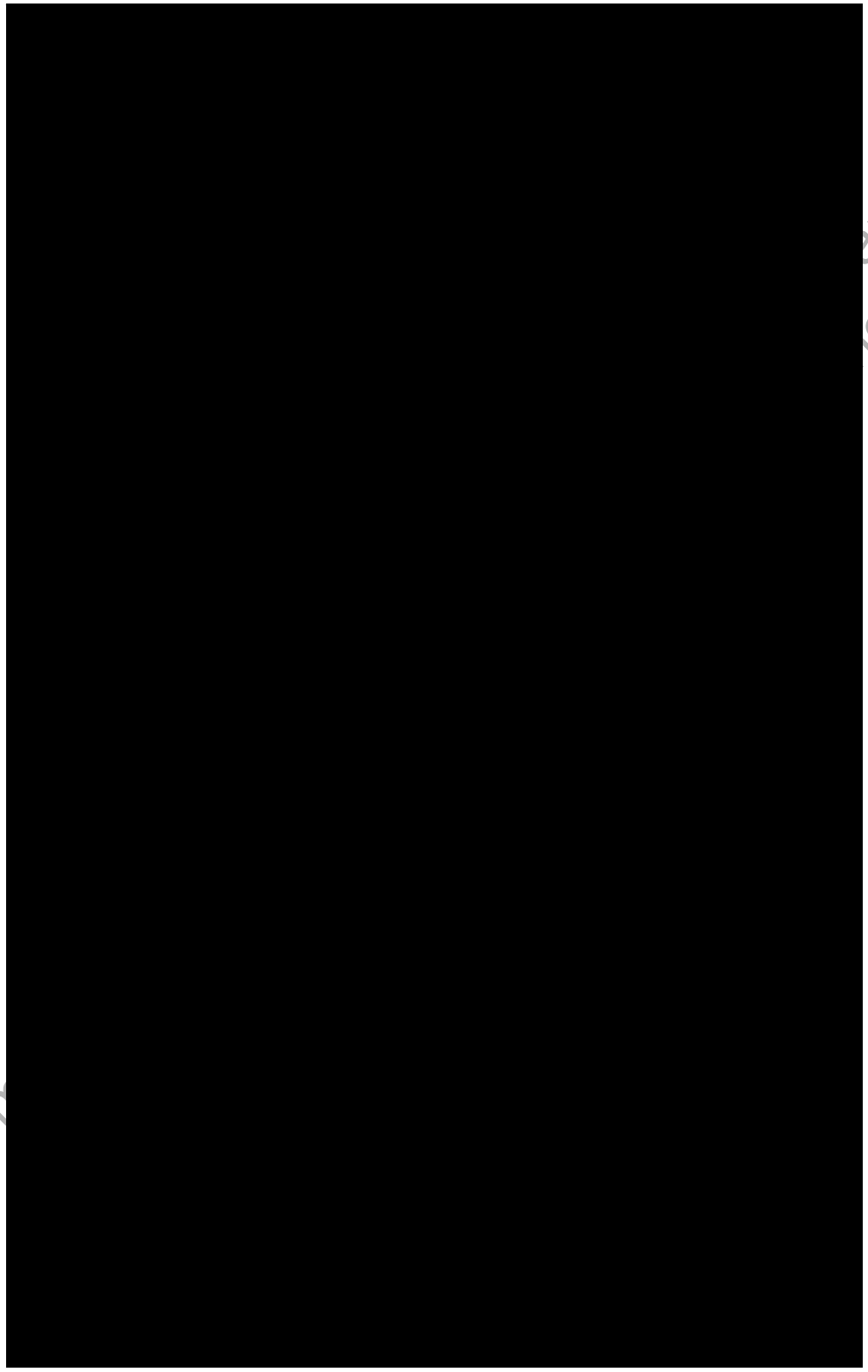
6.14 Appendix 14: Self-Injection Assessment Questionnaire

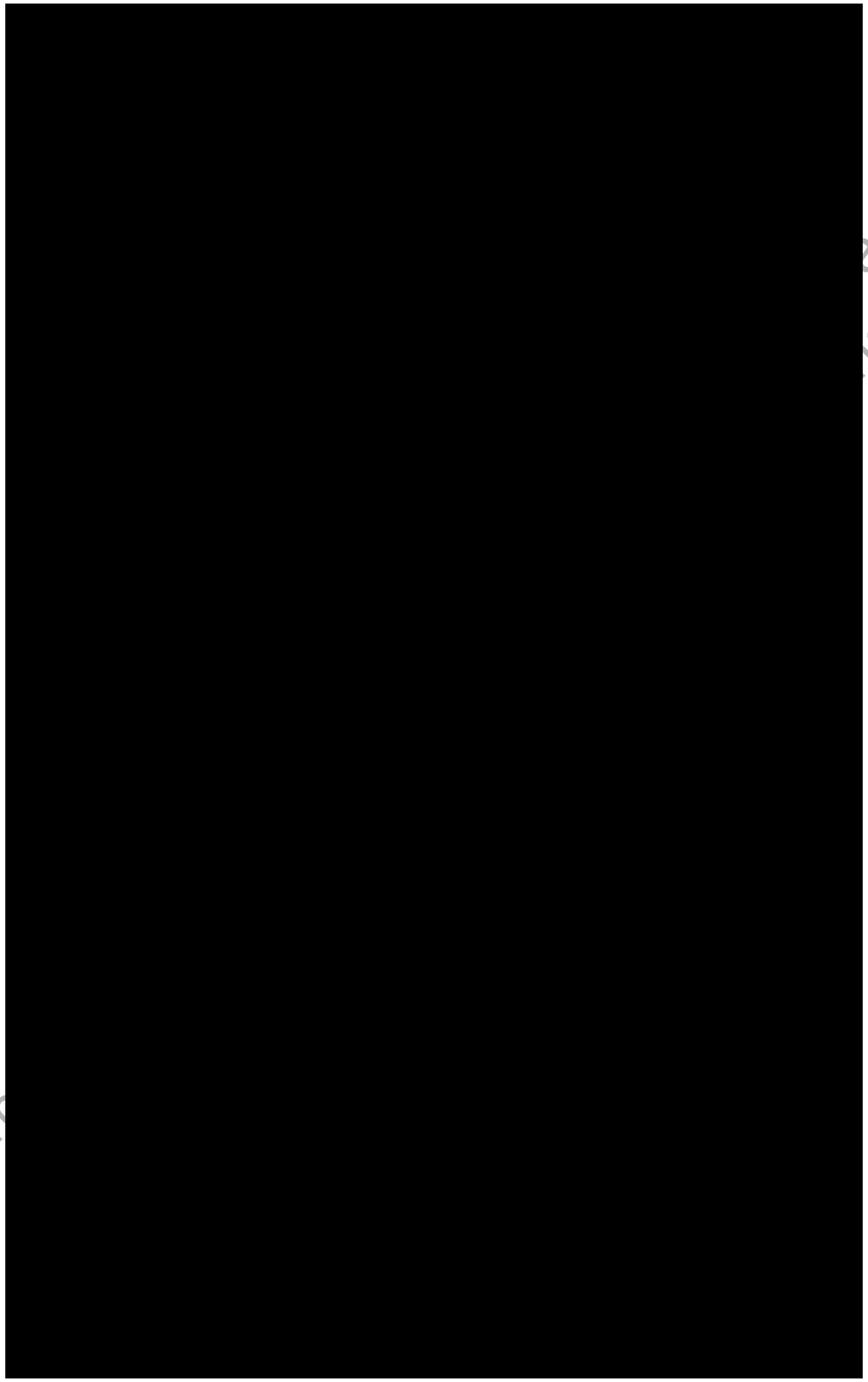


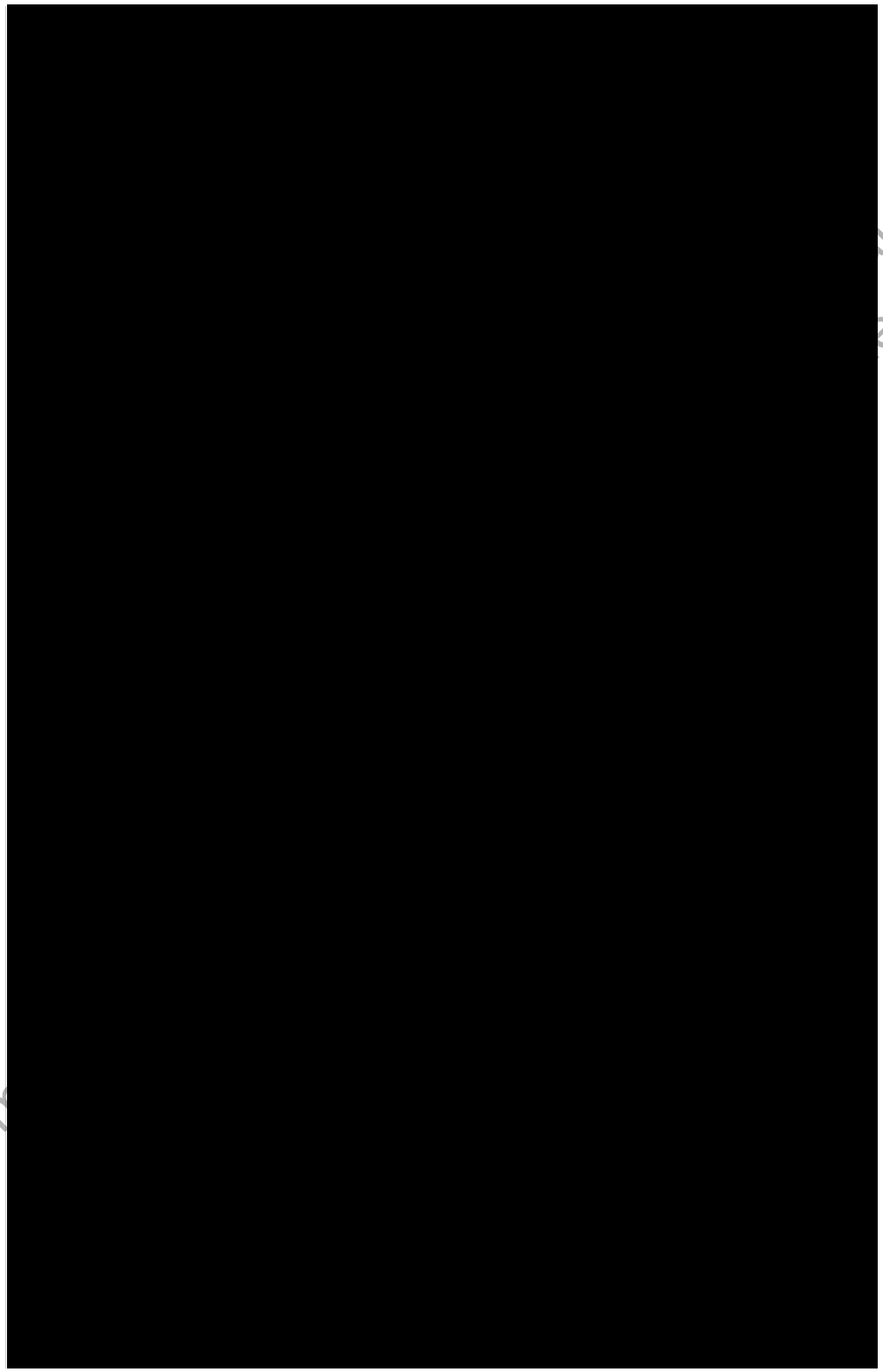




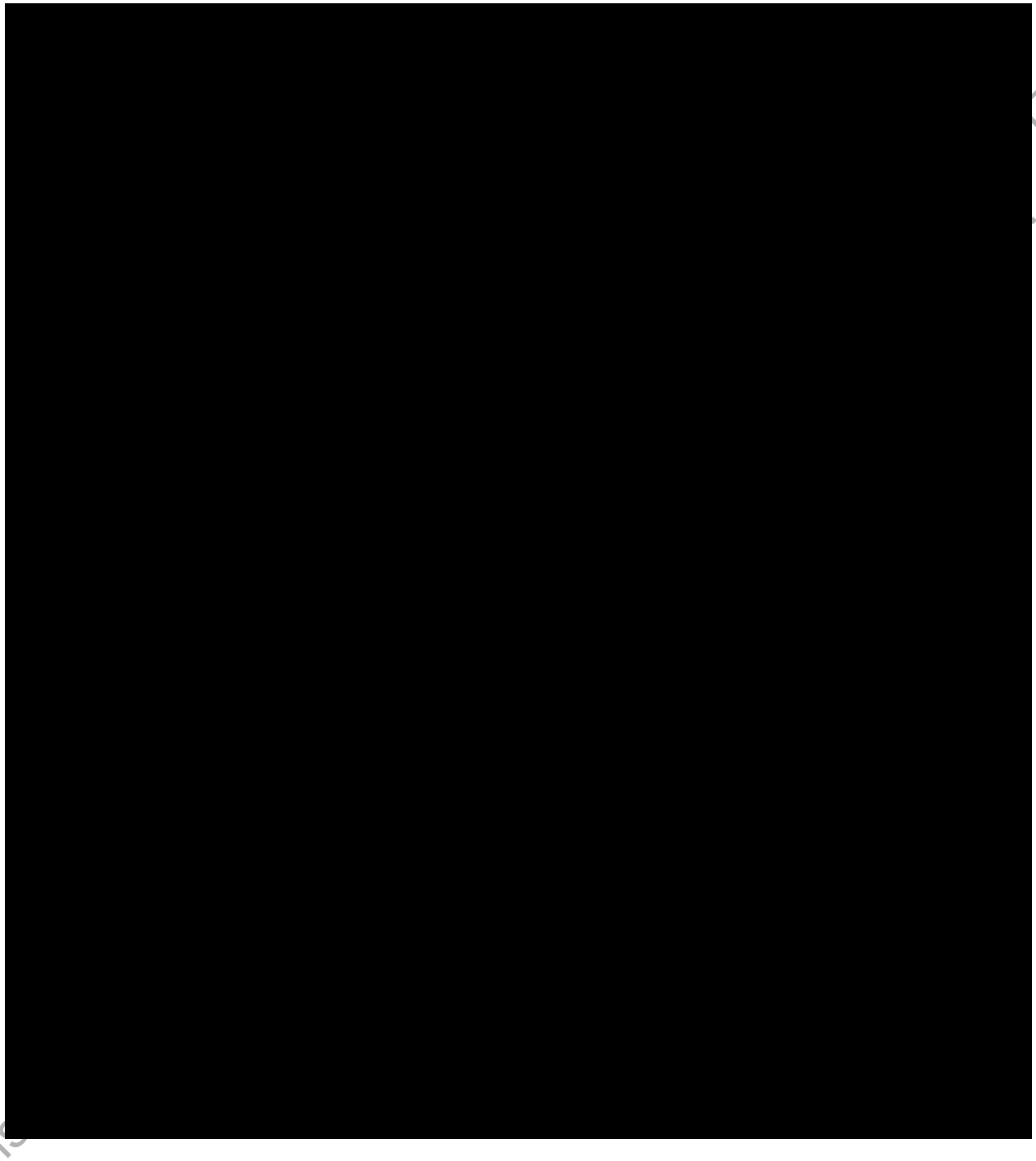








6.15 Appendix 15: Tuberculosis Questionnaire



7 REFERENCES

[1] SIAQ©v2 user manual Feb 2015

[2] Brown, Lawrence D.; Cai, T. Tony; DasGupta, Anirban. Interval Estimation for a Binomial Proportion. Statist. Sci. 16 (2001), no. 2, 101–133. doi:10.1214/ss/1009213286.

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