STATISTICAL ANALYSIS PLAN

AMENDMENT 1

Study: AIE001

Product: Rozanolixizumab

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 2 STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ROZANOLIXIZUMAB IN ADULT STUDY PARTICIPANTS WITH LEUCINE-RICH GLIOMA INACTIVATED 1 AUTOIMMUNE ENCEPHALITIS

SHORT TITLE

A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF ROZANOLIXIZUMAB IN PARTICIPANTS WITH LEUCINE-RICH GLIOMA INACTIVATED 1 AUTOIMMUNE ENCEPHALITIS

Sponsor Name: UCB Biopharma SRL

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

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VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
1	19 Oct 2021	Not Applicable	Original version
Amendment 1	18 Mar 2024	See Section 6.8.1 for details	To implement changes in Protocol Amendments

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AED	Antiepileptic Drug
AESI	Adverse Event of Special Interest
AESM	Adverse Event of Special Monitoring
AIE	Autoimmune Encephalitis
ALP	Alkaline Phosphatase
ALQ	Above the Limit of Quantification
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AR(1)	First Order Autoregressive
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BP	Bodily Pain
BUN	Blood Urea Nitrogen
CGI-S	Clinical Global Impressions of Severity
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 2019
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EDisc	Early Discontinuation
eGFR	Estimated Glomerular Filtration Rate

EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	Euro-Quality of Life 5-Dimensions, 5 Levels
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FWER	Family-Wise Type-I Error Rate
GEE	Generalized Estimating Equations
geoCV	Geometric Coefficient of Variation
geoMean	Geometric Mean
GGT	Gamma Glutamyl transferase
GH	General Health
HCRU	Healthcare Resource Utilization
HD	Health Domain
HLGT	High Level Group Term
HLT	High Level Term
ICE	Intercurrent Event
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IgG	Immunoglobulin G
IGRA	Interferon Gamma Release Assay
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
ITT	Intent-to-treat
IVMP	Intravenous Methylprednisolone
IWRS	Interactive Web Response System
J2R	Jump to Reference
LDH	Lactate Dehydrogenase
LGI1	Leucine-Rich Glioma Inactivated 1
LLOQ	Lower Limit of Quantification
LLT	Lower Level Term
LSMD	Least Squares Mean Difference

MA	Markedly Abnormal
MAR	Missing at Random
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MSE	Minimum Symptom Expression
MSR	Minimum Significant Ratio
n	Number of Participants
NAb	Neutralizing Antibody
OR	Odds Ratio
PCS	Physical Component Summary
PD	Pharmacodynamic
pDILI	Potential Drug Induced Liver Injury
PF	Physical Functioning
PiDMC	Program independent Data Monitoring Committee
PK	Pharmacokinetic
PLS	Population-Level Summary
PT	Preferred Term
PTT	Partial Thromboplastin Time
RBANS	Repeatable Battery for The Assessment of Neuropsychological Status
RBC	Red Blood Cell Count
RE	Role Emotional
RLZ	Rozanolixizumab
RNA	Ribonucleic Acid
RP	Role Physical
RS	Randomized Set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation

SDR	Safety Data Reviews
SF	Social Functioning
SF-36	36-Item Short Form Survey
SFU	Safety-Follow Up
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SS	Safety Set
TB	Tuberculosis
TD	Target Difference
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
TTSFM	Time to Seizure Freedom Maintenance
VAS	Visual Analogue Scale
VT	Vitality
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the statistical analyses of study AIE001, including Program independent Data Monitoring Committee (PiDMC) and final analyses. It also defines the summary tables, figures, and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

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

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- Protocol Amendment 6: 18 July 2023 and all previous protocol versions.

. Changes to the analysis from the protocol are documented in Section 6.7. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

Note that although protocol amendment was approved in both the USA and Canada no participants were randomized to the study under this amendment.

1.1 Objectives and Endpoints

The study objectives and endpoints attributes are listed in Table 1–1 below.

Table 1–1: Objective and Endpoints

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of rozanolixizumab as measured by seizure freedom	• Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
Secondary	
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function	• Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score at the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab on study participants' overall disability	• Proportion of participants with a favorable outcome in the Modified Rankin Scale (mRS) during the Treatment Period, where favorable outcome is defined as no worsening for participants with a Baseline mRS score of ≤1 or improvement of ≥1 point for participants with a Baseline mRS score of ≥2

Objectives	Endpoints
• To assess the efficacy of rozanolixizumab as measured by use of rescue medication	• Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period
• To assess the efficacy of rozanolixizumab as measured by the onset of seizure freedom	• Time to first occurrence of seizure freedom (TTFSF) defined by the number of days after randomization to the first day of the first 28 consecutive days without seizures during the Treatment Period
• To assess the safety and tolerability of rozanolixizumab	• Incidence of treatment-emergent adverse events (TEAEs) during the study
Exploratory	
• To assess the time of onset of efficacy of rozanolixizumab for the subgroup of study participants who achieve the primary endpoint as measured by the onset of seizure freedom	• Time to achieving seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by seizure control	• 'Good' or 'Moderate' seizure control maintained over a period of 4 consecutive weeks until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function (domains of RBANS)	• Change from Baseline in the domain scores of RBANS (immediate memory; visuospatial/constructional; delayed memory; language; and attention) during the Treatment Period
• To assess the efficacy of rozanolixizumab using an integrated ranked analysis of combined clinical and functional outcome measures	• Ranked outcome derived from the combined integrated analysis of clinical and functional assessments (including mRS, seizure freedom, and, cognitive function) at the end of the Treatment Period (Week 25)
• To assess the safety and tolerability of rozanolixizumab	• Change from Baseline in vital signs and laboratory results during the study

Objectives	Endpoints
• To assess the pharmacodynamic (PD) effect of rozanolixizumab as measured by the total IgG concentrations in serum	• Value and change (absolute and percentage) from Baseline in serum total IgG and IgG subclass concentrations during the study
• To assess the PD effect of rozanolixizumab as measured by LGI1 autoantibody levels using the flow cytometry LGI1 quantitative assay	• Value and change from Baseline in LGI1 autoantibody serum levels during the Treatment Period • Value and change from Baseline in LGI1 autoantibody cerebrospinal fluid (CSF) levels during the Treatment Period (for consenting participants)
• To evaluate the effects of rozanolixizumab on patient-reported health-related quality of life (HRQoL)	• Value and change from Baseline in the 36-item Short Form Survey (SF-36) Physical Component Summary (PCS) score, Mental Component Summary (MCS) score, and individual domain scores during the Treatment Period • Value and change from Baseline in the EuroQol-5D-5L (EQ-5D-5L) during the Treatment Period • Value and shift from Baseline in Clinical Global Impression of Severity (CGI-S) during the Treatment Period
• To evaluate the effects of rozanolixizumab on healthcare resource utilization (HCRU)	• Disease-related hospitalizations (number, duration)
• To assess the pharmacokinetic (PK) characteristics of rozanolixizumab	• Plasma concentration of rozanolixizumab during the Treatment Period
• To evaluate the impact of concomitant antiepileptic drugs (AEDs) on rozanolixizumab plasma levels	• Plasma concentration of rozanolixizumab during the Treatment Period

Objectives	Endpoints
• To evaluate the incidence and emergence of antidrug antibody (ADA) of rozanolixizumab and impact on PK and PD	• ADA status
• To evaluate the effects of rozanolixizumab on the concentration of total protein, albumin, [redacted], and serum and plasma complement levels	• Values and change from Baseline in total protein, albumin, and serum immunoglobulin concentrations ([redacted]) during the Treatment Period • Values and change from Baseline in serum complement levels [redacted] and plasma complement levels ([redacted]) in case of infusion or hypersensitivity reaction
• To assess exploratory biomarkers	• Deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and genetic analysis that may be measured to understand the cause and appropriate treatment of LGI1 AIE • Exploratory biomarkers such as but not limited to [redacted] • Proteins and metabolite changes may be measured to understand the cause, progression, and appropriate treatment of LGI1 AIE

1.2 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2-arm, repeat dose study to evaluate the efficacy, safety, and PK of rozanolixizumab for the treatment of LGI1 AIE.

Approximately 68 adult study participants with LGI1 AIE with onset of disease symptoms between 0 to 12 months prior to study entry, as assessed by the investigator, will be randomized to receive rozanolixizumab [redacted] or placebo, administered by subcutaneous (sc) infusion at [redacted] intervals for 24 weeks. A Treatment Period of 24 weeks has been selected to ensure a sufficient time period to evaluate a difference between rozanolixizumab and placebo in key symptoms of the disease. The primary objective of the study is to assess the efficacy of rozanolixizumab as measured by seizure freedom.

Down titration of steroids will begin after at least 3 days on the initial high dose corticosteroids (based on the decision of the investigator).

The study participants will be stratified at randomization by:

- Time from disease symptom onset (≤6 months or >6 months from the disease symptom onset)
- Cognitive function (RBANS score of ≤85 or >85)

After the initial 5 investigational medicinal product (IMP) administrations have been performed at the clinic, the study participant may have the opportunity to be treated at home by a visiting healthcare practitioner.

Although the use of rescue medication is allowed at any time during the study, the use of rescue medications should be delayed, if clinically feasible, for at least 4 weeks following the initiation of study treatment. Study participants who require use of rescue medication will discontinue blinded treatment and complete the assessments for the Early Discontinuation Visit. Following this, the selection of an appropriate rescue medication will be made at the investigators discretion, and the study participant will enter the Safety Follow-Up (SFU) Period. Unscheduled study visits are permitted for any study participant including those study participants who have initiated rescue medication.

An Independent Data Monitoring Committee (IDMC) will be established for the study to monitor the emerging safety data within the clinical study on a periodic basis.

Number of Participants

Sixty-eight participants will be randomly assigned to the study.

Treatment Groups and Duration

The maximum study duration per study participant is 38 weeks. There are 3 study periods:

- Screening Period: Eligibility will be assessed during the Screening Period of up to 42 days. If a study participant becomes seizure free as a result of steroid treatment, the participant may still be randomized in the study, providing the prior occurrence of seizures is well documented.

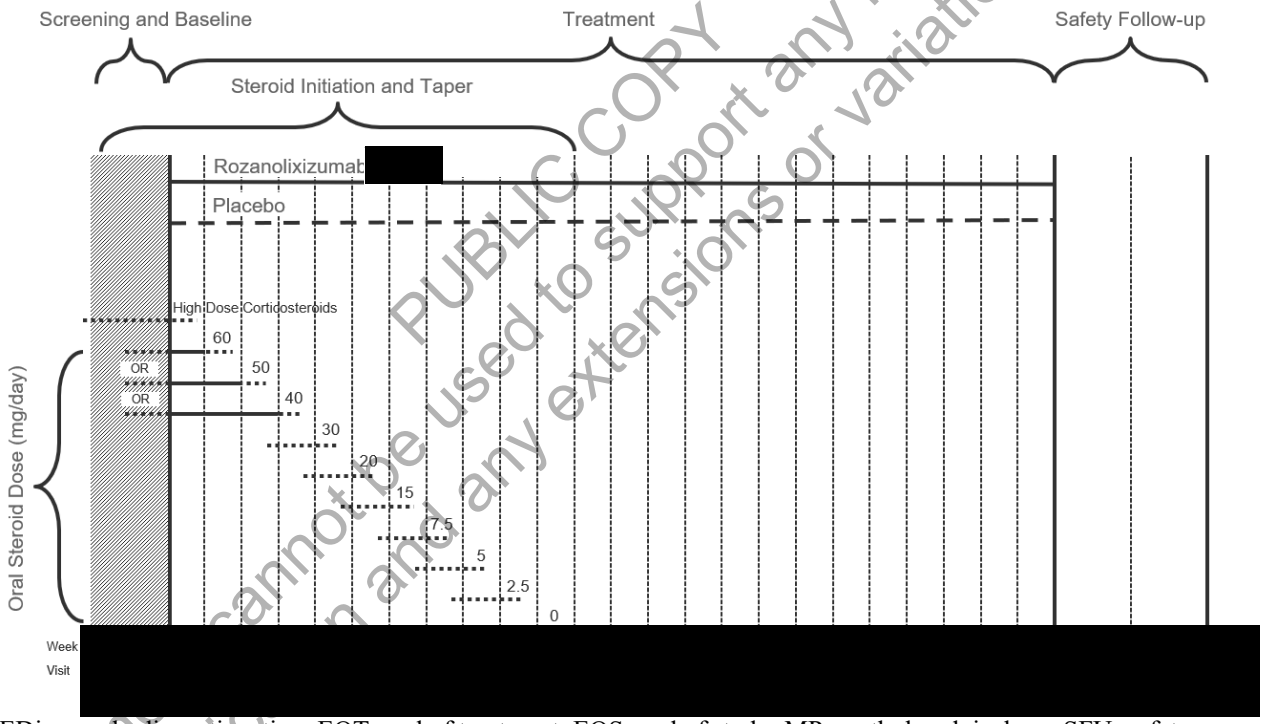
  Following screening and completion of the Baseline assessments, treatment will be initiated in study participants who are deemed appropriate for initiation or re-initiation of high dose corticosteroids (500 to 1000mg methylprednisolone [MP] equivalent /day) based on clinical symptoms and history, or who have initiated corticosteroids within 42 days prior to randomization at a dose of 500 to 1000mg MP equivalent/day. Corticosteroids can be initiated prior to the start of the Screening Period, however, the study participant must be randomized within 42 days of corticosteroids initiation. If the study participant has initiated a steroid taper, the study participant cannot receive oral steroids at a dose lower than 40mg/day when randomized. Study participants receiving a steroid dose of 60mg/day, 50mg/day or 40mg/day at the time of randomization, will have to maintain that dose for 7 days (±2 days), 14 days (±2 days) or 21 days (±2 days), respectively, before resuming [redacted] down-titration steps. Each subsequent down-titration step will last for 7 days (±2 days; see Figure 1–1). For those participants that have not initiated a steroid taper, the

down-titration of the oral steroid dose will begin after at least 3 days on the initial high dose corticosteroids, as per investigator' discretion.

- Treatment Period: Participants who have been confirmed eligible will be randomized in a 1:1 ratio to receive rozanolixizumab [redacted] or placebo at [redacted] intervals over a 24-week Treatment Period. Initially, study participants will receive rozanolixizumab or placebo in addition to intravenous (iv) or oral steroids that will be tapered as described in protocol Section 1.2.
- Safety Follow-Up Period: Study participants who complete the 24-week Treatment Period or prematurely discontinue IMP, as well as study participants who receive rescue medication during the 24-week Treatment Period will undergo the End of Treatment (EOT) Visit/Early Discontinuation Visit and enter the SFU Period. At 4 weeks after the final dose, study participants will undergo a SFU phone call, and at 8 weeks after the final dose, study participants will undergo the End of Study (EOS) Visit.

  A schematic of the study design is provided in Figure 1–1.

Figure 1–1: Study schematic



EDisc=early discontinuation; EOT=end of treatment; EOS=end of study; MP=methylprednisolone; SFU=safety follow-up; W=Week
Note: Rozanolixizumab or placebo will be initiated in study participants who are deemed appropriate for initiation or re-initiation of corticosteroids based on clinical symptoms and history, or have initiated corticosteroids within 42 days prior to randomization at a dose of 500 to 1000mg MP equivalent/day. Study participants will be administered rozanolixizumab or placebo in addition to iv or oral steroids that will be tapered. The dotted line indicates the period in which each down-titration step may occur.
Note: Visit 17 and Visit 18 were removed in Protocol Amendment 4 and Visit 4 was removed in Protocol Amendment 5; however, the Visits were not renumbered.

2 STATISTICAL HYPOTHESES

The null hypothesis (H0) for the primary endpoint is:

There is no association between randomized treatment (Rozanolixizumab) exposure and reaching the primary endpoint (seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)) conditional on the stratification factors (time from the disease onset and RBANS score, see Section 5.1.1.8) as measured by rozanolixizumab versus placebo odds ratio (OR): H0: OR = 1.

Due to the low number of participants recruited into this study due to the study being terminated prematurely, no statistical testing will be carried on the primary endpoint.

3 SAMPLE SIZE DETERMINATION

The study sample size of 60 participants is considered sufficient to provide acceptable study operating characteristics for the primary efficacy endpoint (Section 1.1). To account for an assumed 10% dropouts within each treatment arm and to enable an equal study participant allocation between treatment arms, 68 study participants will be randomly assigned to study treatment arms in a 1:1 ratio.

It should be noted that due to feasibility issues with recruitment, which was suspended as of 29 November 2023, the study has a limited sample size of 12 participants, which does not provide adequate statistical power to address the efficacy objectives defined for this study.

Given that there are limited randomized published studies in the LGI1 AIE patient population, there is uncertainty with respect to the expected proportion of participants who may achieve seizure freedom by 24 weeks in the control arm. While the targeted desirable treatment difference is 40%, a difference of 30% would be considered both clinically relevant and important in this disease area, given the lack of approved treatments and the length of prior corticosteroid treatment that is permissible in the study, along with potential prior disease specific treatment.

The study operating characteristics presented in Table 3–1, were derived based on the expected seizure freedom proportions in the randomized study treatment arms that may be observed at the end of Treatment Period (Week 25). Based on Thompson et al (Thompson, 2018), after 30 and 90 days 51% and 88% of LGI1 AIE patients, respectively, experienced cessation of Faciobrachial Dystonic Seizures (FBDS) once treated with immunotherapy. These rates were consistent with (de Bruijn MAAM, 2019) median time to the FBDS freedom of 28 days once treated with immunotherapy.

For the purposes of the dual criteria framework as presented in Table 3–1, the proportions of seizure freedom at the end of the Treatment Period (Week 25) are assumed not to be lower than 70% in the rozanolixizumab treatment arm and 40% in the placebo arm. The treatment effect evaluation based solely on statistical significance testing, is complemented with an assessment of its clinical relevance following the dual criteria framework as presented by (Fisch, 2015).

Assuming 50% seizure-free proportions in the control arm, the sample size of 60 study participants will be able to detect a resulting 40% proportion difference with approximately 85% and a resulting 30% difference with approximately 55 to 65%. For a target difference (TD)

of 40% in the proportions between the treatment groups, the probability that both significance and relevance criteria are met, given a true difference of 40%, is at least 45% with only 9.5% of studies where none of the key criteria are met. If the TD achieved is 30%, the probability that both key criteria are met is at least 76%.

If the difference in proportions increases to 50%, because of a larger (90%) seizure-free proportion in the rozanolixizumab arm, the power to detect that effect is at least 95% with the sample size of 60. For this design, the probability that both the criteria are met is 79% and 44.5% for TD of 40% and 50%, respectively, with less than 1% probability that none of the criteria are fulfilled.

Decisions with respect to the outcome of this study will utilize the operating characteristics as described for the primary endpoint but will also importantly consider the strength of evidence of treatment effect provided by the secondary endpoints, according to the prescribed criteria for alpha spending, as outlined in protocol Section 9.3.2, as well as consideration to the safety data observed.

Table 3–1: Study Operating Characteristics

Sample size	PBO arm SF proportion (%) at the end of Treatment Period	RLZ arm SF proportion (%) at the end of Treatment Period	Power CMH[a] (%)	Power logistic[b] (%)	Target RLZ-PBO SF proportion difference (%)	Probability[c] (%)		
						Scenario A	Scenario B	Scenario C
60	40	70	54.6	63.2	30	45.7	20.6	33.8
					40	17.3	49.1	33.6
					50	3.7	62.8	33.5
60	40	80	84.5	86.0	30	76.3	14.1	9.6
					40	45.2	45.3	9.5
					50	16.1	74.7	9.2
60	40	90	98.3	95.4	30	95.6	3.8	0.6
					40	79.1	20.0	0.9
					50	44.5	54.8	0.7

CMH= Cochran-Mantel-Haenszel; PBO=placebo; RLZ=rozanolixizumab; SF=seizure freedom

[a] Power to detect a statistical difference at a 2-sided 5% significance level based on the CMH test with continuity correction (Wittes, 1987). The calculations were made using the R package *samplesizeCMH* ver. 0.0.0.

[b] Power to detect a statistical difference at a 2-sided 5% significance level from a standard logistic regression model adjusting for treatment group (Demidenko, 2007). The calculations were made using the R package *WebPower* ver. 0.6.

[c] Derived from the Fisch et al (Fisch, 2015) decision framework based on dual criteria: Significance – high confidence (0.975) that the effect of the investigational drug, relative to placebo, is greater than zero; Relevance – moderate confidence (0.5) that the drug effect, relative to placebo is larger than the target difference. Possible scenarios:

- A – both criteria hold as an evidence of sufficiently high effect
- B – inconclusive as only one criterion holds, suggesting a marginal effect (Significance only) or too much variability to make a clear decision (Relevance only)
- C- neither of the criteria holds.

The probability of each scenario calculated from S=10,000 simulated study outcomes for a given sample size and seizure freedom proportions combination.

4 POPULATIONS FOR ANALYSIS

4.1 Enrolled Set

The Enrolled Set (ES): All study participants who have signed the informed consent.

4.2 Randomized Set

The Randomized Set (RS): All enrolled study participants who were randomized to blinded IMP (Investigational Medicinal Product). This is an equivalent to the Intent-to-Treat (ITT) Population. The study participants will be analyzed according to the randomized treatment.

4.3 Safety Set

Safety Set (SS): All randomized study participants who received at least one dose of IMP. Analysis of this set will be according to the treatment the study participants actually received and will be used for the demographic and safety analyses.

4.4 Pharmacodynamic/Pharmacokinetic Per-Protocol Set

The Pharmacodynamic Per-Protocol Set (PD-PPS) is a subset of the SS, consisting of those study participants who had at least one valid post-Baseline measurement of total IgG, or IgG subclasses, and no important protocol deviations (as defined in Section 5.1.1.2) affecting the PD variable.

Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PD-PPS but may lead to exclusion of specific data

4.5 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those study participants who have at least one quantifiable concentration of rozanolixizumab and no important protocol deviations affecting the PK variable. Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PK-PPS but may lead to exclusion of specific data.

5 STATISTICAL ANALYSES

The RS will be used for all summaries unless it is specified otherwise. For safety summaries, RS will be used as this is the same as the SS.

It should be noted that participants were all randomized under different versions of the protocol up until Protocol Amendment 5. The result of this is that there will be different assessments (eg. Health outcomes and PK/PD) available for the 12 participants. Some assessments may have very limited data.

5.1 General Considerations

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 continuous variables, descriptive statistics will include number of participants with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum.

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

- For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the analysis set and include a “Missing” category (corresponding to participants with missing data for the variable being summarized) as the last row in the list of categories being summarized.

- For summaries of efficacy and safety variables, unless otherwise specified: summarize percentages based only on those participants with observed data for the variable being summarized. As the denominator may be different from the number of participants in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)."

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

All summaries of PK variables will be based on the observed values. No imputation will be used.

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

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

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

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

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

All data will be analyzed based on the visits identified per the Schedule of Activities in the protocol.

Mapping to visit windows will not be applied. For Early Withdrawal visits refer to Section 5.1.1.1.4.

5.1.1.1.1 Relative day

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

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

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

Relative days for an event or measurement occurring on or after the date of first SC infusion are calculated as follows:

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

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

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

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

5.1.1.1.2 End date of the Treatment Period

The end date of the Treatment Period will be either the date of EOT visit (Week 25) for participants completing the Treatment Period, or the date of the early discontinuation (EDisc) visit for participants who discontinued during the Treatment Period. If a subject does not have an EOT/EDisc visit, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of IMP during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

5.1.1.1.3 Study periods

The maximum study duration per study participant is 38 weeks. There are 3 study periods:

- Screening Period: up to 42 days;
- Treatment Period: 24 weeks;
- Safety Follow-Up Period: 8 weeks.

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

- **Screening Period** starts at the time of the informed consent date and ends the day before the first dose administration of IMP (i.e. generally the day before Day 1 visit date).
- **Treatment Period** starts on the day of first dose administration of IMP (Day 1) and ends at EOT visit or at EDisc visit for participants withdrawn from the study before Week 24 visit. Participants who are withdrawn from the study during the Treatment Period should complete the assessments outlined for the EOT/EDisc visit and enter the SFU Period.
- **Safety Follow-Up Period** starts with one day after Treatment Period and ends at the final assessments at the EOS visit. Participants who have a completed status in the study termination CRF are considered to have completed the Treatment and SFU Period (i.e. entire study).

Notes:

- The end of the study is defined as the date of the last visit of the last participant in the study.
- Patients should be dosed within 2 days of being randomized.

5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit

Assessments performed at EDisc Visit will be assigned to the next scheduled site visit (following the last scheduled visit that the participant completed prior to EDisc Visit) where each assessment is evaluated as per protocol. This approach means that there is a chance that EDisc Visit will be mapped to different visits according to the schedule of assessments.

5.1.1.1.5 Definition of Baseline values

Baseline will be derived in the screening period prior to randomization for efficacy assessments including RBANS, seizure counts, and on the date of randomization for PK/PD markers prior to the first dose of IMP. If there are multiple assessments, then the last one available prior to the randomization date will be used. Scheduled or unscheduled measurements can be used as the Baseline value. If a Baseline measurement is not available, but an unscheduled measurement occurs after the planned baseline measurement time point but before randomization, then the unscheduled measurement will be used.

For Modified Rankin Scale (mRS), the Baseline score will be the better (i.e., the lower) score from either the Screening or Baseline visit.

For safety assessments, a Baseline value will be the last available predose value if not otherwise stated.

5.1.1.1.6 Calculation of Baseline Category of Seizure Count

The median category of seizure count will be calculated for each week of the screening period up to 6 weeks prior to randomization, and the average median value will be used as the Baseline category of seizure count.

5.1.1.2 Protocol Deviations

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

5.1.1.3 Treatment assignment and treatment groups

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

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

- Placebo
- Rozanolixizumab

5.1.1.4 Center pooling strategy

It is planned to recruit participants in North America, Europe, Australia, and Asia in this study. The data from all sites will be pooled for analyses.

5.1.1.5 Coding dictionaries

Adverse events (AEs) and medical histories will be coded using version 24.1 or later of the Medical Dictionary for Regulatory Activities (MedDRA®).

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

5.1.1.6 Multicenter studies

Individual center results will not be displayed.

5.1.1.7 Multiple comparisons/multiplicity

A fallback hierarchical testing procedure was planned to be implemented to control the overall type I familywise error rate at 0.05 over the primary endpoint and the 4 defined secondary endpoints. See details in Section **Error! Reference source not found.**. This however will no longer be implemented due to early study termination and the limited number of study participants.

5.1.1.8 Adjustments for covariates

The efficacy analyses was planned to be adjusted for the following stratification factors (as randomized). This adjustment or any summaries that were planned by these factors, will no longer be possible due to the limited number of participants

- Time from disease onset (≤6 months or >6 months from the disease onset),
- Cognitive function (RBANS score of ≤85 or >85 at the Screening).

5.1.2 Rescue medication

Rescue medication considered most appropriate for the study participant will be selected by the investigator. The study site will supply rescue medication that will be obtained locally.

Study participants who require rescue medication will discontinue IMP and complete the assessments for the Early Discontinuation Visit.

5.1.3 Missing Data Strategies for efficacy analyses

Table 5–1: Missing data strategies for the analysis of efficacy endpoints

Efficacy endpoint	Statistical analysis category	Statistical Analysis Methods	Imputation Method
Primary	Primary	OR	Any missing daily seizure count in a given reporting period will be (indirectly) imputed with the daily

			average seizure count observed in that period

OR: odds ratio

5.2 Participant Dispositions

The following summary outputs will be presented.

- **Reasons for screen failures** (as collected on the Study Termination Screen Failure CRF page) will be summarized using the ES.
- **Disposition of study participants screened** will be summarized using the ES for overall, by region and by site. In this summary, the site number, principal investigator name, first participant in date, last participant out date, will be captured by randomized treatment and by each analysis set (RS, SS, FAS).
- **Disposition of Analysis Sets** will be summarized by treatment group and overall for each analysis set (RS, SS) using the RS.
- **Disposition and Discontinuation Reasons** will be tabulated using the RS, and will contain the number and percentage of study participants by treatment group and overall who:
    - Started Treatment Period / SFU Period
    - Ongoing Treatment Period / SFU Period
    - Completed Treatment Period / Study
    - Discontinued Treatment Period / Study

  Primary Reason for discontinuation (reason for treatment discontinuation as collected in the Study Medication Discontinuation CRF and primary reason for premature study termination as collected in the Study Termination Complete/Dropout CRF).
- **Discontinuation due to AEs** will be summarized by treatment group and overall for the following types of AEs using the RS:
  – AE, serious fatal,
  – AE, non-fatal,
  – Other (AE, non-serious fatal).

Listings of study participant disposition, study discontinuation and study participants who did not meet study eligibility criteria will be provided. The impact of COVID data will be listed.

5.3 Primary Endpoint Analysis

5.3.1 Definition of endpoint

Participants who reported no seizures for 28 consecutive days and maintained the seizure count as zero until the end of Treatment Period will be treated as meeting the primary endpoint.

For the purpose of deriving the primary efficacy endpoint, any intermittent missing diary

seizure count recording will not be imputed but considered as non-zero for the purposes of the primary endpoint.

A by-participant listing of daily seizure count will be provided, including seizure freedom, time to first occurrence of seizure freedom, time to seizure freedom, and duration of seizure freedom.
.

5.3.2 Main analytical approach

Participants meeting the primary endpoint will be defined using the strategies indicated below:

Estimand attributes:

1. Treatment conditions:
   - Rozanolixizumab: Subcutaneous infusion, [redacted]
   - Placebo: Subcutaneous infusion, 0.9% sodium chloride aqueous solution (physiological, saline, preservative free).
2. Population of interest: Study participants with LGI1 AIE who comply with the inclusion and exclusion criteria (Protocol Section 5.1 and Section 5.2).
3. Endpoint: Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25).
4. Intercurrent events (ICE) / Intercurrent Event Strategy (ICES) and missing data strategies:
   - ICE1: Temporary discontinuation from the IMP
   - ICE2: Permanent discontinuation from the IMP

The strategies to handle ICEs are summarized below:

Table 5–2: Intercurrent events (ICE) / Intercurrent Event Strategy (ICES) and missing data strategies for the analysis of the primary endpoint

ICE	ICE Strategy	Missing Data Strategy
ICE1	**Treatment Policy**: The occurrence of intercurrent event ICE1 doesn't affect the assessment of primary endpoint. All seizure counts collected during the treatment period will be included in the assessment of primary endpoint.	See Section 5.1.3 for details.
ICE2	**Composite strategy:** Permanent discontinuation of the IMP will be considered as non achieving seizure freedom (non-responder).	

5. Population-level summary:

On the RS, odds ratio will be calculated to investigate the association between the treatment and chance to reach primary endpoint.

The ICEs will be handled per Table 5–2.

The data will be summarized in 2 × 2 contingency table:

Table 5–3: 2 × 2 contingency table

	Rozanolixizumab	Placebo	Row Total
Seizure Freedom	A	B	A + B
No Seizure Freedom	C	D	C + D
Column Total	A + C	B + D	N

Note: A, B, C and D are the number of participants in the cells of the 2 × 2 table. N represents the total number of participants.

Hypothesis testing

Due to the low number of participants randomized to treatment there will be no hypothesis testing for the efficacy endpoints.

Treatment effect estimation

The OR estimate with its 95% CI will be reported in a summary table using the RS.

The estimate of OR will be computed as (see Table 5–3)

$$\widehat{OR} = \frac{AD}{BC}$$

and reported to assess the strength and direction of the association with its 95% CI. Resulting OR>1 indicates a clinical benefit from the RLZ, and the magnitude from 1 shows its strength.

In the case where none of the Placebo subjects reaches the primary endpoint, the calculation of the odds ratio estimate is not feasible as it requires division by zero (B = 0). In this situation, the OR is not estimable and the median unbiased estimator of the odds ratio (lower end of the 1-sided 50% CI) and 1-sided exact 95% CI will be reported.

5.4 Secondary Endpoints Analyses

All secondary efficacy endpoints will be summarized only and not tested for statistical significance due to the low number of participants recruited due to the study being terminated early.

5.4.1 Change in cognitive function (RBANS)

RBANS 5 domain index scores and total scale index score will be captured and calculated at the Screening visit, then post-Baseline visits 8, 16, 26, early treatment discontinuation visit and end of study visit according to the RBANS US v2.0 (13Nov2019) (see Section 6.2). The last available results of RBANS scores prior to first dose will be served as Baseline.

The observed Baseline and post-Baseline RBANS total scale index score at each scheduled visit where RBANS is collected will be summarized using descriptive statistics by randomized treatment group, together with the changes from Baseline. A by-participant listing of RBANS scores will be provided.

5.4.2 Change in overall disability: mRS

The mRS score will be captured according to the mRS manual (see Section 6.3).

The observed Baseline and post-Baseline mRS scores at each scheduled visit will be descriptively summarized on the RS by treatment group, together with the change from Baseline.

A by-participant listing of mRS category/score will be provided.

5.4.3 Use of rescue medication due to an absence or loss of clinical benefits

Use of rescue medications with associated reasons will be recorded as part of the assessment of prior and concomitant medications during the study. Participants with use of any rescue medications during Treatment Period due to an absence or loss of clinical benefit will be considered as meeting this endpoint.

A by-participant listing of use of rescue medication, PT of rescue medications and associated reasons will be provided.

5.4.4 Time to first occurrence of seizure freedom (TTFSF)

TTFSF will be summarized as a continuous variable by treatment group on the RS. A by-participant listing of time to first occurrence of seizure freedom will be provided.

5.5 Exploratory Endpoints Analyses

5.5.1 Seizure control

Seizure frequencies will be recorded on a daily basis across the 24 weeks of randomized therapy and during a variable Screening Period, based on the following categories:

1. 0 seizures
2. 1-5 seizures
3. 6-10 seizures
4. 11-20 seizures
5. >20 seizures

For each participant, a median category of seizure count categories will be calculated for each week that the participant is in the randomized treatment period, such that each participant has one average median category for that week, along with a minimum and maximum category range. In case of missing seizure count category, calculated median category will be rounded up to fit into the 5 categories. For example, if the calculated median is 2.5, then this value will be rounded up to 3 as the final median.

For the Screening Period, a Baseline median category will be calculated for each participant, in the same way as described for each week of randomized treatment. This will be to utilize the screening data collected in the period up to 6 weeks immediately prior to randomization.

The frequency counts and percentages of participants falling into each of the median categories across the 24 weeks will be summarized by treatment group using RS.

In the case of 7 missing data points over an entire week, this will be imputed from the previous weeks data. For 1 week of data, the median will not be calculated if more than 5 missing values.

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5.5.2 Duration of seizure-free period

The duration of the seizure-free period will be measured from the first day the participant reports no seizures of at least 28 consecutive days until the last day reported without seizures during the Treatment Period. Missing daily seizure counts will be treated as non-zero reports, without any value assigned. This statistic will be provided for each participant.

The endpoint will be included on the listing related to participants seizures; listed on the RS and by randomized treatment arm.

5.5.3 Change in RBANS domains

The individual RBANS domain index scores (immediate memory, visuospatial/constructional, delayed memory, language, and attention) will be calculated per RBANS US v2.0 (13Nov2019) (see Section 6.2).

The observed Baseline and post-Baseline individual RBANS domain index scores at each scheduled visit will be descriptively summarized on the RS by treatment group, together with the change from Baseline. All scores will be listed for each participant; produced by randomized treatment arm.

5.5.4 Short Form 36-item (SF-36)

By-participant listings of the SF-36 V2 questionnaire responses only, SF-36 V2 will be provided by treatment group. Domains and component scores will not be calculated.

5.5.5 Euro-Quality of Life 5-Dimensions, 5 Levels (EQ-5D-5L)

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

A by-participant listing will be produced using the RS to summarize answers provided to each of the 5 dimensions of the EQ-5D descriptive system at each scheduled visit for each participant by treatment group.

5.5.6 Clinical Global Impression of Severity (CGI-S)

The CGI-S is a clinician reported outcome that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention.

A frequency table will be produced using the RS to summarize answers provided to the CGI-S (“none,” “mild,” “moderate,” “severe", “very severe”) at each scheduled visit by treatment group

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

If any other data is available on PGI-S, PGI-C for any participants this will be listed.

5.6 Safety Analyses

All safety analyses will be presented using the RS unless RS and SS are different and then SS will be used. Listings will be presented by treatment group, participant, and stratification factors (time from the disease onset and RBANS score, see Section 5.1.1.8); tabulations will be presented by treatment group . Unless otherwise specified, safety analyses will be presented by safety treatment group as defined in Section 4.3.

5.6.1 Extent of Exposure

The following summaries will be generated using descriptive statistics based on the SS:

a) Study IMP duration (day) calculated as follow:

   Study IMP duration (day) = Date of last dose – Date of first dose + 1

   If data cut-off is applied and date of last dose > date of cut off, date of last dose will be replaced by the cut-off date in the above formula.

b) Cumulative study IMP Duration using > 0 weeks, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 20 weeks, and 24 weeks;

c) Number of Infusions Received as continuous and using the following categorical values: 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24;

All drug administration details will be listed.

5.6.2 Adverse Events

5.6.2.1 Data considerations

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (see Section 5.1.1.5).

In addition, AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 or later for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described below:

Grade: Intensity

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

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

Any AE that occurred during the study will be defined as "**any AE**".

A TEAE is defined as an AE starting on or after the time of first administration of IMP or any unresolved event already present before the first administration of IMP that worsens in intensity following exposure to treatment up to the end of the Treatment Period and including the 8-week (56 days) SFU. Adverse events starting before the date of the first administration of IMP or after SFU will not be considered TEAEs. Such events will be listed only.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless evidence exists that does not allow the AE to be treatment-emergent. Handling of missing dates for classification of AEs as TEAEs is described in Section 6.1.7.1.2.

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

- **Treatment Period:** a TEAE will be assigned to the Treatment Period for the tabulations if the start date of the event is on or after the date of the first administration of IMP on Day 1, up to 7 days following the final dose of IMP;
- **SFU Period:** a TEAE will be assigned to the SFU Period for the tabulations if the start date of the event is greater than 7 days after the date of the final dose of IMP until 8 weeks following the final dose; events starting later than 8 weeks (56 days) following the final dose of IMP are not considered TEAEs.

In the case of early withdrawal in the Treatment Period, a TEAE will be assigned to the Treatment Period based on the last received IMP plus 168 hours (7 days). Subsequent TEAEs (up to 8 weeks (56 days) post-last dose) will be assigned to the SFU Period.

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

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

5.6.2.2 Adverse events summaries

The number and percentage of participants who experience AEs will be summarized by treatment group. The following outputs will be created:

- Incidence of TEAEs (defined as the number and percentage of participants with at least one TEAE (incidence proportion) – Overview. The following categories will be included by treatment arm:
  - Any TEAEs
  - Serious TEAEs
  - Participant discontinuation due to TEAEs (defined as TEAEs with "Did the Adverse Event Lead to Dropout ticked" as "Yes")
  - Permanent withdrawal of IMP due to TEAEs (defined as TEAEs with an action taken with study medication of "drug permanently withdrawn")
  - Temporary withdrawal of IMP due to TEAEs (defined as TEAEs with an action taken with study medication of "drug temporarily interrupted")
  - Treatment-related TEAEs
  - Severe TEAEs

All Deaths (AEs leading to death). Note: Above TEAEs will be summarized to capture the overall and by MedDRA Primary SOC (PSOC), Higher level term (HLT) and PT. Additionally, the frequency of TEAEs will be summarized by MedDRA PSOC and PT.

- The number, percentage of participants and frequency of the following TEAEs will be summarized by SOC, HLT and PT for:
  - Incidence of any TEAEs
  - Incidence of Serious TEAEs
  - Incidence of Permanent withdrawal of IMP due to TEAEs
  - Incidence of Any TEAEs by Maximum Intensity (mild, moderate and severe)Incidence of Any TEAEs by Relationship
  - Incidence of Any TEAEs by Event Outcome
  - Incidence of any TEAE's per 100 Patient years.

AESIs are the cases of potential Hy's Law (see Section 6.1.9).

AESMs or AESIs will be identified based on the assessment by the Investigator as recorded in the CRF. An AE will be counted as an AESMs or AESIs if there is a 'yes' response to the question "Adverse Event of Special Interest or Event of Special Monitoring?" and not otherwise. These flags will be included in the listings.

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

Listings of all AEs, permanent withdrawal of IMP due to AEs, participant discontinuation from study due to AEs, and AEs leading to death will be presented by treatment group.

5.6.3 Additional Safety Assessments

5.6.3.1 Clinical laboratory evaluations

The following Table 5– lists safety laboratory assessments that are collected throughout the study:

Table 5–9: Clinical Laboratory Parameters

Laboratory Assessments	Parameters		
Hematology	Platelet Count	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red Blood Cell (RBC) Count		
	Hemoglobin		
	Hematocrit		

Laboratory Assessments	Parameters			
Clinical Chemistry	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
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Albumin
	Lactate dehydrogenase (LDH)	C-reactive protein (CRP)	Low-density lipoprotein (LDL) High-density lipoprotein (HDL) Total cholesterol Triglycerides	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum (at Screening) or urine (all other visits) human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[a] • Serology testing (for Hepatitis A, Hepatitis B, Hepatitis C, and HIV)			

Note: The tests detailed in the table will be performed by the central laboratory. Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation.

[a] IGRA, TB and Dipstick uri-analysis and urine pregnancy dipstick tests will be performed locally.

Chemistry, hematology and quantitative urinalysis (observed value, absolute change from Baseline) will be listed in standard unit by treatment group at each scheduled visit.

All lab data will be used for the listings.

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

quantification limit for the purpose of any quantitative individual participant data. These rules will be applied to all safety laboratory data including clinical chemistry and urinalysis.

All central and local laboratory test results will be listed using the SS, including Baseline, scheduled and unscheduled visits with results in standard unit. Values outside the reference range for the continuous variables and any MA values will be flagged in the listings. The reference ranges will also be reported in the listings. Additional lab test, including pregnancy testing, will be listed separately.

5.6.3.2 Potential drug-induced liver injury (pDILI)

The number and percentage of participants who meet one or more of the following pDILI criteria will be summarized by treatment group at any visit (including unscheduled visit):

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

In order to meet the above criteria, a study participant must experience the elevation in bilirubin and ALT or AST (and the absence of the ALP elevation) at the same visit. For example, a study participant who experiences a ≥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 by treatment group at any visit (including unscheduled visit).

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.

5.6.3.3 Vital Signs

A by-participant listing of all vital sign measurements and change from Baseline will be presented by treatment group and timepoint. The listing will include a flag for values identified as MA outlined in Section 6.5.

Repeated and unscheduled measurements will be handled as described in Section 6.1.7.2.

5.6.3.4 12-Lead Electrocardiograms (ECG)

The following 12-Lead ECG variables will be listed if the data is available. (NB. These assessments were removed from protocol amendment 4).

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

A listing of electrocardiogram data will be presented, including repeated and unscheduled measurements. Electrocardiogram findings for the individual triplicate measurements will be listed separately.

5.6.3.5 Physical examination

Data from the Physical Examination are provided in subject data listings presented by treatment group, subject and visit, displaying all data collected for all subjects. No summaries will be provided. Findings that are considered clinically significant will be reported as AEs.

5.6.3.6 Neurological examination

Data from the Neurological Examination are provided in subject data listings presented by treatment group, subject, and visit, displaying all data collected for all subjects. No summaries will be provided. Findings that are considered clinically significant will be reported as AEs.

5.6.3.7 Childbearing potential

Childbearing potential will be collected at Screening. A by participant listing will be provided using the RS.

5.6.3.8 Assessment and management of Tuberculosis (TB)

Results of the interferon gamma release assay (IGRA) TB test, chest X-ray and TB signs and symptoms questionnaire for TB will be listed.

5.6.3.9 Headache questionnaire

The results of the headache questionnaire will be listed for each participant.

5.6.3.10 Suicidal risk monitoring

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

[redacted]

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

[redacted]

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

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

A by-participant listing of the C-SSRS questionnaire data will be provided by treatment group if this data is reported by any participant in the study

5.7 Other Analyses

5.7.1 Other endpoints and/or parameters

All analyses described in Section 5.7.1.1 will be performed on the RS, and all other analyses will be performed on Safety set.

5.7.1.1 Pharmacokinetics

5.7.1.1.1 Rozanolixizumab

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

Individual plasma concentrations of rozanolixizumab will be summarized by scheduled sampling day for the RS on an individual participant basis due to the low participant numbers.

- Scatter dot plot of individual rozanolixizumab postdose plasma concentrations categorized by Day (Days 3, 5, 164, 166) with all days in the same plot.

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

- Values below the LLOQ will be reported as below the limit of quantification (BLQ)
- Descriptive statistics of concentrations will be calculated if at most 1/3 of the individual data points at a timepoint are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance. If more than 1/3 of the

individual data points at a timepoint are missing or are not quantifiable, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank.

- If n<3, then only the n, minimum and maximum will be presented. If no study participants have data at a given timepoint, then only n=0 will be presented.
- The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geoCV) is 0
- The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data

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

Individual concentrations of rozanolixizumab will be listed for the RS and will include the actual sampling time in days relative to the previous dose and the IgG observed at the same visit, for the same visit, IgG and IgG subclasses by achievement of primary endpoint of seizure freedom (yes/no).

5.7.1.2 Pharmacodynamics

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

5.7.1.2.1 Total serum Immunoglobulin G (IgG) and IgG subclasses

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

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

The following plots will be generated:

- Geometric mean change from Baseline values in total serum IgG, IgG subclasses over time by treatment group, with all PD endpoints and treatment groups overlaid on the same plot.
- Spaghetti plots for absolute IgG over time stratified by treatment group.
- Serum concentrations of total IgG and IgG subclasses will be listed together with concentrations of rozanolixizumab, LGI1 serum and CSF levels by achievement of primary endpoint of seizure freedom (yes/no), as specified in Section 5.7.1.1.

5.7.1.2.2 Serum concentrations of [redacted] will be listed together with concentrations of rozanolixizumab, LGI1 serum and CSF levels by achievement of primary endpoint of seizure freedom (yes/no), Leucine-Rich Glioma Inactivated 1 (LGI1) autoantibody levels

LGI1 autoantibody serum levels will be summarized at scheduled visit for observed values, absolute and percentage changes from Baseline. Same summary will be repeated for LGI1 autoantibody CSF levels for consenting participants. Individual participant will be plotted representing percentage change from Baseline in LGI1 autoantibody serum levels, total IgG,

IgG1 and IgG4 with all endpoints in the same plot and indication of dosing time points and flag if dosing was missed. The sub-title of the graph will include achievement of primary endpoint of seizure freedom (yes/no).

LGI1 autoantibody serum levels and CSF levels will be listed, together with total IgG, IgG subclasses as described in Section 5.7.1.2.1.

It should be noted that these summaries and plots will not be produced for the CSR as the data will not be available.

5.7.1.3 ADA will not be performed or evaluated in this study. Immunology

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

Serum complements levels and plasma complement levels Serum [redacted] and plasma ([redacted]) complement variables will be listed by visit and time point including changes from Baseline. Descriptive summaries will be presented for both absolute values and changes from Baseline for all participants, and separately for participants who experience an infusion reaction or hypersensitivity reaction at site. The selection criteria of infusion reaction or hypersensitivity reaction are described in Section **Error! Reference source not found.**.

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

5.7.1.4 Healthcare resource utilization

The following data, if it is available, will be listed by treatment group on the RS. a:

- Number of participants with hospitalization/ ER visit
- Total number of hospitalization/ ER visit
- Reason of hospitalization/ ER visit
- Number of participants discharged from hospitalization/ ER visit
- Total number of days in hospitalization/ ER visit, calculated as follow:

Note: /

- Total number of days in hospitalization/ ER visit = Discharge date – hospitalization/ER visit date +1. If a participant does not have discharge date, last available visit date will be used.
- Only hospitalization started after first IMP and before last visit will be considered in the summary.
- In case of missing or incomplete discharge date, the following imputation rules will be applied:
  - Hospital start date of next hospital stay – 1 as end date of this hospital stay;
  - Death date in case subject died and previous case does not apply;
  - Last visit date if previous cases do not apply.

A listing will be provided for the hospitalization/ ER visit.

5.8 Interim Analyses

There is no interim analysis planned for this study.

5.9 Data Monitoring Committee (DMC)

There is no individual DMC set up for this study. Instead, an overarching Rozanolixizumab program independent DMC (PiDMC) will oversee the safety of this study by reviewing safety data at periodic data reviews in collaboration with other Rozanolixizumab studies. The timing and data required for the overarching PiDMC will be described in overarching Rozanolixizumab PiDMC charter.

6 SUPPORTING DOCUMENTATION

6.1 Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

Unless otherwise specified, all summaries will be based on the RS.

6.1.1.1 Demographics

Demographic variables will be summarized using descriptive statistics by treatment group and overall on the RS for categories mentioned below.

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

- Age at the time of first study entry (years),

  Note: Missing age (captured on Demographics CRF) will be calculated as year of informed consent signed – year of birth
- Weight (kg),
- Height (cm),
- BMI (kg/m^2) calculated as: $BMI = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$;

Categorical variables (using frequency counts and percentages):

- Age (18 -<65, 65 - <85, ≥85 years),
- Age (≤18, 19 -<65, ≥65 years),
- BMI (<30, ≥30 kg/m^2),
- Weight (35kg-<50 kg, 50-<70kg, 70-<100kg, ≥100kg),
- Gender (Male, Female),
- Race (American Indian or Alaska native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- Region (North America, South America, Europe, Australia, Asia [excluding Japan], Japan and Africa),
- Country.

- Alcohol Use

A by-participant listing of demographics will be provided.

Childbearing potential will also be listed for the RS separately.

6.1.1.2 Baseline disease characteristics

The following variables will be summarized using descriptive statistics on the RS by treatment group and overall. All baseline characteristics will be provided in by-participant listings using the RS.

Continuous variables (including n, mean, SD, Median, Min and Max):

- Baseline RBANS score
- Baseline total IgG value
- Baseline LGI1 level

Categorical variables (using frequency counts and percentages):

- Baseline median category of seizure count over the Screening Period (1: 0 seizures, 2: 1-5 seizures, 3: 6-10 seizures, 4: 11-20 seizures, 5: >20 seizures)
- Time from disease onset (≤6 or >6 months)
- Cognitive function (RBANS score of ≤85 or >85)
- Baseline AIE medication
- Baseline mRS score

Notes:

- Historical seizures will be listed only:
  - Number of seizures (Week of any seizure experienced during the past 2 weeks prior to screening visit (week -2 or week -1))
  - Seizure description experienced during the past 2 weeks prior to screening visit
- Time from disease onset and cognitive function (RBANS score) will be based on the values recorded in the eCRF. This should be the same as the data entered into the interactive web response system (IWRS) at randomization, if for any reason eCRF values are missing then IWRS will be used.
- Baseline AIE medication will be collected in Prior and Concomitant Medication CRF where indication is AIE and presented by Preferred Terms.

6.1.2 Protocol deviations

A by-participant listing of important protocol deviations will be provided using the RS.

6.1.3 Medical history

Previous and ongoing medical history will be listed using the RS. Besides, procedure history will be provided in a separate by-participant listing using the RS.

6.1.4 Prior/concomitant/follow-up medications

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

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

6.1.4.1 Categories of prior and concomitant medications

Definitions:

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

Table 6–1 below summarizes concomitant medication classification with details around medication start and finish.

Table 6–1: Prior and Concomitant Medications Classification

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

6.1.4.2 Assignment of Treatment and/or SFU Period

The following rules will be used to assign a Prior, Baseline, Concomitant or Concomitant Only to following two study periods:

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

6.1.5 Rescue medications

Rescue medication considered most appropriate for the study participant will be selected by the investigator. The study site will supply rescue medication that will be obtained locally. The effect of rozanolixizumab on the efficacy of IgG biologics and Fc-fusion proteins is not known.

6.1.6 Antiepileptic Drug (AED)

The number and percentage of subjects receiving AEDs (determined by medical review) over the course of the study will be summarized using the RS. Data will be presented at 6-week intervals (i.e., at Week 6, 12, 18 24 etc.).

6.1.7 Data derivation rules

6.1.7.1 Handling of dropouts or missing data

6.1.7.1.1 Efficacy data

Seizure freedom, time to seizure freedom, will be derived based on the weekly reported seizure frequency categories captured on Seizure Count CRF. Imputation methods to handle the missing data (including missing data due to intercurrent events)

In the case of all other endpoints (RBANS and mRS), the observed case method will be applied. This is also the case for any ordinal endpoints (EQ-5D-5L, CGI-S). No imputation of data will be applied.

6.1.7.1.2 Dates and times

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

- Classification of AEs as TEAEs;
- Classification of medications as past, prior, or concomitant medications;
- Durations of AEs.
- Imputed dates will not be shown in listings. All dates will be displayed as reported in the database.

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

- If year, month and day are all missing then assign the date of first dose of IMP. If an imputed start date is after the specified end date, then assign January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).
- If month and day are missing, and year is:

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

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

The following rules will be applied for 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 dates is after last contact date, then assign last contact date as the stop date;
- If only the year is specified, then use December 31 of the known year. If an imputed stop dates is after last contact date, then assign last contact 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 and time unknown, will be assumed to be concomitant.

Imputed AE dates will be used for the calculation of duration of AEs as described in Table 6–2.

Table 6–2: 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.

Data availability	Onset date	Outcome date	Calculation 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.

6.1.7.2 Handling of repeated and unscheduled measurements

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

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

See Section 5.6.3.1 for the rules applied to repeated lab results.

See Section 5.6.3.4 for the rules applied to ECG triplicate measurements.

6.1.8 Treatment Compliance

Not applicable. The number of infusions will be recorded as detailed in Section 5.6.1.

6.1.9 AEs of Special Interest

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin (>35% direct bilirubin) in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality must always be reported to UCB as an AESI (ie, without waiting for any additional etiologic investigations to have been concluded).

6.2 Appendix 1: RBANS

To be added.

6.3 Appendix 2: mRS

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale runs from 0 (perfect health) to 6 (death).

Modified Rankin Scale

MODIFIED RANKIN SCALE (MRS)

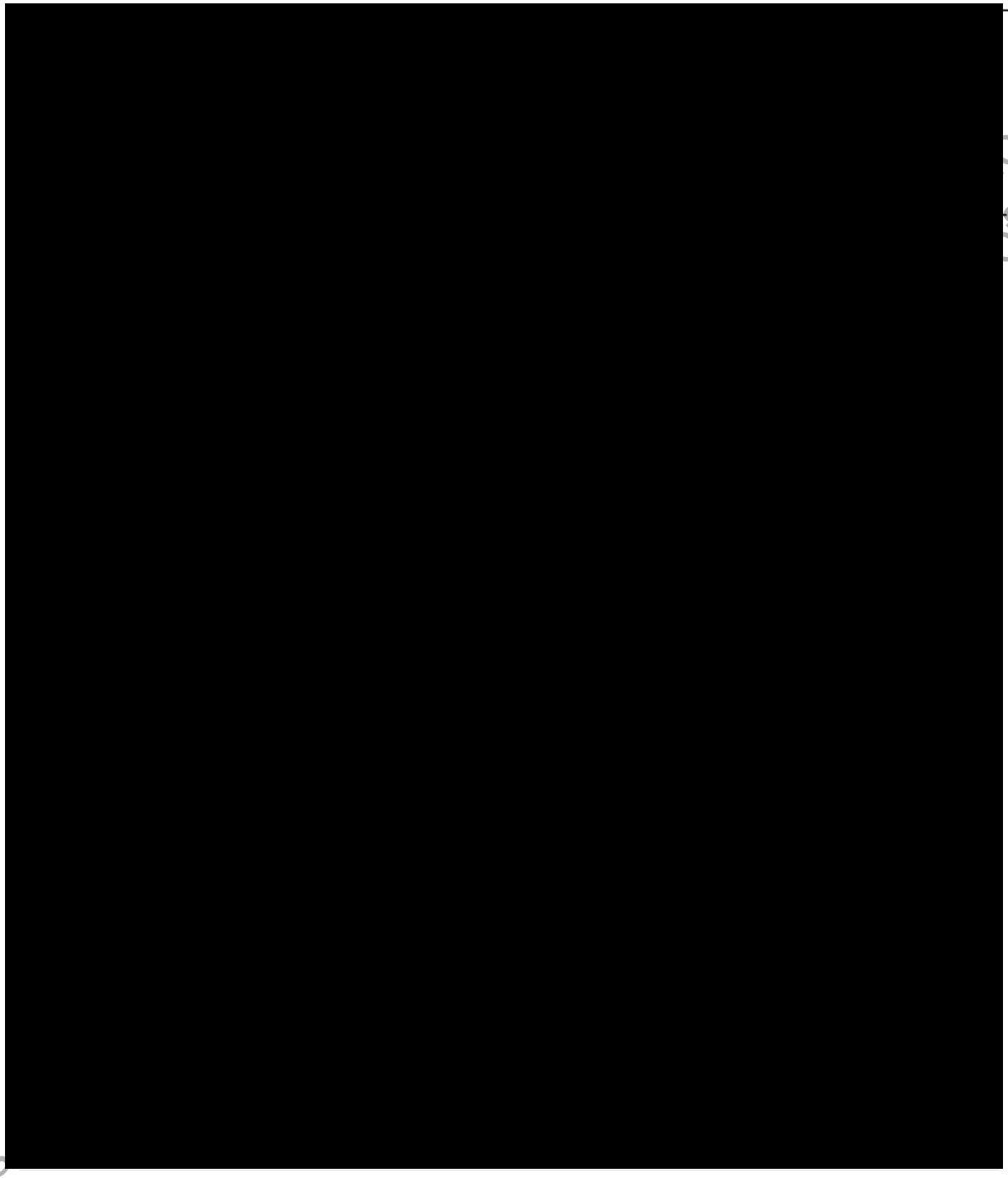
Patient Name: _____
Rater Name: _____
Date: _____

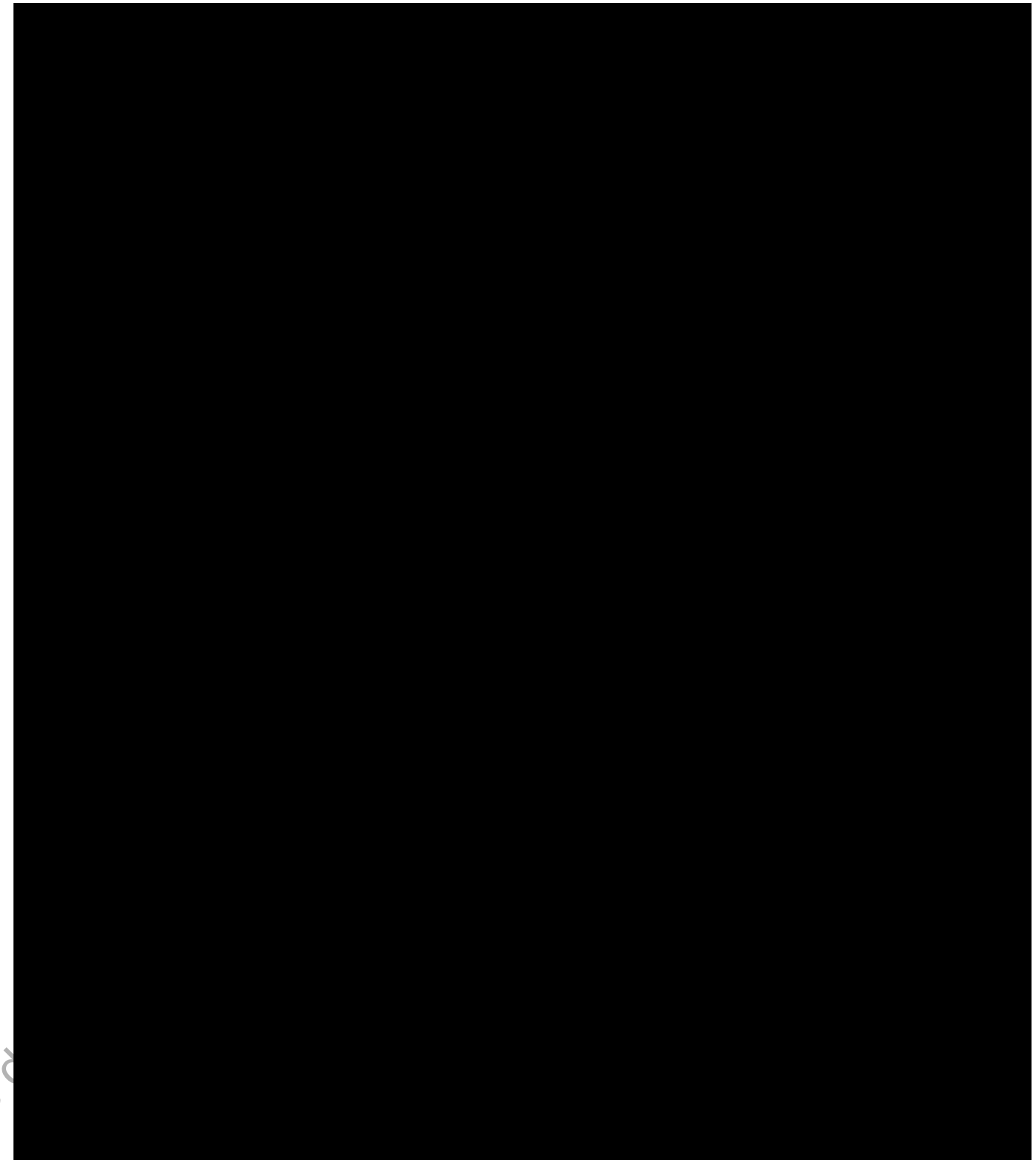
Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

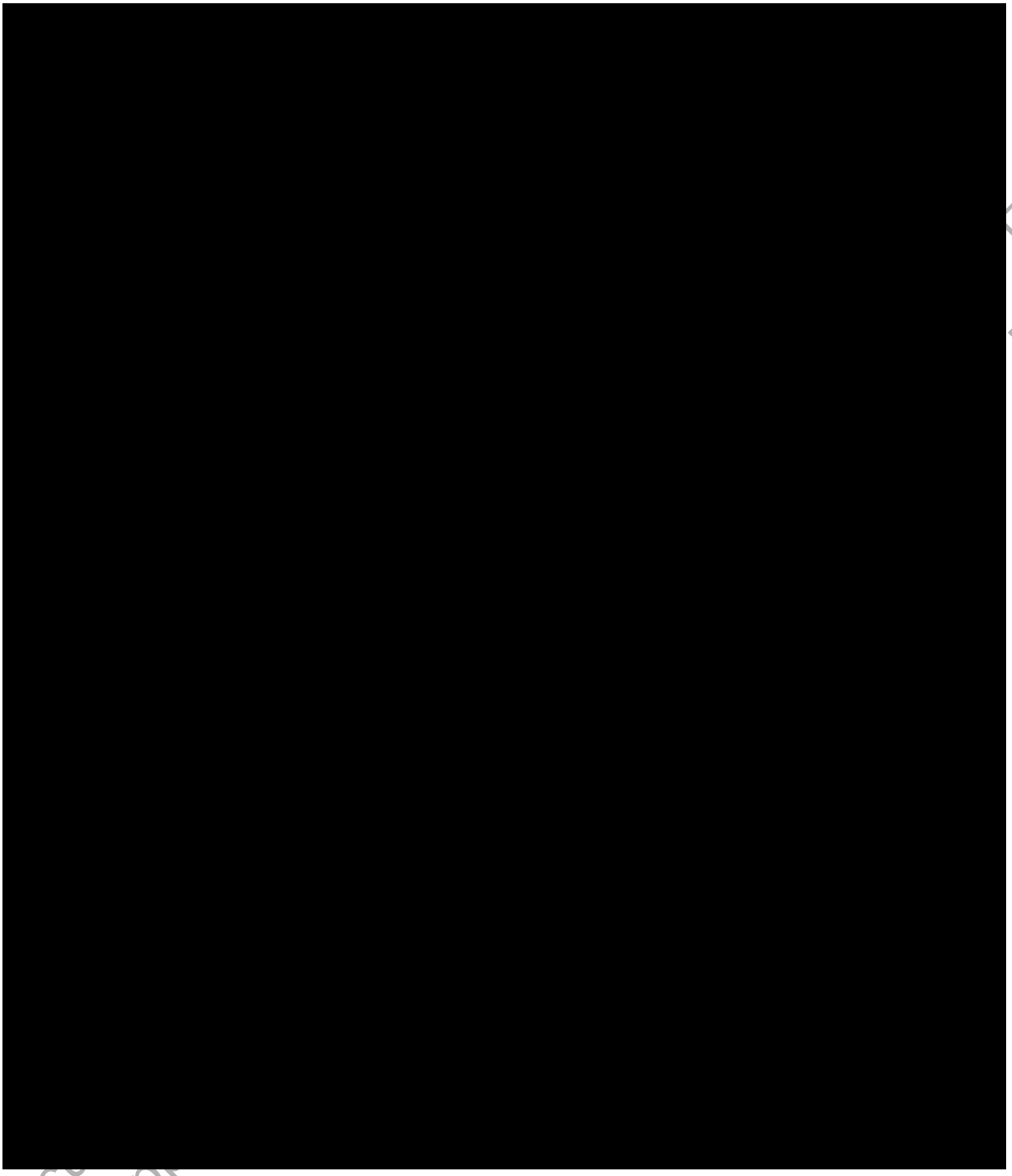
TOTAL (0–6): _____

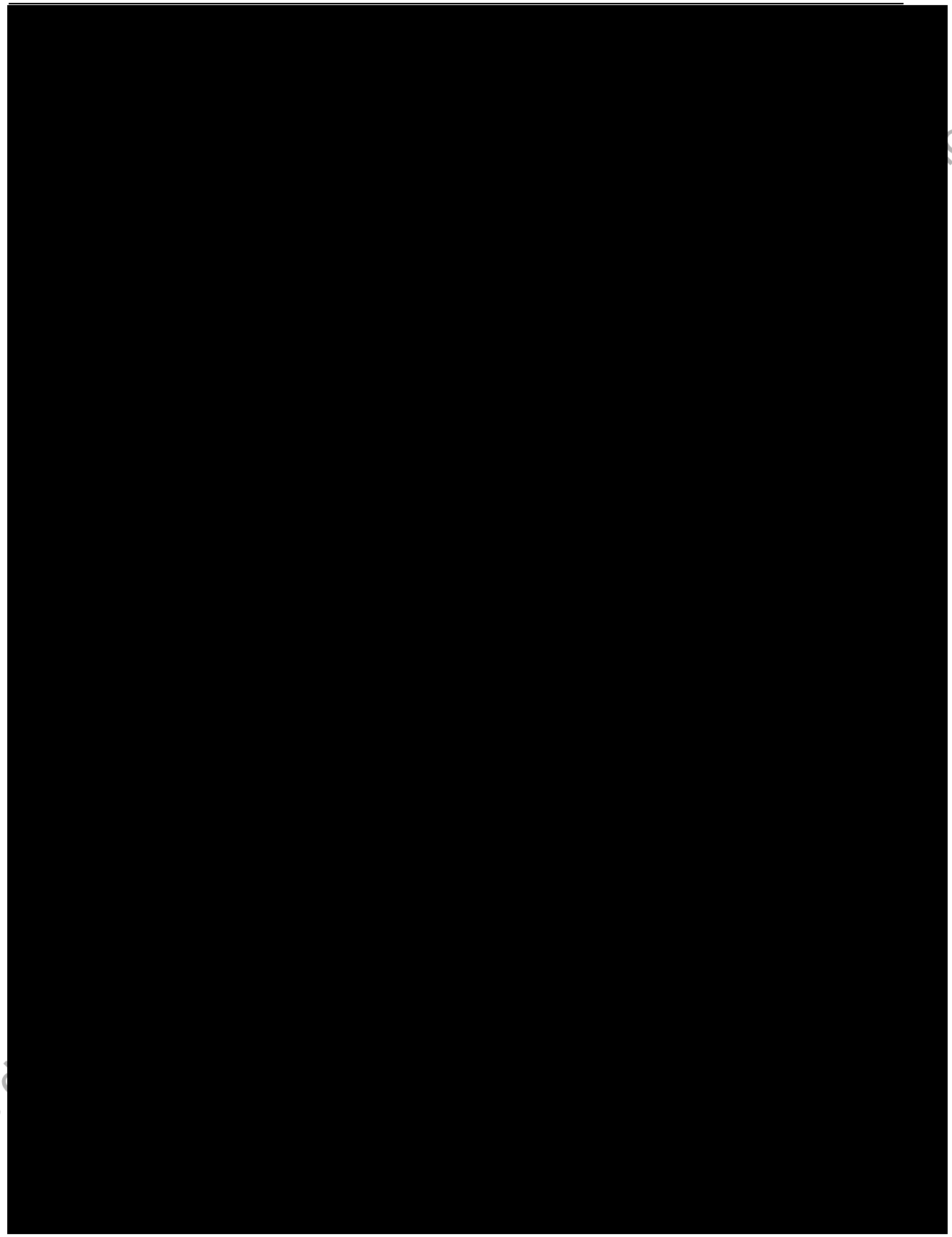
6.4 Appendix 3: Classification of the SF-36v2 questionnaire

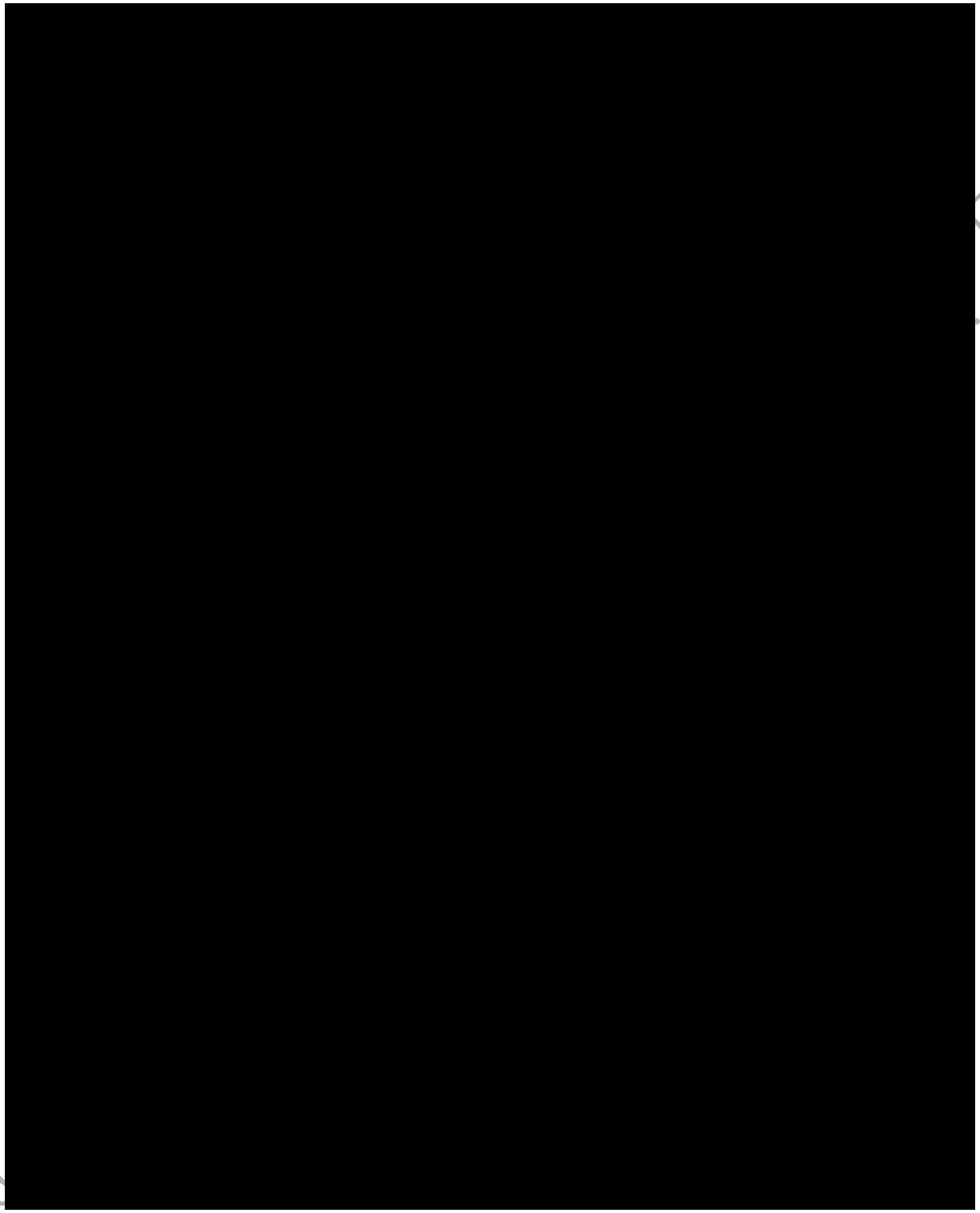
Table 6–3: SF-36v2® Health Survey Acute, United States

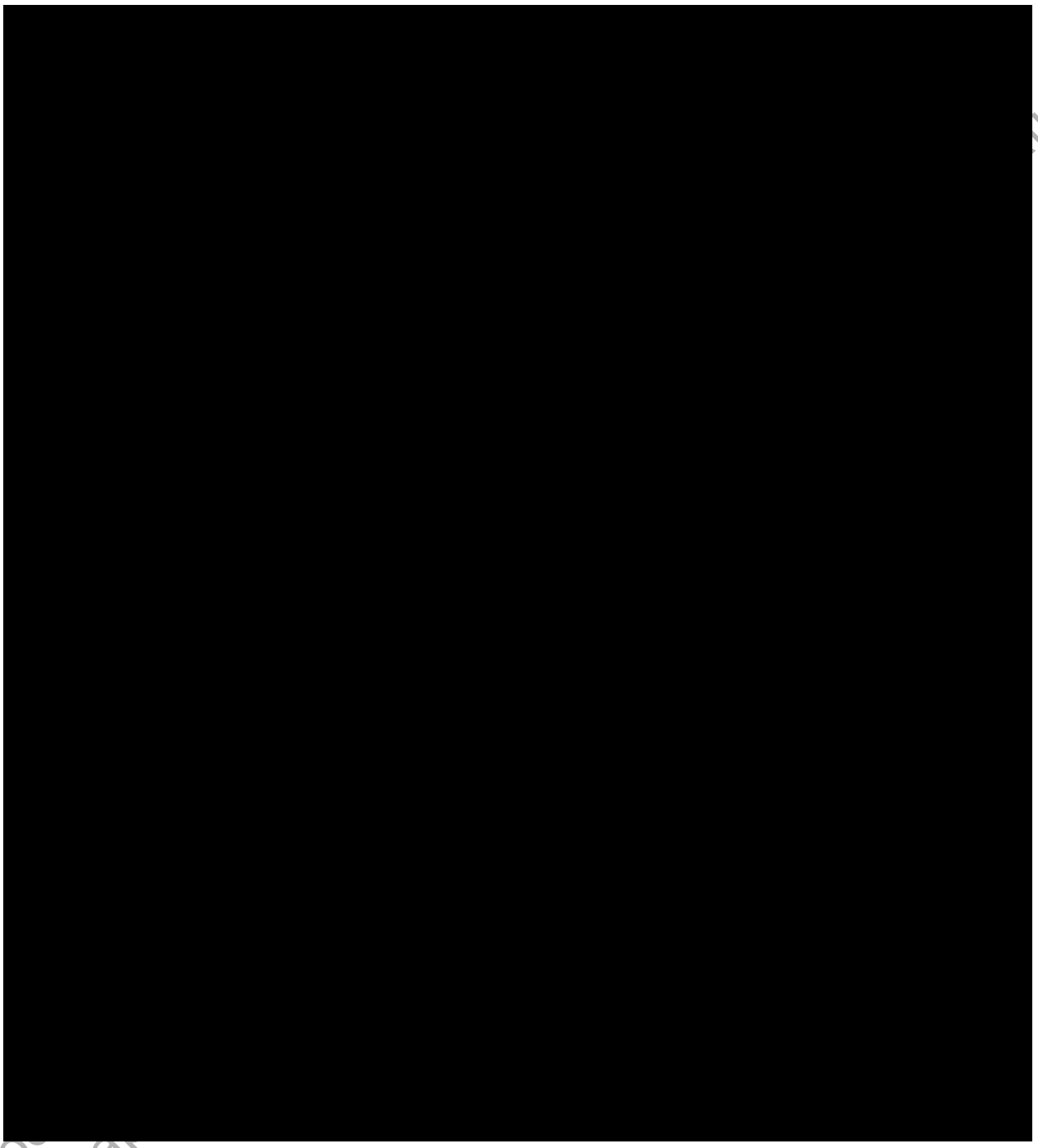












6.5 Appendix 4: Markedly abnormal criteria for Rozanolixizumab program

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 6–4: 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 6–5: Chemistry

Parameter	Unit (conventional)	Unit (standard)	Marked Abnormality Criteria
AST (SGOT)	U/L	U/L	>5.0 x ULN
ALT (SGPT)	U/L	U/L	>5.0 x ULN
ALP (Alkaline Phosphatase)	U/L	U/L	>5.0 x ULN
GGT (Gamma Glutamyl Transferase)	U/L	U/L	>5.0 x ULN
Bilirubin (Total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal; >3.0 x Baseline value if Baseline is abnormal
Albumin	g/dL	g/L	<2 g/dL; <20 g/L
Creatinine	mg/dL	umol/L	>3.0 x ULN
Estimate glomerular filtrate rate (eGFR)[1]	mL/min/1.73 m^2	mL/min/1.73 m^2	eGFR <29 mL/min/1.73 m^2
C reactive protein (CRP)[2]	mg/L	mg/L	>10 mg/L
Calcium	mg/dL	mmol/L	Low: Corrected serum calcium[3] of <7.0 mg/dL; <1.75 mmol/L

			High: Corrected serum calcium[3] of >12.5 mg/dL; >3.1 mmol/L
Immunoglobulin G[4]	(g/L)	(g/L)	≤1 g/L
Potassium	mmol/L	mmol/L	Low: <2.5 mmol/L
			High: >6.0 mmol/L
Sodium	mmol/L	mmol/L	Low: <125 mmol/L
			High: >155 mmol/L
Glucose[5]	mg/dL	mmol/L	Low: <40 mg/dL; <2.2 mmol/L
			High: > 250 mg/dL; >13.9 mmol/L
Total Cholesterol	mg/dL	mmol/L	>400 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-glutamyl transferase; L = liter; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal

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

[1]eGFR is calculated by 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/.

[3]corrected calcium will be calculated using the formular: corrected calcium (mmol/L) =0.02 * (40 – albumin (g/L)) + calcium(mmol/L); (40 because Normal albumin level is typically assumed to be equal to 40 g/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 6–6: Vital Signs

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

Table 6–7: Electrocardiogram

Parameter	Abnormality Criteria
QT interval (ms)	≥500ms
	≥60ms increase from Baseline

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

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

6.6 Appendix 6: Genetics

Biomarker analyses may evaluate genetic features and epigenetic changes associated with the cause, progression, and appropriate treatment of LGI1 AIE.

Use and Analysis of DNA

- Genetic variation may impact a participant's response to study medication, susceptibility to, and severity and progression of disease. Variable response to study medication may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- Deoxyribonucleic acid samples and exploratory biomarker samples will be used for research related to cause, progression, and appropriate treatment of LGI1 AIE. They may also be used to develop tests/assays including diagnostic tests related to rozanolixizumab and LGI1 AIE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- Deoxyribonucleic acid samples will be analyzed for genetic and epigenetic changes that may promote understanding of the cause, progression, and appropriate treatment of LGI1 AIE. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to the study medication to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on study medication continues but no longer than 20 years or other period as per local requirements.

6.7 Appendix 7: Changes to Protocol-Planned Analyses

Not applicable.

6.8 Appendix 8: Amendment(s) to the Statistical Analysis Plan

6.8.1 Amendment 1

Rationale for the amendment

This amendment is to apply following changes:

- Changes caused by Protocol Amendment 3, 4 and 5
- Incorporate the changes in the objectives relating to PK/PD in Protocol Amendment 6
- Reduce the scope of the analyses and data reporting planned for this study due to the fact that recruitment was terminated early, meaning that only a total of 12 participants were randomized to the study. This meant that it was not possible to carry out the extensive statistical analyses that had been planned.
- Minor cosmetic updates
- Incorporate the changes in the objectives relating to PK/PD in Protocol Amendment 6
- Reduce the scope of the analyses and data reporting planned for this study due to the fact that recruitment was terminated early, meaning that only a total of 12 participants were randomized to the study. This meant that it was not possible to carry out the extensive statistical analyses that had been planned.

Section # and Name	Description of Change	Brief Rationale
1 INTRODUCTION	Removed PiDMC Charter	Not relevant
1.1 Objectives and Endpoints	Removed Cytokines; Updated endpoint definition for the effect of rozanolixizumab on whole brain and hippocampal volume; Removed NF-L, α- and β- globulins, and MRI from Exploratory Endpoints; Moved mRS from Exploratory to Secondary Endpoints; Seizure reduction was replaced by seizure control as Exploratory Endpoint; CASE, ECG, AED plasma concentration, [redacted] and COVID-19 antibody were removed from Exploratory Endpoint; PGI-S and PGI-C were replaced by CGI-S.	To be consistent with Amendment 3, Amendment 4 and Amendment 5
1.2 Study Design	Text update and study schematic update	To be consistent with Protocol Amendment 3 and Protocol Amendment 5
3 Sample Size Determination	Text update	To be consistent with Protocol Amendment 5

Section # and Name	Description of Change	Brief Rationale
5 STATISTICAL ANALYSES	Removed COVID-19 related ICEs	The COVID-19 impact will be covered in exploratory analysis and protocol deviations.
5.1.1.1.5 Definition of Baseline values	Updated the definitions of mRS Baseline and removed CASE, added Baseline definition for safety assessments	To be consistent with Protocol Amendment 3 and Protocol Amendment 5
5.1.1.1.6 Calculation of Baseline Category of Seizure Count	Specified the calculation of Baseline median category of seizure count	To be consistent with Protocol Amendment 5
5.1.1.7 Multiple comparisons/multiplicity	Added hierarchical testing	To be consistent with Protocol Amendment 5
5.1.2 Rescue medication	Removed irrelevant text	For clarity
5.1.3 Missing Data Strategies for efficacy analyses	Added imputation method for intermittent missing daily seizure counts; Added analyses for secondary endpoint mRS and sensitivity analysis for time to event secondary #4 analysis; Added sensitivity analysis for Primary and Secondary Endpoint #1	For missing data imputation; To account for the informative censoring resulting from study participant withdrawals from the randomized treatment group
5.2 Participant Dispositions	Removed analysis by COVID-19 periods	Not relevant
5.3.1 Definition of endpoint	Text update	For clarity
5.3.2 Main Analytical Approach	Hypothesis Testing removed for primary endpoint	Not meaningful for small sample size
5.3.3.2 Sensitivity analysis #2	Removed the extended analysis with prior seizure freedom information	Data not collected
5.3.3.3 Sensitivity analysis #3	Added sensitivity analysis to account for existence of a prior undertreated AIE event	To understand the impact of existence of a prior undertreated AIE event
5.4.1 Change in cognitive function (RBANS)	Updated total score to total scale	To adjust for demographic factors
5.4.1.2.3 Sensitivity analysis #3	Added sensitivity analysis to account for existence of a prior undertreated AIE event	To understand the impact of existence of a prior undertreated AIE event
5.4.2 Change in overall disability: mRS	Added secondary analysis for mRS	To be consistent with Protocol Amendment 5
5.4.3 Use of rescue medication due to an absence or loss of clinical benefit	Removed Sensitivity Analysis for the use of rescue medication	To be consistent with Protocol Amendment 4
5.4.4 Time to first occurrence of seizure freedom (TTFSF)	Removed Sensitivity Analysis based on FAS	To be consistent with Protocol Amendment 4
5.4.4.2 Sensitivity analysis	Added a sensitivity analysis for time to first occurrence of seizure freedom	To account for the informative censoring resulting from study participant withdrawals from the randomized treatment group

Section # and Name	Description of Change	Brief Rationale
5.4.5 Hierarchical testing	Added hierarchical testing	To control the overall type I familywise error rate
5.5 Exploratory Endpoints Analyses	Removed analysis for NF-L, MRI, seizure reductions, Clinical Assessment Scale in Autoimmune Encephalitis and mRS; Added the analysis of seizure control; analysis for PGI-S and PGI-C were replaced by analysis for CGI-S	To be consistent with Protocol Amendment 4 and Protocol Amendment 5
5.5 Exploratory Endpoints	Time to seizure freedom maintenance, and ranked outcome from integrated score removed	Not meaningful for small sample size
5.5 Exploratory Endpoints	For SF-36 and EQ-5D-5L, only item responses listed, summaries not calculated	Summaries not meaningful for small sample size
5.5.2 Seizure reductions	Added imputation method for intermittent missing daily seizure counts	For missing data imputation
5.6.1 Extent of Exposure	Number of infusions received excluding mock infusions not summarized	Only listing excluding mock infusions is needed.
5.6.2.2 Adverse Events summaries	Most adverse events summaries have been removed	Summaries not needed for small sample size, all adverse events have been listed.
5.6.2.2 Adverse events summaries	Removed incidence of non-serious TEAEs above reporting threshold of 5% of participants by relationship; Updated AESM definition	The summary was already covered by other analyses; To be consistent with Rozanolixizumab program SAP
5.6.3.1 Clinical laboratory evaluations	Removed most laboratory summaries	Summaries not meaningful for small sample size; listings being retained.
5.6.3.2 Potential drug-induced liver injury (pDILI)	Updated laboratory criteria for pDILI	To be consistent with Rozanolixizumab program SAP
5.6.3.3 Vital signs	Removed most vital signs summaries	Summaries not meaningful for small sample size; listings being retained.
5.6.3.4 12-Lead Electrocardiograms (ECG)	The summary analysis for ECG were removed and only listing will be provided	To be consistent with Protocol Amendment 5
5.6.3.8 MRI	MRI listings removed	No meaningful data collected in study
5.6.3.10 Headache questionnaire	Summary of headache questionnaire was removed	Listing of headache is enough to present the data
5.7 Other Analyses	Analysis for plasma concentration of AEDs was removed	Plasma concentration will not be collected according to PA5

Section # and Name	Description of Change	Brief Rationale
5.7.1.1 Pharmacokinetics	All figures removed	Not meaningful for small sample size
5.7.1.3 ADA	Entire section remove	ADA and NAb samples not analyzed
5.7.1.4 Immunology	Removed analysis for cytokines and serum immunoglobulin concentration	To be consistent with Protocol Amendment 3 and Protocol Amendment 5
6.1 Non-key analysis specifications	AED was separated from prior/concomitant medication summaries	For better presentation of data
6.1.1.1 Demographics	Removed demographic by COVID-19 periods analysis	Not relevant
6.1.1.2 Baseline disease characteristics	Removed CASE and weekly seizure frequency; Added median category of seizure count; Removed table for historical seizures	To be consistent with Protocol Amendment 5
6.1.2 Protocol deviations	Removed protocol deviation summary by COVID-19 periods analysis	Not relevant
6.1.2 Protocol Deviations	Summary removed	Not meaningful for small sample size, listing retained
6.1.3 Medical History	Summary removed	Not meaningful for small sample size, listing retained
6.1.6.1.2 Dates and times	Updated the calculation rules for duration of AEs	To be consistent with other studies within Rozanolixizumab program
6 Supporting Documentation	Removed appendix for CASE	To be consistent with Protocol Amendment 5
6.5 Appendix 4: Markedly abnormal criteria for Rozanolixizumab program	Updated eGFR formula by removing race correcting factor	To be consistent with current scientific consensus
6.6 Appendix 5: AEs of focus for Rozanolixizumab program	Removed Section	Not Needed

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