STATISTICAL ANALYSIS PLAN

Study: FM0001

Product: Rozanolixizumab

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 2A, PROOF-OF-CONCEPT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ROZANOLIXIZUMAB TO TREAT ADULT STUDY PARTICIPANTS WITH SEVERE FIBROMYALGIA SYNDROME

SHORT TITLE:

A Phase 2A proof-of-concept study to evaluate the efficacy and safety of rozanolixizumab to treat adult study participants with severe fibromyalgia syndrome

Sponsor Name: UCB Biopharma SRL

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

Regulatory Agency Identifier Number(s):

Registry	ID
EudraCT Number:	2022-001523-32
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LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AESM	adverse event of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ALQ	above the limit of quantification
AST	aspartate aminotransferase
ASP	All Study Participants Set
BLQ	below the limit of quantification
BMI	body mass index
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
CV	coefficient of variation
DEM	Data Evaluation Meeting
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDV	Early Discontinuation Visit
EMA	European Medicines Agency
ePRO	electronic patient reported outcome
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIQR	Revised Fibromyalgia Impact Questionnaire
FMS	Fibromyalgia syndrome

geoCV	Geometric coefficient of variation
geoMean	Geometric mean
ICF	Informed Consent Form
ICH	International Council For Harmonisation
Ig	immunoglobulin
IGRA	Interferon-Gamma Release Assay
IMP	Investigational Medicinal Product
IPD	important protocol deviation
LLOQ	lower limit of quantification
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NI	Negative immunodepletion
NRS	Numeric rating scale
NS	Negative Screen
PD	Pharmacodynamic
pDILI	Potential drug-induced liver injury
PDS	Pharmacodynamic Set
PI	Positive immunodepletion
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PS	Positive Screen
PT	Preferred Term
PBO	Placebo
RLZ	Rozanolixizumab
RS	Randomized Set
QTcF	QT interval corrected using Fridericia's formula
QW	Once Weekly
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation

SOC	System Organ Class
SFU	Safety follow-up
SMC	Safety monitoring committee
SS	Safety Set
SS-r	Safety Set - as randomized
SS-t	Safety Set - as treated
SSD	Safety signal detection
TB	Tuberculosis
TFL	tables, figures and listings
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	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 required statistical analysis of study FM0001. The SAP summarizes what will be provided in the tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol, as well as defining the output to be generated for safety signal detection (SSD) and for the Early Readout Analysis. The TFL specifications are contained in a separate document and are based on the UCB Standard TFL Shells. The requirements for the Early Readout Analysis will be defined in the Unbinding Plan and the Safety Monitoring Committee (SMC) procedures will be defined in a separate charter.

Unless specified in the sections below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of primary or secondary endpoints must be modified or updated prior to unblinding, a SAP amendment will be required. If, after unblinding, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. Other minor changes to non-key analyses will also be documented in the CSR.

The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003).

1.1 Objectives and Endpoints

Objectives, endpoints and applicable estimands are described in Table 1-1 below.

Table 1-1: Objectives and Estimands/Endpoints

Objectives	Endpoints/Estimands
Primary	
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	Primary estimand (efficacy): • Treatment: rozanolixizumab 560 mg QW or Placebo QW • Target Population: study participants with severe FMS • Endpoint: BPI-SF average interference score after 12 weeks of double-blind treatment. • Intercurrent event handling: – The ICE discontinuation of treatment will be handled using a hypothetical strategy assuming that the study participants did not experience the events, with data following discontinuation excluded from analysis.

Table 1-1: Objectives and Estimands/Endpoints

Objectives	Endpoints/Estimands
	• Population level summary: mean difference in average BPI-SF interference score between the two treatments
Secondary	
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Occurrence of TEAEs during the study • TEAEs leading to withdrawal of IMP
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• BPI-SF average interference score after 24 weeks of treatment • FIQR score after 10 weeks of treatment • Mean 7-day average daily pain score (Pain NRS) after 12 weeks of treatment • Mean 7-day fatigue score (Fatigue NRS) after 12 weeks of treatment
Exploratory	
• To assess the PK of rozanolixizumab in study participants with severe FMS	• Plasma concentration of rozanolixizumab prior to dosing on Week 13 and Week 25
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• Pressure pain threshold as measured by pressure algesiometry
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Change from Baseline in vital signs and laboratory results at scheduled assessments during the Treatment Period through the Run-Out Period
• To evaluate the incidence and emergence of ADA of rozanolixizumab in study participants with severe FMS	• Antidrug antibody incidence at scheduled assessments during the Treatment Period
• To assess the PD effect of rozanolixizumab in study participants with severe FMS	• Value (absolute) and change from Baseline (absolute and percentage) in serum total IgG and IgG subclasses at scheduled assessments during the Treatment Period
• To assess the effect of rozanolixizumab on exploratory biomarkers in study participants with severe FMS	• Assessment of IgG binding in in vitro cell assay at scheduled assessments during the Treatment Period and the Run-Out Period • Assess genetic variation for potential effects on disease progression and/or drug

Table 1-1: Objectives and Estimands/Endpoints

Objectives	Endpoints/Estimands
	response and also any changes in epigenetics • Exploratory biomarkers may be measured to evaluate changes from Baseline in response to rozanolixizumab

1.2 Study Design

This is a Phase 2A, multi-center, randomized, double-blind, placebo-controlled, proof-of-concept study to evaluate the efficacy, safety, PK, and PD of rozanolixizumab for the treatment of severe FMS. Study participants who have a confirmed diagnosis of FMS and have been diagnosed for at least 6 months, with symptoms for at least 2 years before enrollment will be considered for the study.

Study participants enrolled under Protocol Amendments 1 and 2, must meet the following criteria during the Screening Period:

- BPI-SF interference score ≥6
- FIQR score ≥64
- Fatigue NRS score ≥5
- Completed a pain management program of at least 36 hours duration, completion must have been >6 months from study entry date
- Mean daily average 24h pain intensity ≥5 and <10 assessed by Pain NRS for at least 7 of the last 10 consecutive days of the Screening Period.
- Pain NRS scores ≥4 at all completed assessments in the last 10 consecutive days of the Screening Period.

Study participants enrolled under Protocol Amendment 3 must meet the following criteria during the Screening Period:

- BPI-SF interference score ≥6
- Mean daily average 24 hours pain intensity ≥6 and <10 assessed by Pain NRS. This will be assessed over a 10-day period within the Screening Period. Study participants require a minimum of 7 out of 10 assessments over the 10-day period.
- Pain NRS scores ≥4 at all completed assessments within the 10-day period.

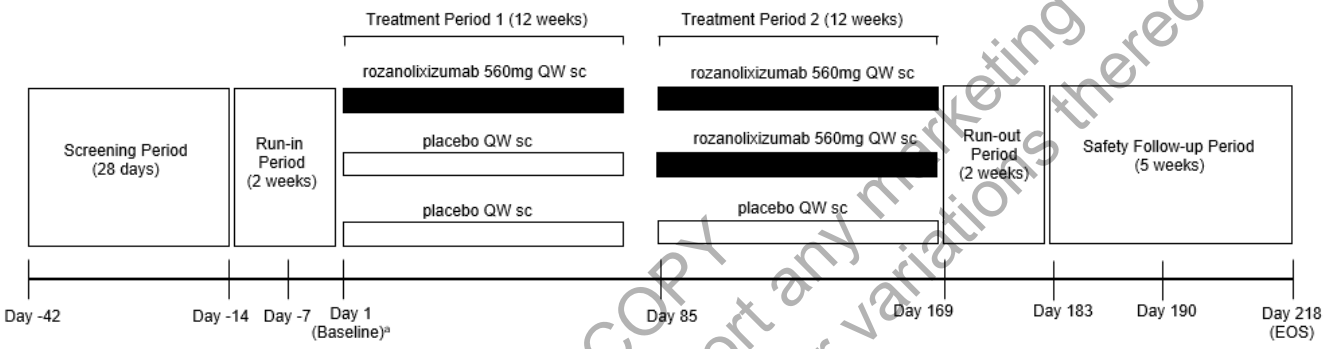
In total and allowing for a dropout rate of 25%, approximately 60 study participants are planned to be enrolled and randomized in the study at up to 8 centers from the UK, with a target of 48 study participants completing the study.

The study will consist of a Screening Period of up to 28 days, a 2-week, single-blind Run-In Period, 2 subsequent 12-week, double-blind Treatment Periods, followed by a 2-week, single-blind Run-Out Period and a 5-week SFU Period.

Study participants will be randomized in a 1:1:1 ratio to 1 of 3 sequences. The study participants in each sequence will receive the following treatment regimen during the double-blind Treatment Periods (see Figure 1-1):

- Sequence 1: Rozanolixizumab 560 mg sc QW for 24 weeks (12 + 12 weeks Treatment Period) (N=20, Group 1)
- Sequence 2: Placebo sc QW for 12 weeks, followed by rozanolixizumab 560 mg sc QW for 12 weeks (N=20, Group 2)
- Sequence 3: Placebo sc QW for 24 weeks (N=20, Group 3).

Figure 1-1: Study Schematic



[a] The baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1. This may be measured on Day 1 prior to treatment or during Weeks -1 or -2 depending on the endpoint.

EOS=end of study; QW=once weekly; sc=subcutaneous.
Note: All study participants receive placebo in a single-blind manner during the Run-In and Run-Out Periods.

The two 12-week period design allows for both intra- and inter-study participant comparisons. Sequence 2 allows for intra-study participant comparison of 12 weeks receiving placebo and 12 weeks receiving rozanolixizumab. Sequence 3, which has placebo throughout, enables adjustments for any period effects, and Sequence 1 Treatment Period 1 allows for inter-study participant comparisons with both Sequence 2 (Treatment Period 1) and Sequence 3 (Treatment Period 1 and Treatment Period 2).

In addition, comparing treatment effects after 24 weeks of treatment is possible through comparing the 24-week assessments from Sequence 1 and Sequence 3.

The initial 2-week Run-In Period and the final 2-week Run-Out Period will be study participant-blind, with study participants not informed that they are receiving placebo, to limit the impact of any start-of-study or end-of-study induced placebo effects. The two 12-week treatment periods will be study participant-, investigator-, and sponsor-blind. It is important that study participants do not know when their treatment changes, whether it is going from Run-In to Treatment Period 1, Treatment Period 1 to Treatment Period 2, or Treatment Period 2 to Run-Out.

The endpoint-specific Baseline definitions are summarized in Section 5.1.1.

For study participants enrolled under Protocol Amendments 1 and 2, the mean average daily pain over the previous 24 hours will be captured by the Pain NRS through a diary for at least 7 of the last 10 consecutive days of the Screening Period.

For study participants enrolled under Protocol Amendment 3, the daily average pain over the previous 24 hours will be captured using the Pain NRS through a diary over a 10-day period within the Screening Period. Study participants require a minimum of 7 out of the 10 daily Pain NRS assessments over this 10-day period to be eligible for randomization.

All recorded Pain NRS scores over the 10-day period within the Screening Period will be used to calculate the mean daily average 24 hours pain intensity score (for example, if 10 daily scores are available take the mean of the 10 days; if 9 daily scores are available take the mean of the 9 days and so on).

During the Run-In Period and at the end of the Treatment Periods, the Pain NRS will be collected at the assessment visit and for the 6 consecutive days following the visit, as described in the protocol. For all other visits, the average pain for the preceding 24 hours prior to the visit will be captured by the Pain NRS for that day only.

2 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing is planned in this study.

3 SAMPLE SIZE DETERMINATION

The operating characteristics of the design were evaluated using a simulation approach and based on estimates of variability and treatment effects from fibromyalgia studies reported in clinicaltrials.gov and other papers. BPI-SF was used consistently in duloxetine studies. A sample size of 48 completed study participants gives more than 80% probability that if the true difference of the mean BPI-SF interference score after 12 weeks of treatment on rozanolixizumab compared with placebo was 1.0 units or better, then the comparison would pass a 1-sided 10% significance test. This assumes a between-study participant standard deviation component for the BPI-SF interference score of 1.74 units, and a within-study participant SD of 1.5 units (a total between-study participant SD of 2.3 units) after accounting for the Baseline BPI-SF interference score. Through simulations of the design, it was estimated that 60 study participants starting the study would achieve the desired power, assuming a drop-out rate of 25%, and assuming a uniform distribution of drop-out timings. This accounts for the fact that drop-out participants contribute partial information up to the point of discontinuation and corresponds to an effective sample size of 48.

Simulations including the interim analysis were also conducted, and based on the impact on the operating characteristics, it was decided that no multiplicity adjustment was needed for the final analysis.

4 POPULATIONS FOR ANALYSIS

All Study Participants Set:

The All Study Participants Set (ASP) consists of all study participants that sign the informed consent form. This set includes screening failures.

Randomized Set:

The Randomized Set (RS) will consist of all participants randomized into the study.

Safety Set –as Randomized:

The Safety Set as randomized (SS-r) consists of all study participants who received any study treatment, including during the Run-In period. The study participants will be analyzed according to the randomized treatment groups during the specific treatment period.

The SS-r will be used for production of safety analysis by visit and demographic and immunogenicity analysis.

Safety Set – as Treated:

The Safety Set as treated (SS-t) consists of all study participants who received any study treatment, including during the Run-In period.

For analysis purposes, the SS-t is used only for tabulating AEs, as described in Section 5.6.25.6.2.

Full Analysis Set:

The Full Analysis Set (FAS) consists of all study participants in the SS-r who have a Baseline value and at least one post-Baseline efficacy endpoint assessment. Study participants who receive at least one dose of treatment not per randomization schedule will be excluded from the FAS.

This analysis set will be used for the summaries and analyses of primary, secondary, and exploratory efficacy variables data.

Pharmacokinetic Set:

The Pharmacokinetics Set (PKS) consists of all study participants in the SS-r who have at least one dose of active IMP and at least one measurable PK concentration, including below limit of quantification (BLQ) samples. The PKS will be used for all PK summaries and analyses. If a study participant in the PKS is missing individual time points or are otherwise unobservable, they will be included in the PKS but those time points will be omitted from the PK summaries, as appropriate.

Pharmacodynamic Set:

Pharmacodynamic set (PDS) is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PD variables, (as confirmed during a pre-analysis review of the data prior to unblinding), and who had at least one valid post-Baseline measurement of serum total IgG or IgG subclasses. The final PDS will be identified after unblinding to confirm availability of at least one post-baseline valid measurement due to blinding. PDS will be used for all PD summaries and analyses.

Participants who had important protocol deviations affecting the relevant efficacy/PK/PD variables, as confirmed during a pre-analysis review of the data prior to unblinding may be excluded from relevant analyses. Such exclusions will be agreed and documented prior to unblinding and will be described in TFLs and/or the CSR.

5 STATISTICAL ANALYSES

5.1 General Considerations

All tables, figures, and listings (TFLs), including statistical evaluation, will be produced by Veramed using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). Analysis data will adhere to Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the UCB interpretation.

Listings will be presented by study participant and planned treatment sequence. The presentation of tables and figures varies from variable to variable and will be specified in the respective section.

All tabulations will be performed per specified analysis set, visit and time point (where applicable). Details of planned tabulations will be described in the TFL shells. Data listings containing all documented data and all derived data will be generated.

1) Categorical Variables

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentage calculations will be based on the number of study participants in the respective analysis set, treatment sequence, treatment group, visit and time point (as applicable) with non-missing data. If there are any study participants with missing values for a categorical variable, an additional row displaying the number of study participants with missing data will be added.

2) Continuous Variables

Summary statistics will be presented for continuous variables including number of participants (n), mean, standard deviation (SD), median, minimum and maximum. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of PK concentration data. The 25th and 75th percentiles (Q1 and Q3) will be included for descriptive statistics of ePRO data.

When reporting descriptive statistics, the following rules will apply:

- Mean (arithmetic and geometric), SD, Q1, Q3, and median will use 1 decimal place more, or 1 significant figure more than the original data
- Confidence intervals will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the value around which the confidence interval is constructed
- Coefficient of variation (CV) will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value
- If no participants have data at a given time point, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, minimum, mean, median and maximum will be presented. The other descriptive statistics will be left blank.

5.1.1 General Study Level Definitions

5.1.1.1 Study and Period Day

Study day for an event or measurement occurring before the date of the first dose of Treatment Period 1 will be calculated as follows:

Study Day=Event/Measurement Date−Date of First Dose

Study day for an event or measurement occurring on the date of the first dose of Treatment Period 1 is 1. Study day for an event or measurement occurring on or after the date of the first dose to the date of the last dose including Run-Out period will be calculated as follows:

Study Day = (Event/Measurement Date−Date of First Dose) + 1

For events or measurements occurring after the date of the last dose including Run-Out period study day will be prefixed with '+' in the data listings and will be calculated as follows:

Study Day = + (Event/Measurement Date−Date of Last Dose of the study)

Period day for an event or measurement occurring on the date of the first dose in a Treatment Period is 1. Period day for an event or measurement occurring on or after the date of the first dose to the day before the date of the first dose in the following Treatment Period will be calculated as follows:

Period Day = (Event/Measurement Date−Date of First Dose in a Treatment Period) + 1

There is no Study Day 0. For the purpose of the study participant data listings, study day or period day will not be calculated if the event/measurement date is partial. Instead, study day or period day will be presented as '--'in the relevant participant data listing. Table 5-1 below describe the ranges of study and period days during the study.

Table 5-1: Study days and periods

	Screening & Run-In	Treatment Period 1	Treatment Period 2	Run-Out Period	Safety FU Period
	Day-42 to Day -1	Day 1 to Day 84	Day 85 to Day 168	Day 169 to Day 182	Day 183 to Day 218
Study Day	-42 to -1	1 to 84	85-168	169-182	+1 to +35
Period Day		1 to 84	1 to 84		

5.1.1.2 Study Periods

The maximum study duration per study participant will be 37 weeks.

- Screening Period (Day -42 to Day -15): Eligibility will be assessed during the Screening Period of up to 28 days
- Run-In Period (Day -14 to Day -1): Study participants who have been confirmed eligible to participate in the study will be randomized 1:1:1 to study treatment. During the 2-week Run-In Period, all study participants will receive placebo sc QW and will be blinded to this treatment.

- Treatment Period 1 (Day 1 to Day 84): Study participants will receive their randomized treatments for the first 12-week Treatment Period.
- Treatment Period 2 (Day 85 to Day 168): Study participants will receive their randomized treatments for the second 12-week Treatment Period.
- Run-Out Period (Day 169 to Day 182): At the end of both 12-week Treatment Periods, all study participants will receive placebo sc QW during a 2-week Run-Out Period and will be blinded to this treatment.
- Safety Follow-up Period (SFU, Day 183 to Day 218): Study participants who complete both Treatment Periods and Run-Out Period will enter the 5-week SFU Period.
- Study participants who permanently discontinue IMP are encouraged to complete the EOT/EW Visit and the SFU/End of Study (EOS) Visit. In these cases, the SFU will not take place between study Day 183 to Day 218.
- Safety analysis will include periods from Run-In through end of SFU period. Efficacy, PK and PD analysis will include data collected from Treatment Period 1 to end of SFU Period.

Efficacy, PK and PD measurements collected post-Baseline and up to and including Visit 15 will be allocated to Treatment Period 1. Efficacy, PK and PD measurements collected after Visit 15 and up to and including Visit 27 will be allocated to Treatment Period 2.

For the purposes of analysis, data including AEs, IPDs, and medications will be assigned a study period using the rules summarized in Appendix 4 Section 8.4.

5.1.1.3 Definition of Baseline Values

Endpoint-specific Baseline definitions are presented in Table 5-2. Scheduled or unscheduled measurements may be used as the Baseline value. If a measurement is missing or repeated at Baseline, and is obtained prior to the first dose of IMP in the Run-In Period/at Day 1 (dependent upon the endpoint), then the last available measurement will be used as the Baseline value. In rare circumstances the latest observation may be a data point collected at an unscheduled visit - such an observation would also be allowable as Baseline value.

Table 5-2: Definition of Baseline

Endpoint	Definition of Baseline
Hematology, serum chemistry, urinalysis, vital signs	Baseline is defined as the most recent value obtained prior to the first dose of IMP in the Run-In Period, or Screening if this is missing.
Efficacy	Baseline is defined as the measurements on Day 1 (Visit 3, Week 1) prior to administration of treatment or during Run-In Period depending on the endpoint: • For BPI-SF, the Baseline measurement is at Day 1 (Visit 3, Week 1). If Day 1 measurement is missing, then the Screening measurement will be used. • For Pain NRS, and Fatigue NRS, the Baseline measurement will be the average of the 7 days prior to Day 1 (Visit 3, Week 1), not including Day 1 data. If there are <3 assessments available within the 7 days, the Baseline measurement will be missing. • For FIQR, the Baseline will be the last assessment before Day 1. This is Day -7 (Visit 2, Week -1) or Screening visit if Day-7 is missing. Note that for all endpoints listed above, if a dose of study medication was not received at Visit 3, but the efficacy assessment was performed at Visit 3 (or Visit 2 for FIQR), the Baseline assessment would be defined as above.
Pharmacodynamics (PD)	Baseline is defined as the latest non-missing assessment performed prior to dosing on Day 1 (Visit 3, Week 1). If Day 1 measurement is missing, the Run-In (Visit 1, Week -2) measurement will be used. Note that if a dose of study medication was not received at Visit 3, but the PD assessment was performed at Visit 3, this would still be used as the Baseline assessment.
Pressure Pain Threshold	Baseline is defined as the average of the three assessments performed per site, prior to dosing on Day 1 (Visit 3, Week 1). Note that if a dose of study medication was not received at Visit 3, but the Pressure Pain Threshold assessment was performed at Visit 3, this assessment would still be used as the Baseline assessment.
Anti-drug antibody (ADA)	Baseline is defined as the last measurement prior to receiving the first dose of rozanolixizumab. For participants randomized to Sequence 1, Baseline is the Day 1 (Visit 3, Week 1) pre-dose assessment, or Day -7 (Visit 1, Week -1), if missing. For participants randomized to Sequence 2, Baseline is the Day 85 (Visit 15, Week 13) pre-dose assessment, or Day 1 (Week 3, Visit 1), if missing. Note that if a dose of study medication was not received at Visit 3, or Visit 15 (dependent upon the participant), but the ADA assessment was performed at Visit 3 or Visit 15, this assessment would still be used as the Baseline assessment.

5.1.1.4 Treatment Assignment and Treatment Group

Table 5-3: Treatment Group Descriptions

Treatment groups	Full Description	Data Display Description	Included data
1	Placebo	PBO	Sequence 2, Treatment Period 1, and Sequence 3, both Treatment Periods
2	Rozanolixizumab exposure up to12 weeks	RLZ 12 weeks	Sequence 1, Treatment Period 1, and Sequence 2, Treatment Period 2
3	Rozanolixizumab extended exposure from 12 to 24 weeks	RLZ 24 weeks	Sequence 1, Treatment Period 2

Table 5-4: Sequence Descriptions

Sequences	Full Description	Data Display Description
1	Sequence 1: Rozanolixizumab 12 weeks in Treatment Period 1, rozanolixizumab 12 weeks in Treatment Period 2	Seq1: RLZ 12w +RLZ 12w
2	Sequence 2: Placebo in Treatment Period 1, rozanolixizumab 12 weeks in Treatment Period 2	Seq2: PBO+RLZ 12w
3	Sequence 3: Placebo in Treatment Period 1 and Treatment Period 2	Seq3: PBO+PBO

Table 5-5: Period descriptions

Periods	Full Description	Data Display Description
	Pre-Screening	Pre-Screening
0	Screening (Day -42 to Day -15)	Screening
1	Run-In (Day -14 to Day -1)	Run-In
2	Treatment Period 1 (Day 1 to Day 84)	TP1
3	Treatment Period 2 (Day 85 to Day 168)	TP2
4	Run-Out (Day 169 to Day 182)	Run-Out
5	Safety follow-up (Day 183 to Day 218, note that if a participant withdraws prior to this point SFU will not take place between Day 183 and 218)	SFU

5.1.2 Changes to Protocol-Defined Analyses

According to the protocol, the Baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1 (Visit 3, Week 1). However, this rule is specific to

efficacy endpoint assessments only. For safety variables the Baseline will be the most recent value prior to the first dose in the Run-In period. The Baseline definitions for all endpoints are summarized in Section 5.1.1.3.

According to the protocol, the mean 7-day pain and fatigue scores after 10 weeks of treatment will be used for the secondary efficacy endpoint analysis. However, it has been clarified in the SAP that this is based on 12 weeks of treatment (Visits 3-14 in Treatment Period 1, and Visits 15-26 in Treatment Period 2).

Per the protocol, as a secondary analysis strategy, dropouts will be imputed as if they belong to the placebo group, under the conservative assumptions that dropouts are due to a lack of drug efficacy. This analysis will not be produced for the CSR.

5.1.3 Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data (primary or key secondary outcomes) or that may significantly affect a participant's rights, safety, or well-being.

The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

Important protocol deviations will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Treatment non-compliance
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning and data evaluation process. All protocol deviations will be discussed at data cleaning meetings for identification of individual IPDs and will be classified by the deviation types in the IPD document. IPDs identified at the data cleaning meetings will be listed by planned treatment sequence for the RS and will include the period of onset, deviation type and description. The period of onset of IPDs is derived per the rules stated in Appendix 4 Section 8.4. All IPDs will be summarized by treatment group and period.

At least one Data Evaluation Meeting (DEM) will be performed prior to unblinding for the Early Readout Analysis. During this meeting, attendees will decide whether any study participants or data should be excluded from any of the analysis sets. A final DEM will be performed prior to database lock to confirm the analysis sets prior to the final analysis. The exclusion of any participants and the rationale will be clearly documented within the relevant TFLs.

5.1.3.1 COVID-19 Related Protocol Deviations

UCB guidance on deviations and amendments related to SARS-CoV2 pandemic states that the identified COVID-19 related protocol deviations need to be reviewed on an ongoing basis in case they collectively or individually may give reason to consider a protocol amendment (for example study design changes or changes to primary analysis methods etc.).

Additionally, at data cleaning meetings and DEMs, entries on COVID-19 impact pages will be reviewed and assessed whether they are also IPDs. In this case, the COVID impacts will be queried to be reported on the protocol deviation log document.

5.1.4 Handling of Dropouts or Missing Data

Unless otherwise specified, there will be no imputation of missing data.

For Pain and Fatigue NRS, the 7-day average scores will be calculated based on available data. If there are any missing records in the 7-day periods (inclusive of the assessment visit and the following 6 days), the scores will be calculated as the average amongst the recorded scores, ignoring the missing data. A minimum of 3 completed scores are required to calculate the average; otherwise, the average will be treated as missing. Missing data from visits associated with single assessments will not be imputed.

For details regarding PK data, see Section 5.5.1.

Handling missing or partial missing date and time described in Appendix 2, Section 8.2.

5.1.5 Handling Repeated and Unscheduled Measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than one measurement at the same time point. Unscheduled and repeated measurements will not be used in the descriptive statistics unless otherwise specified.

Assessments performed at the Early Withdrawal (EW) visit and which are within the protocol defined window of a scheduled visit will be assigned to that scheduled visit, and summarized accordingly. If any such data are already recorded at the given scheduled visit, data from the EW visit will not be re-mapped. Data will be re-mapped on a 'per assessment' basis where assessments are grouped as follows:

- All hematology assessments
- All clinical chemistry assessments
- All urinalysis assessments
- Vital signs assessments; systolic blood pressure, diastolic blood pressure, pulse rate and temperature)
  - Re-mapped vital signs assessments will be mapped to the pre-dose time point only.
- Height and weight
- All IgG assessments (total and subclasses)

The grouping above defines which measurements will be retained together for any re-mapping. An individual parameter would not be re-mapped in isolation of the other parameters performed at the EW visit. For example, a measurement of diastolic blood pressure would only be re-mapped together with the other vital signs assessments performed at the EW visit. If at least one data point is already available at the respective scheduled visit (eg, systolic blood pressure), the data at the EW will not be re-mapped.

Re-mapped EW visit data will be displayed in the by visit summary tables only if the assessment was planned for the particular visit.

Assessments performed at the EW visit which are not within the protocol defined window of a scheduled visit will not be mapped to a scheduled visit and will be listed only.

5.1.6 Center Pooling Strategy

The data from different centers will be pooled for TFLs.

5.1.7 Coding Dictionaries

Adverse events and medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 24.1). Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) Global B3 (Version 1 Mar 2021). Medical procedures will not be coded.

5.2 Study Population Characteristics

5.2.1 Participant Disposition

Study participant disposition will be listed by planned treatment sequence for the ASP and will include the following information: study participant status (screen failure, completed or discontinued), date of informed consent, date of randomization, date and time of first and last dose of IMP (including during Run-In and Run-Out Periods), date of premature study termination (if applicable), and primary reason for study termination (if applicable). The listing will also include the date and reason for breaking the randomization code (if applicable) as well as the date of final contact for each study participant.

Study discontinuations will be listed by planned treatment sequence for the RS and will include the reason for discontinuation and the period in which the participant discontinued. The period of discontinuation is derived as follows:

- If a participant receives a dose of IMP in the Run-In Period and withdraws prior to the first dose of IMP in Treatment Period 1, then the period of discontinuation is Run-In.
- If a participant withdraws after starting Treatment Period 1 (defined as receiving a dose of IMP during Treatment Period 1) and prior to receiving a dose of IMP in Treatment Period 2 or attending one or more visits between Visit 16 and 26, the period of discontinuation is Treatment Period 1.
- If a participant withdraws after starting Treatment Period 2 (defined as receiving a dose of IMP during Treatment Period 2 or attending one or more visits between Visit 16 and 26) and prior to receiving a dose of IMP in Run-Out, the period of discontinuation is Treatment Period 2.
- If a participant withdraws after starting Run-Out (defined as receiving a dose of IMP during Run-Out, or attending Visit 27 or Visit 28), and did not attend the end of treatment (EOT) visit, the period of discontinuation is Run-Out.

The study discontinuation listing will also include the total number of days on study medication, calculated in the following way:

Total days on study medication = Date of the last dose of study medication (including Run-Out)– date of the first dose in the Run-In Period +1 day

In addition, there will be separate listings for re-screened study participants, of participants who did not meet eligibility criteria, and of visit dates.

Study participant disposition will be shown in tables. The number of participants who screened, the number of screen failures, and reasons for screen failure will be summarized overall (note: re-screened subjects will only be counted once). Additionally, the number of participants who completed the study, the number of participants who discontinued, and reasons for discontinuation of study will be summarized overall and by (planned) treatment sequence and period. The percentages for discontinuation will be calculated based on the number of participants that started each period.

Study participant disposition will also be summarized by site and investigators using the ASP, showing first participant in, last participant out, the number of participants screened, and the number and percentage of study participants included in each of the RS, SS-r, SS-t, FAS, PKS and PDS, overall and for each planned treatment sequence.

Discontinuation due to AEs and the disposition of analysis sets will also be tabulated.

5.2.2 Impact of COVID-19 on Study Visits

A listing of visits impacted by COVID-19 will be presented for all participants based on the ASP. This will include visit, visit date, study day, impact category, relationship to COVID-19 and the narrative of the event. Participants who discontinue treatment or stop study participation due to COVID-19 pandemic will be included in participant disposition summaries.

The number and percentage of participants with visits impacted by COVID-19 for any reason will be summarized by planned treatment sequence and impact category (overall and for each category separately). The denominator for the percentages will be the number of participants in the RS.

5.3 Demographics and Other Baseline Characteristics

5.3.1 Demographics

All demographic characteristics will be summarized for the FAS and RS by treatment sequence and overall. The following continuous variables will be summarized using descriptive statistics:

- Age at Screening (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Body mass index in kg/m^2 will be calculated based on the height (in m) and the weight (in kg) using the following formula:

BMI (kg/m^2) = weight (kg)/[height (m)]^2

The following categorical variables will be summarized using frequency counts and percentages:

- Age (18-<65, 65-<85, ≥85 years) based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting
- Age (≤18, 19-<65, ≥65 years) based on requirements for clinicaltrials.gov reporting
- Weight (<100kg, >=100kg)
- BMI (<30 kg/m^2 and ≥30 kg/m^2)
- Gender
- Race
- Ethnicity
- Country

A listing of demographics by study participant and planned treatment sequence will be presented for the ASP. This will include participant ID, the year of birth, country, age at Screening (in years), gender, race, ethnicity, height (cm), weight (kg) and body mass index (BMI) at Screening.

5.3.2 Other Baseline Characteristics

Descriptive statistics of BPI-SF Interference, Fatigue and Pain NRS and FIQR Baseline scores will be summarized by planned treatment sequence. Additionally, time (year) since diagnosis and time (year) since first symptoms of FMS based on the Screening date will be summarized in years using the SS-r (see Appendix 2 Section 8.2.4 for details on how to handle partial dates). Time since diagnosis and time since first symptoms of FMS will also be listed.

5.3.3 Medical History

Medical history and ongoing medical conditions will be listed for the RS and summarized for the SS-r by planned treatment sequence and overall, MedDRA system organ class (SOC) and preferred term (PT). The reported term will be included in the listing. The summary will include the number and percentage of study participants and will be sorted alphabetically by SOC, High Level Group Term (HLGT) and, within HLGT, by descending incidence of PT, based on the 'All Participants' column. Family medical history collected for PDILI events will be listed.

5.3.4 History of Headache

A listing of the history of headache responses will be presented by planned treatment sequence for the SS-r.

5.3.5 Medical History on Pain Management Programs

A by participant listing of the information collected on the medical history of pain management programs electronic case report form (eCRF) will be presented by planned treatment sequence for the SS-r.

5.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be classified in the below categories. Past medications are a subset of prior medications.

Prior medications include medications that started prior to the first dose of IMP in Run-In. This includes Pre-Screening medications which are received prior to the date of Screening and includes any medications that started prior to dosing in Run-In and continued after the first dose in Run-In (prior and concomitant).

Concomitant medications include any medications that have been taken at least once on or after the date of first administration of IMP in Run-In. Permitted concomitant medications are limited to those listed in Section 6.5.1 of the protocol.

Based on the above definitions a medication may be considered as both prior and concomitant.

Prior and concomitant medications will be listed for the SS-r by planned treatment sequence and will include WHO-DD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text], PT and reported term where applicable. All periods for which medication was received will be included in the listing. Periods are assigned based on whether a participant entered the given period. Full details of the rules for period assignment are described in Appendix 4 Section 8.4.2

Prior medications will be summarized by planned treatment sequence for the SS-r and will include WHO-DD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. This table will include all medications that started and stopped prior to the first dose of IMP in Run-In and medications that started prior to and continued after the first dose of IMP in Run-In.

Concomitant medications will be summarized by treatment group and period for the SS-r and will also include WHO-DD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT.

5.3.7 Prior and Concomitant Medical Procedures

Prior and concomitant medical procedures will be classified in the below categories.

Prior medical procedures are defined as procedures occurring prior to the date of informed consent.

Concomitant medical procedures are defined as procedures occurring on or after the date of informed consent.

Prior and concomitant medical procedures will be listed only. The listing will contain the date of procedure and the period of onset. For the purpose of assigning the medical procedure to a category and to define the period of onset, partial and missing start dates will be imputed based on the rules defined in Appendix 2 Section 8.2.3. Medical procedures will be assigned to a period based on the date of the procedure.

5.4 Measurements of Treatment Compliance

As dosing is performed in-house by the investigator or member of staff, no specific assessment of compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR.

5.5 Pharmacokinetics and Pharmacodynamics

5.5.1 Pharmacokinetics

All pharmacokinetic summaries will be presented using the PKS and listings will be presented based on the SS-r. PK samples from study participants on placebo will not be analyzed. Consequently, participants randomized to Sequence 3 will be excluded from the analyses described in this section and will not be included in TFLs. PK samples taken prior to the intended dose will be associated with the relevant dose for the purpose of tables and analyses. Samples taken after intended dose will be excluded from the analysis.

The listing of plasma concentrations will include treatment sequence, visit, actual blood sampling time (presented as time relative to the start time of dosing of the respective visit), scheduled sampling time, and days since the previous dose.

The plasma concentrations of rozanolixizumab at each scheduled assessment will be summarized by treatment group and period using descriptive statistics and presented in the form of table and figures. In addition, individual plasma concentrations will be shown in a figure by participant and actual time since the time of first active dose.

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

- Values below the LLOQ will be reported as BLQ.
- Descriptive statistics of concentrations will be calculated if at least 2/3 of the concentrations are quantified at the respective time point.
- Values that are BLQ will be replaced by the numerical value of the LLOQ/2 (0.1ug/mL).
- The 95% CI lower and 95% CI upper will be left blank if the SD (or equivalently, the geoCV) is 0
- The geometric coefficient of variation (CV) is calculated as sqrt (exp(std ln^2)-1)*100, where std ln is the standard deviation of the log-transformed data.

5.5.2 Pharmacodynamics

Venous blood samples will be collected for measurement of total serum IgG and subclass IgG concentrations as PD assessments. The observed concentration, change and percent change from Baseline in total serum IgG and IgG subclasses will be listed. The listings will also report the maximum change and maximum percent change from Baseline in each Treatment Period, based on the maximum decrease or smallest increase if no decrease is observed.

The observed concentration, change and percent change from Baseline, and maximum change and percent change, in total serum IgG and IgG subclasses will be summarized for each planned treatment sequence on the PDS.

The observed concentration, change and percent change from Baseline in total serum IgG and IgG subclasses will be summarized by each assessment for each treatment group on the PDS. There will be three treatment groups: placebo, rozanolixizumab for up to 12 weeks [Sequence 1, Period 1 and Sequence 2, Period 2], or rozanolixizumab given beyond 12 weeks [Sequence 1, Period 2].

The observed concentration and percent change from Baseline in Total IgG will be summarized by each visit by planned treatment sequence and Baseline body weight categories (<100kg, and >=100kg).

The observed Baseline Total IgG, and the maximum percent change from Baseline for each Treatment Period will be summarized by planned treatment sequence and the Baseline body weight categories (<100kg, and >=100kg).

For the purpose of calculating change from baseline or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLOQ).

Median percent change from Baseline values in Total IgG will be plotted against study week for the entire study duration, by planned treatment sequence.

Median percent change from Baseline values in Total IgG will be plotted against assessment number (1-4 within the given treatment period), by treatment group.

Median percent change from Baseline in total IgG will be plotted against study week for the entire study duration, by planned treatment sequence and Baseline body weight categories (<100kg, and >=100kg).

Spaghetti plots will be provided for Total IgG and percent change from Baseline in Total IgG over time stratified by treatment sequence.

For correlation analysis between clinical endpoints and PD data, scatterplots including regression lines and Pearson correlation coefficients will be provided for change and percent change from Baseline at Visit 15 (or Visit 27) in total IgG versus:

- Change from Baseline at Visit 15 and Visit 27 in BPI-SF interference.
- Change from Baseline at Visit 13 and Visit 25 for FIQR
- Change from Baseline based on the average score at Visit 14 and Visit 26 and the following 6 days, for pain NRS and fatigue NRS.

Scatterplots will be summarized by treatment group.

Boxplots of maximum change and percent change from Baseline for Total IgG will also be plotted by sequence and period, for a total of 6 box plots.

All pharmacodynamic summaries and figures will be presented based on the PDS, and listings will be presented using the SS-r.

5.6 Safety Analysis

Overall safety summaries and listings will be performed using the SS-r. AE tables will be summarized using SS-t.

5.6.1 Extent of Exposure

Administration of treatments will be listed by participant and planned treatment sequence. The listing will include the actual and planned treatment received, start and stop date and time of drug administration, total volume of treatment given, and site of injection (L/R side of the body and upper/lower abdomen).

Study medication duration will be calculated in two ways:

- For the entire study duration (in days):
  - Calculated as the date of last dose of IMP (including Run-Out) - date of first dose of IMP in the Run-In Period + 1.
- For Treatment Periods 1 and 2 only (in days):
  - Calculated as the date of the last dose of IMP (excluding Run-Out) – date of first dose of IMP in Treatment Period 1 +1.

Study medication durations will be summarized by sequence using descriptive statistics.

An additional summary of the number of infusions received in Treatment Periods 1 and 2 will also be generated. The following summaries will be generated based on the SS-r, by planned treatment sequence:

- 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;
- Number of infusions received excluding mock infusions, using similar approach as the point above.

An additional by participant listing of the exposure to IMP will be generated.

5.6.2 Adverse Events

All AEs will be coded using MedDRA® and characterized as pre-treatment and treatment-emergent according to the intake of each treatment. Adverse events with a start date prior to the first dose of IMP in the Run-In Period will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date on or after the first dose of IMP in Run-In, and on or before the earliest of the following: the last date of infusion (including Run-Out, if applicable) +56 days, final contact date or death. A TEAE is also defined as any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment.

Adverse events will be summarized by treatment period and treatment group based on the SS-t. If a participant receives an incorrect treatment per the randomization schedule, the participant will be excluded from the summaries, and the AEs for this participant will be listed only. In such cases these will be noted in the footnotes for the relevant tables. Pre-treatment AEs will not be included in any summaries.

Adverse events will be assigned to the respective treatment period and treatment group based on the start date of the AE. The assignment of AEs to a given treatment period is summarized in Appendix 4 Section 8.4. The treatment groups will be summarized per treatment period in the following way:

- Run-In:
  - PBO (All 3 sequences)
- Treatment Period 1
  - RLZ (Sequence 1)
  - Pooled PBO (Sequence 2 and 3)
- Treatment Period 2

  - RLZ/RLZ (Sequence 1)
  - PBO/RLZ (Sequence 2)
  - PBO/PBO (Sequence 3)
- Run-Out and SFU (pooled)
  - RLZ/RLZ (Sequence 1)
  - PBO/RLZ (Sequence 2)
  - PBO/PBO (Sequence 3)

The total N within the summary tables will correspond to the number of participants randomized to the respective treatment sequence who receive at least one dose of IMP in the given treatment period or who entered the SFU period.

For details regarding partial dates, see Appendix 2 Section 8.2.

The number and percentage of participants who experience TEAEs will be summarized by MedDRA™ SOC, HLT, and PT as described above.

Summaries of TEAEs will include the following:

- Incidence of overall TEAEs (overview including number and percentage of study participant with any TEAEs, serious TEAEs, discontinuations due to TEAEs, permanent withdrawal of study medication due to TEAEs, drug related TEAEs, severe TEAEs and TEAEs leading to death; event counts will also be included)
- Incidence of any TEAEs
- Incidence of any serious TEAEs
- TEAEs leading to permanent withdrawal of IMP
- Incidence of severe TEAEs
- Incidence of treatment-related TEAEs
- Incidence of TEAEs by maximum causal relationship with IMP
- Incidence of TEAEs by maximum intensity
- Incidence of serious TEAEs by maximum causal relationship with IMP
- Incidence of serious TEAEs by causal relationship
- Incidence of fatal TEAEs by causal relationship with IMP
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants
  - For the purpose of this table, the 5% reporting threshold will be considered based on all TEAEs reported within each of the following groups:
    - PBO Run-In
    - PBO Treatment Period 1
    - RLZ Treatment Period 1

- PBO/PBO Treatment Period 2, Run-Out, SFU
- PBO/RLZ Treatment Period 2, Run-Out, SFU
- RLZ/RLZ Treatment Period 2, Run-Out, SFU

ie, non-serious TEAEs occurring with incidence >5% within any of the above groups will be included.

- Incidence of drug-related TEAEs (overview including number and percentage of study participant with any drug-related TEAEs, serious drug-related TEAEs, discontinuations due to drug-related TEAEs, permanent withdrawal of study medication due to drug-related TEAEs, severe drug-related TEAEs and drug-related TEAEs leading to death; event counts will also be included)
- Incidence of drug-related TEAEs by preferred term
- Incidence of serious drug-related TEAEs by preferred term

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. Participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be sorted in the following way:

- For Run-In:
  - Sort by alphabetical SOC and HLT within SOC. Within SOC and HLT within SOC, sort by descending frequency of PT in Run-In.
- For Treatment Period 1 and Treatment Period 2:
  - Sort by alphabetical SOC and HLT within SOC. Within SOC and HLT within SOC, sort by descending frequency of PT in the RLZ/RLZ (Treatment Period 2) group. In the case of ties, sort these alphabetically within the RLZ/RLZ (Treatment Period 2) group.
- For Run-Out and SFU group:
  - Sort by alphabetical SOC and HLT within SOC. Within SOC and HLT within SOC, sort by descending frequency of PT in the RLZ/RLZ group. In the case of ties, sort these alphabetically within the RLZ/RLZ group

All listings will be presented by planned treatment sequence and will include study participant, SOC/HLT/PT/reported term, the onset date and outcome date of the event, the Treatment Period of onset, most recent actual treatment received, days since the most recent dose (derived), the event duration (derived), days since the first dose in the Run-In Period (derived), days since the first dose in Treatment Period 1 (derived), pattern of event, flag for a serious event, intensity,

relationship, action taken, AESM flag, AESI flag, Adverse Event of Focus (AEOF) flag, and outcome, unless specified.

The following listings of AEs and TEAEs will be provided:

- All AEs
- All TEAEs

5.6.3 COVID-19 AEs

Confirmed COVID-19 cases will be recorded as AEs and will be reported under the AE section. An overall summary of TEAEs related to COVID-19 will be provided. This summary table will include the number and percentage of participants, as well as event counts, with any TEAE, any TEAE related to study drug, any severe TEAE, any severe TEAE related to study drug, any TESAE, any TESAE related to study drug, any TEAE leading to treatment discontinuation, any study drug related TEAE leading to treatment discontinuation, any TEAE leading to study withdrawal, and any deaths. In addition, to the above summary, TEAEs related to COVID-19 will be summarized by SOC, HLT, and PT in a separate table. Both COVID-19 AE tables will be summarized by treatment period and treatment group based on SS-t.

MedDRA has a COVID-19 Standardised MedDRA Query (SMQ). The query used in this study will be the broad MedDRA COVID-19 SMQ as defined at the specified analysis time points (see https://www.meddra.org/COVID-19-terms-and-MedDRA).

5.6.4 AEs of Special Interest and AEs of Special Monitoring

An AE of special interest (AESI) listing will be produced of Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), by treatment sequence and participant including most recent treatment received prior to the AE.

An AE of special monitoring (AESM) is a product-specific AE, adverse reaction, or safety topic requiring special monitoring by UCB. AESM will be listed.

Following events will be listed under AESM

- Severe and/or serious headache
- Suspected aseptic meningitis

Summaries of the incidence of AESM and incidence of AESI will be generated. AESM and AESI summaries will be based on investigator assessment as recorded on the eCRF and confirmed during data review.

5.6.5 Adverse Events of Focus (AEOF)

Rozanolixizumab treatment-emergent adverse events of focus (AEOF) include the following categories:

- Headaches
- Possible aseptic meningitis
- Gastrointestinal disturbances

- Hypersensitivity reactions
- Anaphylactic reactions
- Injection site reaction
- Infections
- Opportunistic infections
- Effects on the kidney
- Drug related hepatic disorders
- Effect on lipids

Further details are described in Section 8.3.

A by-participant listing of all treatment-emergent AEOF by category (as listed above) will be provided. The number and percentage of study participants who experience each treatment-emergent AEOF will be summarized by treatment period and treatment group based on the SS-t.

The following tables will be presented:

- Incidence of each AEOFs by SOC, High Level Group Term (HLGT), HLT and PT
- Incidence of each Serious AEOFs by SOC, High Level Group Term (HLGT), HLT and PT
- Incidence of each AEOFs by relationship, SOC, HLGT, HLT and PT
- Incidence of each AEOFs by maximum intensity, SOC, HLGT, HLT and PT

Note that each of the AEOF categories will be tabulated independently, eg, for the overall incidence summary, there will be one page showing the incidence of headaches, one page showing incidence of gastrointestinal disturbances, one for hypersensitivity reactions, etc.

5.6.6 Clinical Laboratory Evaluations

All laboratory results values (clinical chemistry and hematology) will be listed by study participant, planned treatment sequence, time point and parameter. Changes from Baseline for numeric variables, the reference ranges and a flag to indicate whether values are below the lower limit of the reference range or above the upper limit of the reference range will be presented.

Separate listings of all clinical chemistry and hematology laboratory results for participants who had at least one treatment-emergent marked abnormality (as defined in the abnormality criteria in Section 8.1.1.) during the study will be presented.

Urinalysis results will be listed for all study participants by treatment sequence, and will include changes from Baseline for numeric variables, and the reference ranges (if applicable).

Any additional laboratory variables which were not collected for screening eligibility and are not included in the outputs described previously will be listed separately for all time points collected. These will include the following:

- Serology
- Serum pregnancy test (for women of childbearing potential, if taken post screening)

- Urine pregnancy tests
- Urine toxicology screen (if taken post screening)
- IGRA assessments
- COVID-19 testing (for participants enrolled under Protocol Amendments 1 and 2 only)

Clinical chemistry and hematology parameters will be summarized by planned treatment sequence and periods and time point for both absolute values and changes from Baseline. Summaries will be based on the SS-r.

Treatment-emergent marked abnormalities with abnormalities defined in Appendix 1 Section 8.1.1 will be summarized by clinical chemistry and hematology groups, planned treatment sequence and visit. Treatment-emergent here refers to measurements obtained on or after the date of the first dose of IMP in Run-In, and on or before the earliest date of the following: the last infusion (including Run-Out if applicable) +56 days, final contact date, or death, and which did not meet the abnormality criteria at Baseline.

Measurements that are below the limit of quantification (BLQ) or above the limit of quantification (ALQ) will be presented as received in the listings. For the purpose of calculating change from baseline or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLOQ) and ALQ values will be imputed to the upper quantification limit (ULOQ).

5.6.7 Vital Signs

The following vital signs measurements will be assessed:

- Systolic and diastolic blood pressure
- Pulse rate
- Body temperature (oral, tympanic or axillary)
- Body weight

Vital signs assessment values and changes from Baseline will be summarized by planned treatment sequence, period, and time point where applicable, based on the SS-r. The time points summarized will be per Protocol Amendment 3. Therefore, any assessments completed by participants enrolled under any prior version of the protocol which are not required under Protocol Amendment 3, will be listed only.

Vital signs measurements will be listed by planned treatment sequence, period, and time point including changes from Baseline and details of abnormal values. Body weight will be listed only.

Treatment-emergent vital signs abnormalities defined as in Appendix 1, Section 8.1.2 will be summarized by planned treatment sequence, period and by time point as applicable.

5.6.8 Electrocardiograms (ECG)

The following ECG parameters will be reported:

- Heart rate
- PR interval

- RR interval
- QT interval
- QRS interval
- QTc interval (QT corrected for heart rate using Fridericia's formula [QTcF])

The individual measurements will be reported in the by-participant listings and will be presented by planned treatment sequence and time point. ECG findings will be listed separately.

5.6.9 Other Safety Variable(s)

5.6.9.1 Physical examination

Study participants with abnormalities in the physical examination at Screening will be listed by planned treatment sequence for the SS-r including details of the abnormality.

5.6.9.2 Neurological Examination

In study participants who report severe and/or serious headache or suspected aseptic meningitis at the clinic visit, a full neurological examination (including fundoscopy) should be performed. Neurological examination and fundoscopy results will be listed by planned treatment sequence.

5.6.9.3 Suicidal Risk Monitoring - C-SSRS

Study participants will be monitored appropriately for suicidal ideation and behavior or any other unusual changes in behavior. Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. Collected C-SSRS data will be listed by planned treatment sequence for participants where suicidal ideation or behavior has been reported. Module of the questionnaire, time point, question and the associated response will be listed for all the visit days where this questionnaire is collected.

5.6.9.4 Assessment of Tuberculosis and Tuberculosis Risk Factors

TB will be evaluated via various assessments as specified below during the study. Findings for TB assessment performed during PE after screening will be reported as AEs. No separate TB listing or table will be produced for PE TB assessment.

The TB questionnaire will not be reported. TB assessment by IGRA will be reported together with other laboratory parameters.

No separate TB listing or table will be produced for IGRA TB assessment.

TB assessment by chest X-ray or other assessments will not be reported.

IGRA test conversions should be reported as AEs as described in the protocol. The AE term would need to be updated with final diagnosis once available.

No specific listing will be provided for test conversion.

Latent TB

Any latent TB infection will be reported as an AE and graded appropriately as described in this protocol. No specific listing will be provided for Latent TB infection.

Active TB or NTM infection

Study participants who develop active TB or NTM infection during the study (conversion demonstrated by IGRA) will be withdrawn from the study. The study participant will be immediately and permanently discontinued from the IMP. The study participant should complete the assessments outlined for the EOT/EW Visit and encouraged to enter the 5-week SFU Period.

Confirmed active TB is always considered an SAE and will be reported in AE section.

5.6.9.5 Potential Drug-Induced Liver Injury (pDILI)

The number and percentage of participants who meet one or more of the following pDILI criteria at any visit (including unscheduled visits) will be summarized by treatment period and treatment group, based on the SS-r:

- 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 at any visit (including unscheduled visits) will be summarized by treatment period and treatment group, based on the SS-r.

A listing of results obtained for all scheduled and unscheduled visits will also be provided for study participants who meet at least one of the following criteria:

- (ALT or AST>=3xULN) and (TBL >= 1.5 x ULN)
- (ALT or AST>=3xULN) and (TBL >= 2 x ULN) and (ALP < 2 x ULN)

The listing will show the new ratio, nR, calculated as the ratio of either ALT or AST (whichever is higher) to ALP, expressed as multiples of their ULN, ie, Max (ALT x ULN or AST x ULN) / ALP x ULN.

5.7 Immunogenicity

The immunogenicity analysis will be summarized based on the SS-r by treatment sequence or by visit when applicable. Samples from study participants on placebo will not be tested for anti-drug antibodies (ADA). Consequently, participants randomized to Sequence 3 will be excluded from the analyses described in this section and will not be included in TFLs.

Anti-drug antibodies will be measured using a three-tiered assay approach: screening, confirmatory and titration assay. Any sample confirmed positive for ADA will be assayed to determine whether there is neutralizing potential.

Samples will first be evaluated in the screening assay (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay to confirm the true positivity of the samples (reported as 'negative immuno-depletion' or 'positive immuno-depletion'). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution (MRD)).

The ADA sample status will be determined for each pre-treatment (Baseline) and post-treatment (post-Baseline) visit where samples were taken for ADA analysis (both scheduled and any unscheduled visits):

Table 5-6: ADA Sample Status

ADA sample status	Definition
ADA negative (ADA-)	Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' if corresponding rozanolixizumab concentrations are equal or below the validated drug tolerance limit of the ADA assay (200ug/ml rozanolixizumab) allowing detection of 100 ng/ml ADA. Note that if an ADA sample does not have a corresponding PK sample (at the same visit), then it is assumed that the drug concentration is below the drug tolerance limit.
ADA positive (ADA+)	Sample values that are 'positive screen' and 'positive immuno-depletion'
ADA inconclusive	Sample values that are either 'negative screen' or 'positive screen' and 'negative immuno-depletion' but with corresponding rozanolixizumab concentrations above the validated drug tolerance limit of the ADA assay (200ug/ml rozanolixizumab) allowing detection of 100 ng/ml ADA.

ADA sample status	Definition
	Note that if an ADA sample does not have a corresponding PK sample (at the same visit), then it is assumed that the drug concentration is below the drug tolerance limit and therefore this sample cannot be classified as 'Inconclusive'.
Missing	Samples that were collected per schedule but could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.
Evaluable ADA sample	A sample for which the sample status is not missing nor ADA inconclusive

Neutralizing antibody (NAb) sample status (positive/negative/inconclusive/missing) will be determined for ADA positive samples. Samples that are NAb positive will be evaluated in a titration assay to quantify the NAb level and will be reported as titer.

Definition of ADA Baseline

The Baseline values for ADA will be based on the last measurement prior to receiving the first dose of rozanolixizumab. For participants randomized to Sequence 1, Baseline is the Visit 3 (Week 1) pre-dose assessment, or Visit 1 (Week -1), if missing. For participants randomized to Sequence 2, Baseline is the Visit 15 (Week 13) pre-dose assessment, or Week 3 (Visit 1), if missing.

ADA/NAb Participant Status

The ADA/NAb participant status will be further classified on study participant level as outlined below (Shankar et al. 2014; Rup et al. 2015, Presentation Immunogenicity Summit, 2021, Joleen White, Enabling Clinical Immunogenicity Impact Assessment with Standardized Data Tabulation Models).

The by-participant classifications for ADA status will be derived 3 times:

- For the entire study duration (ie, including all samples from Treatment Periods 1 and 2, and SFU). Note that participants in Sequence 2 will not have samples from Treatment Period 1.
- Based on RLZ 12 weeks exposure:
  - Sequence 1 Baseline (Visit 3) to Day 85 (Visit 15)
  - Sequence 2 Baseline (Visit 15) to Day 169 (Visit 27)
- Based on RLZ 24 weeks exposure:
  - Sequence 1 Baseline (Visit 3) to Day 169 (Visit 27)

Based on the above, participants in Sequence 1 will have 3 ADA classifications, and participants in Sequence 2 will have 2 ADA classifications. The combined ADA/NAb participant status will be derived only based on the ADA status for the entire study duration (ie, each participant will have only 1 ADA/NAb classification).

The ADA participant status is composed of 6 individual categories: ADA negative, inconclusive, and ADA positive whereby a positive participant's status is further subdivided into treatment-induced, treatment boosted, or non-treatment-emergent ADA positive.

However, the ADA participant status as defined in category 1 (ADA-NEG) can only be applied for participants having 2/3 (66.6%) of the protocol scheduled post-baseline ADA samples 'evaluable', (ie, neither missing as per schedule nor inconclusive) which is equivalent to the following:

- For the entire study duration
  - For Sequence 1, a minimum of 6/8 samples
  - For Sequence 2, a minimum of 4/5 samples
- RLZ 12 weeks
  - For Sequence 1, a minimum of 2/3 samples
  - For Sequence 2, a minimum of 2/3 samples
- RLZ 24 weeks
  - For Sequence 1, a minimum of 4/6 samples

Study participants that have a positive baseline value and no post-baseline values collected will be categorized as categories 2 (ADA-POS) and 5 (Non-TE-POS).

For a dropout participant, the participant status would be evaluated on the basis of the sample collection compared to all anticipated protocol scheduled samples assuming that they had actually completed the study.

Table 5-7: ADA Participant Status Categories

Term	Definition	Category
ADA participant status categories		
ADA-NEG (Pre ADA negative – treatment induced ADA negative)	Study participants who have negative ADA sample status at baseline and at all sampling time points post-baseline with the number of evaluable samples (non- missing per schedule nor inconclusive) more or equal to 2/3 as defined above. [Note: study participants with baseline samples missing and negative ADA status at all sampling time post-baseline are included in this category; based on the following rationale: in case the participant would be pre-Ab positive, the participant is expected to present ADA positive samples post-baseline]	1
ADA-POS	Study participants who have a positive ADA sample status at any time point (either Baseline, or post-Baseline)	2

Term	Definition	Category
TI-POS (Pre ADA negative – Treatment Induced ADA positive)	Study participants who have a negative ADA status at baseline and positive ADA status at any sampling point post-Baseline.	3
TB-POS (Pre ADA positive – Treatment Boosted ADA positive)	Study participants who have a positive ADA status at baseline and positive ADA status at any sampling point post-baseline with non-missing increased titer values compared to baseline (>fold difference from Baseline value as determined by the MSR of the assay).	4
Non-TE-POS (Pre-ADA positive- Non-Treatment - Emergent ADA positive)	Study participants who have a positive ADA status at baseline and 1) negative ADA status at all evaluable sampling points post-baseline or 2) positive ADA status at any evaluable sampling points post- baseline with non-missing titer values of the same or lower magnitude as baseline (≤ fold difference from Baseline value as determined by the MSR of the assay).	5
Inconclusive	Study participant for who the ADA participant status cannot be defined due to missing or inconclusive samples. Inconclusive [1]: Study participant that had negative ADA status at baseline and post-baseline samples missing per schedule or inconclusive that is higher than the % allowed as defined above, while others post-baseline samples are ADA negative up to the time point of interest. Inconclusive [2]: Participants who do not satisfy any of the above criteria.	6
Combined ADA participant status categories		
TE-POS (TE ADA positive)	Includes study participants defined in category 3 and 4	7
Treatment emergent ADA positive – NAb positive (TE-POS, NAb-POS)	Study participants in category 7 who have at least one NAb positive sample	8
Treatment emergent ADA positive – NAb negative (TE-POS, NAb-NEG)	Study participants in category 7 who have no NAb positive samples	9
Non-treatment emergent ADA positive–- NAb positive (Non-TE-POS, NAb-POS)	Study participants in category 5 who have at least one NAb positive sample	10
Non-treatment emergent ADA positive–- NAb negative (Non-TE-POS, NAb-NEG)	Study participants in category 5 who have no NAb positive samples	11

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

Calculation of Fold Increase for use of MSR, and for classifying 'Non-TE-POS (Pre-ADA positive- Non-Treatment-Emergent ADA positive)' and 'TB-POS (Pre ADA positive – Treatment Boosted ADA positive)' category:

Fold increase= post-dose titer/baseline titer

The following summaries, figures and listings will be produced and will be presented using the SS-r:

Tables:

- Summary table displaying the number and percentage of study participants with a positive ADA, negative ADA, inconclusive or missing ADA sample status at the time of each visit by planned treatment sequence.
- Summary table displaying the number and percentage of study participants with a positive NAb, negative NAb, inconclusive or missing NAb sample status at the time of each visit by planned treatment sequence.
- Number and percentage of study participants in each of the individual and combined ADA participant status categories and combined categories (1-11) presented in Table 5-7 for each time period specified above. The denominator will be the total number of study participants with an individual ADA participant category defined for each time period.
- Total prevalence of pre-existing ADA and NAb, defined as number and percentage of participants having an ADA/NAb positive sample status at baseline, with the denominator being the total number of study participants having an evaluable ADA/NAb sample result at baseline.
- The first occurrence of treatment-emergent ADA positivity: cumulative number and percentage of TE-ADA positive participants (category 7) who are ADA positive for the first time based on samples collected over the entire study duration, including SFU.
- Summary table of mean maximum percentage change from Baseline in total IgG summarized by ADA participant categories (1-6) for the following:
  - Sequence 1, Treatment Period 1 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and maximum percent change from Baseline in total IgG in Treatment Period 1.
  - Sequence 2, Treatment Period 2 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and maximum percent change from Baseline in total IgG in Treatment Period 2.
  - Sequence 1, Treatment Period 1 and Treatment Period 2 (RLZ 24 weeks) using ADA participant category based on RLZ 24 weeks exposure and maximum percent change from Baseline in total IgG in Treatment Period 2

  - Sequence 1 Treatment Period 1 and Sequence 2, Treatment Period 2 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and maximum percent change from Baseline in total IgG in Treatment Period 1 for Sequence 1, and Treatment Period 2 for Sequence 2.

- Summary table of mean change from Baseline in BPI-SF Interference score in Treatment Periods 1 and 2, summarized by ADA participant categories (1-6) for the following:
  - Sequence 1, Treatment Period 1 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and change from Baseline in BPI-SF interference score at Visit 15.
  - Sequence 2, Treatment Period 2 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and change from Baseline in BPI-SF interference score at Visit 27.
  - Sequence 1, Treatment Period 1 and Treatment Period 2 (RLZ 24 weeks) using ADA participant category based on RLZ 24 weeks exposure and change from Baseline in BPI-SF interference score at Visit 27.
  - Sequence 1 Treatment Period 1 and Sequence 2, Treatment Period 2 (RLZ 12 weeks) using ADA participant category based on RLZ 12 weeks exposure and change from Baseline in BPI-SF interference score at Visit 15 for Sequence 1, and Visit 27 for Sequence 2.
- Overall summary table of TEAEs summarized by ADA participant categories 1, 5, 6, and 7 where the participant category is based on ADA data for the entire study duration. This table will include the following:
  - Sequence 1 – all TEAEs occurring on or after the first dose in Treatment Period 1, up to the SFU Visit.
  - Sequence 2 – all TEAEs occurring on or after the first dose in Treatment Period 2, up to the SFU Visit.
- Summary table of incidence of TEAE by ADA participant category 1, 5, 6, and 7 for the where the participant category is based on ADA data for the entire study duration, as described for the overall summary table. This table will be repeated for the AEOF hypersensitivity reactions, anaphylactic reactions and injection site reactions (defined as AEOF in Section 13.7).

Figures:

- Individual time course plots for ADA positive study participants, (within categories 3,4 and 5) representing ADA and NAb titers (on log-scale), percentage change from Baseline for total IgG and change from Baseline for BPI-SF Interference Score. This will include the following:
  - For Sequence 1: All data from Visit 3 (ADA Baseline) to SFU, with the x-axis presented in weeks
  - For Sequence 2: All data from Visit 15 (ADA Baseline) to SFU, with the x-axis presented in weeks

- A plot of the median change from Baseline in Total IgG over time by cumulative ADA positivity status and planned treatment sequence. The ADA positive status will be considered in a cumulative manner at each time point (ie, if a participant has had at least one positive sample at any time point up to and including the given time point, that participant will be counted as positive at that time point, regardless of any subsequent negative measurements. In addition, if the Baseline sample is missing then the sample will be classified as being negative for the cumulative ADA status). This plot will include the following:
  - For Sequence 1: All data from Visit 3 (ADA Baseline) to SFU, with the x-axis presented in weeks
  - For Sequence 2: All data from Visit 15 (ADA Baseline) to SFU, with the x-axis presented in weeks
- A plot of median percent change from Baseline in Total IgG over time by cumulative ADA positivity status and planned treatment sequence, as described above.
- A box-and-whisker plot of maximum post-Baseline ADA titer (on log-scale) versus ADA participant category (where the participant category is based on ADA/NAb data for the entire study duration) for categories 8, 9, 10, and 11 by treatment sequence. The same plot will be repeated for NAb titer for ADA participant categories 8 and 10.
- Time course plot of mean CFB in BPI-SF Interference score, summarized by ADA participant categories 1, 6, 8, 9, 10, and 11, where the participant category is based on ADA/NAb data for the entire study duration. Separate plots for each treatment sequence will be generated.
  - For both Sequence 1 and Sequence 2, BPI-SF Interference scores from Visits 7, 11, 15, 19, 23 and 27 will be presented, with the x-axis presented in weeks.
- Spaghetti plots of percentage CFB for total IgG, for each of the ADA participant categories 1, 6, 8, and 9 (where the participant category is based on ADA/NAb data for the entire study duration). Individual samples that tested positive for ADA will be indicated on the plot. Separate plots for each treatment sequence will be generated.
  - For both Sequence 1 and Sequence 2, BPI-SF Interference scores from Visits 7, 11, 15, 19, 23 and 27 will be presented, with the x-axis presented in weeks.
- Scatterplot of individual change from Baseline in BPI-SF Interference score categorized by ADA titer tertile (including category ADA not present) for each scheduled assessment. The same plot will be repeated for NAb titer. Positive ADA/NAb samples that do not have an associated titer, will not be included in the plot.
  - For Sequence 1, ADA/NAb and BPI-SF data for Visits 11, 15, 23, and 27 will be displayed.
  - For Sequence 2, ADA/NAb and BPI-SF data for Visits 23 and 27 will be displayed. These visits will be overlaid with Visits 11 and 15 for Sequence 1, to reflect 12 weeks of exposure.
- Scatterplot of individual percentage change from Baseline for total IgG categorized by ADA titer tertile (including category ADA not present) for each scheduled assessment. The same

plot will be repeated for NAb titer. Positive ADA/NAb samples that do not have an associated titer, will not be included in the plot.

- For Sequence 1, ADA/NAb and BPI-SF data for Visits 4, 11, 15, 16, 23, and 27 will be displayed.
- For Sequence 2, ADA/NAb and BPI-SF data for Visits 16, 24, and 27 will be displayed. These visits will be overlaid with Visits 4, 11, and 15 for Sequence 1, to reflect 12 weeks of exposure.

Listings:

- A listing of the by visit ADA/NAb results including the results from the screening assay, confirmatory assay, and titration assay (titer level), the fold change compared to baseline and the ADA/NAb sample status will be presented by planned treatment sequence and participant. This listing will also contain the time since the previous administration of IMP (in days).
- A listing of the ADA and ADA/Nab participant categories will be presented by planned treatment sequence.
  - Participants randomized to Sequence 1 will have 3 ADA classifications (based on ADA data for the entire study duration, 12 weeks and 24 weeks), and 1 ADA/NAb classification (based on ADA/NAb data for the entire study duration)
  - Participants randomized to Sequence 2 will have 2 ADA classifications (based on ADA data for the entire study duration, and 12 weeks) and 1 ADA/Nab classification (based on ADA/NAb data for the entire study duration).
- A listing of the by visit ADA and NAb sample status, ADA titer, NAb titer, rozanolixizumab plasma concentration, percentage change from Baseline for total IgG and IgG subclasses, and change from Baseline for BPI-SF Interference score will be presented.
- A listing of the following TEAEs will be generated:
  - For participants randomized to Sequence 1 – all TEAEs occurring on or after the first dose in Treatment Period 1, up to the SFU Visit.
  - For participants randomized to Sequence 2– all TEAEs occurring on or after the first dose in Treatment Period 2, up to the SFU Visit.

  This listing will include the ADA and NAb sample status and ADA and NAb titers at the closest sampling time point to the date of onset of the TEAE (this could be prior to or after the date of onset). If both sampling points are equidistant to the TEAE, then the prior one is selected.

5.8 Efficacy Analysis

The observed result and change from Baseline of each efficacy assessment (including the individual items as well as the summary scores) will be tabulated by planned treatment sequence and visit (including Screening and Run-In, if applicable), based on the FAS.

The observed result and change from Baseline of each efficacy assessment (including the individual items as well as the summary scores) will also be summarized by treatment group, based on the FAS.

Mean change from Baseline (with 95% confidence intervals based on summary statistics) for BPI-SF and FIQR will be summarized by treatment sequence and period using a Forest plot. The BPI-SF plot will contain all BPI-SF interference questions as well as the BPI-SF interference score. The FIQR plot will include all individual questions as well as the domain scores and overall FIQR score. Plots will be based on the mean change from Baseline at Assessment 3 in each treatment period.

Figures for mean change from Baseline over time will be generated for each efficacy parameter by treatment sequence over both Treatment Periods, and by treatment and period day. For the latter all combinations of treatment and sequence will be displayed separately (6 symbols per plot) and the periods will be superimposed.

For the NRS measurement collected over multiple days, the average of the measurements related to a given visit will be summarized in the tables and figures, rather than the individual measurements. If two or more pain or fatigue NRS results are recorded on the same calendar day, the latest result of the day will be used for the purpose of calculating the average score, and for display in the summaries. All measurements will be presented in the listings and duplicate scores will be indicated as appropriate.

5.8.1 Derivations of Efficacy Variables(s)

The different efficacy variables will have different Baseline and endpoint measurement time points, depending on when the relevant data is being collected. Table 5-8 gives details on the timing of these baseline and effect measurements.

Table 5-8: Efficacy endpoint time points

Endpoint	Baseline measurement	Effect measurement for period 1	Effect measurement for period 2
BPI-SF interference (and other endpoints derived from BPI-SF)	**start of Treatment Period 1** Visit 3, D1 pre-dose	**pre-dose start of Treatment Period 2** Visit 15, Week 13, D85 (12 weeks of treatment)	**Run-Out visit 1** Visit 27, Week 25, D169 (12 weeks of treatment)
Pain and fatigue assessment (NRS)	**Run-In visit 2** (starting at D-7 and going to D-1)	**Visit 14, Week 12** starting at D78 and going to D84 (12 weeks of treatment)	**Visit 26, Week 24** starting at D162 and going to D168 (12 weeks of treatment)
FIQR (and endpoints derived from the FIQR)	**Run-In visit 2** Visit 2, D-7	**Visit 13, Week 11, D71** (10 weeks of treatment)	**Visit 25, Week 23, D155** (10 weeks of treatment)

- BPI-SF interference score is calculated as the mean of the seven pain interference items of the BPI-SF questionnaire. The BPI-SF interference score will be calculated if more than 50%, of the total items have been completed on a given administration. For more details on BPI-SF see (Cleeland and Ryan, 1991).

- The FIQR is scored in 3 steps:
    - Step 1. Sum the scores of the items within each of the three domains (domain 1: activities, domain 2: overall impact, and domain 3: symptoms).
    - Step 2. Divide domain 1 score by three, domain 2 score is unchanged, and divide domain 3 score by two. (So if the scores in domains 1, 2 and 3 are 60, 9 and 40, respectively, then domain 1 score divided by three = 20; domain 2 remains unchanged at = 9; domain 3 score divided by two = 20)
    - Step 3. Add the three resulting domain scores to obtain the total Revised Fibromyalgia Impact Questionnaire (FIQR) score. In the example above the total FIQR score would be 20+9+20 = 49
    - Missing answers: For unanswered questions the following "weighting" factor should be used. If only x questions from the first section (function) were answered, one would weigh the summated score of the x questions by 9/x (as there are 9 items in the function set of questions) Likewise the second section (overall impact) would have a weighting of 2/x (there are only 2 items) and the third section (symptoms) would have a weighting of 10/x (there are 10 items).

5.8.2 Primary Efficacy Variable

The primary efficacy endpoint is the average BPI-SF interference score after 12 weeks of double-blind treatment, adjusted for Baseline score.

For the purpose of analysis, there will be three treatment groups: placebo, rozanolixizumab for up to 12 weeks [Sequence 1, Period 1 and Sequence 2, Period 2], or rozanolixizumab given beyond 12 weeks [Sequence 1, Period 2]. The main difference of interest is that between rozanolixizumab for up to 12 weeks and placebo.

In order to estimate the mean difference in the average BPI-SF interference scores after 12 weeks of treatment, the BPI-SF interference scores measured at Visits 7, 11, 15, 19, 23, and 27 will be modelled using a longitudinal linear mixed effect model (LMM). The pre-dose value taken at the first visit of Treatment Period 2 (Visit 15) will be used as the measure of treatment effect after 12 weeks of treatment for Period 1, while the pre-dose value taken at Run-Out Visit 27 will be used as the measure of treatment effect after 12 weeks of treatment for Period 2. Any BPI-SF assessments which are not completed within the protocol defined window of the scheduled visit will not be included within the primary efficacy analysis.

5.8.2.1 Primary Analysis of Primary Efficacy Variables(s)

The LMM for the BPI-SF interference score will have treatment as a fixed effect and the study participant ID will be included as a random effect.

The following additional fixed effects will be included:

• Treatment Period (1 or 2)

• assessment number within the period (1_{st}, 2_{nd}, or 3_{rd} assessment categorical) number corresponding to Visit 7, 11, and 15 for Treatment Period 1, or Visit 19, 23, or 27 for Treatment Period 2)

• an interaction of treatment by assessment number

• an interaction of assessment number-by-Treatment Period

The following covariates will also be included:

• BPI-SF interference scores at Baseline (taken at Visit 3, prior to dosing)

The model can also be written as follows:

$$Y_{ij} = Y_{i,bl} + Period_{ij} + Assessment_{ij} + TRT + Assessment_{ij} \times TRT_{ij} + Period_{ij} \times Assessment + (1|s_i)$$

Where Y indicates the measurement of interest (BPI-SF interference score in this case), i the i-th participant, j the j-th observation for each participant, × indicate an interaction, and $(1|s_i)$ indicate the random intercept effect for participant i. $Y_{i,bl}$ indicates the baseline value for participant i. Note that this model is specified as-is for conceptual clarity, but is over-parameterized, which may need to be taken into account during model fitting.

The model will utilize an unstructured covariance pattern for the repeated measures. If the model does not converge using the unstructured pattern, then an autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The LS Means estimate for each of the treatments with 95% CI should be reported. LS Means should be estimated assuming assessment effects of assessment 3 and using the period effect for period 2. In addition, the LS Means estimate of the differences between rozanolixizumab 12 weeks and 24 weeks, respectively, and placebo should be reported, using the same period and assessment effects as before.

- Rozanolixizumab 12 weeks – Placebo
- Rozanolixizumab 24 weeks – Placebo
- Rozanolixizumab 12 weeks - Rozanolixizumab 24 weeks

P-values for the baseline, treatment period, assessment number, treatment by assessment number, and treatment period by assessment number interaction terms will be reported.

All study participants in the FAS with Baseline BPI-SF score and one or more post-Baseline assessments will be included in the model.

Inter current event (ICE): Permanent discontinuation of treatment will be handled using a hypothetical strategy assuming that the study participants did not experience the events, with data following discontinuation excluded from analysis.

In addition, summary statistics of all results at assessment number 3 (in Treatment Periods 1 and 2) for all participants included in the model will be reported in the primary efficacy table by treatment group.

5.8.2.2 Secondary Analysis of Primary Efficacy Variable(s)

As secondary analysis strategy, each period will be analyzed separately using a mixed effect model, with study participant as random effect and treatment, assessment number, treatment by

assessment number interaction, and Baseline as fixed effects. For Treatment Period 1, there will be 2 treatment groups: placebo and rozanolixizumab. For Treatment Period 2, there will be 3 as defined for the primary analysis.

The LS Means estimate for each of the treatments with 95% CI should be reported, as well as the LS Means estimate of the differences between relevant treatment groups. See below treatment differences to be estimated at by period analysis.

Treatment Period 1;

- Rozanolixizumab 12 weeks – Placebo 12 weeks_Seq2 (between Seq1 and Seq2)
- Rozanolixizumab 12 weeks – Placebo 12 weeks_Seq3 (between Seq1 and Seq3)
- Rozanolixizumab 12 weeks – Placebo 12 weeks (between Seq1 and pooled placebo from Seq2 and Seq3)

Treatment Period 2;

- Rozanolixizumab 24 weeks – Placebo 24 weeks (between Seq1 and Seq3)
- Rozanolixizumab 12 weeks - Rozanolixizumab 24 weeks (between Seq2 and Seq1)
- Rozanolixizumab 12 weeks – Placebo (between Seq2 and Seq3)

P-values for the baseline, assessment number, and treatment by assessment number interaction should also be reported.

In addition, summary statistics of all results at assessment number 3 (in Treatment Period 1 and 2, as appropriate) for all participants included in the model will be reported in the secondary analysis summary tables.

5.8.3 Supportive and Sensitivity Analyses of the Primary Efficacy Variable

As a sensitivity analysis to evaluate the assumption of treatment effect being independent from site, site (center) will be included in the primary analysis model as an additional covariate. Other covariates may be included if considered appropriate.

The primary analysis of the primary efficacy endpoint will be repeated as an additional sensitivity analysis, using the same ICE strategy as described in Section 5.8.1. This analysis will be based on the study population which includes all participants in the FAS who have received at least 80% of the doses of randomized study medication (up to the point of withdrawal or completion), per treatment period. Note that for participants randomized to rozanolixizumab, mock infusions which are given as a result of temporarily discontinuing IMP will be classified as a 'missed' dose. In addition, summary statistics of all results at assessment number 3 (in Treatment Periods 1 and 2) for all participants included in the model will be reported in the sensitivity analysis tables.

5.8.4 Derivations of Secondary and Exploratory Efficacy Variables

Analyses of the following secondary efficacy endpoints will be conducted using an LMM in the same way as for the primary estimand analysis, using the same ICE strategies:

- FIQR total score after 10 weeks of treatment

- FIQR individual domain score (activities, overall impact and symptoms) after 10 weeks of treatment
- Mean 7-day pain score (NRS) after 12 weeks of treatment (collected during the 12th week).
- Mean 7-day fatigue score (Fatigue NRS) after 12 weeks of treatment (collected during the 12th week).

For these endpoints, the time points to be used for analysis and baseline are as described in Table 5-8; the value taken at Week 11 (Visit 13) will be used as the measure of treatment effect for FIQR after 10 weeks of treatment for Treatment Period 1, while the FIQR assessed at Week 23 (Visit 25) will be used as the measure of treatment effect after 10 weeks of treatment for Treatment Period 2. Any FIQR assessments which are not completed within the protocol defined window of the scheduled visit will not be included within the efficacy analysis.

Note that for NRS, the participant will be asked at Visit 14 and Visit 26 to complete the pain and fatigue NRS assessment for that day and every day for the following 6 days, and the average of these 7 measurements will be taken as the endpoint. A minimum of 3 valid records among 7-day assessments is required to use participant's average score. The scores measured at Visits 7, 11, and the average of Visit 14 and the following 6 days for Treatment Period 1, and Visit 19, 23, and the average of Visit 26 and the following 6 days for Treatment Period 2 will be used within the LMM.

5.9 Other Analyses

5.9.1 Pressure Pain Threshold

Pressure pain threshold will be assessed by pressure algesiometry. Pressure algesiometry will be performed at 2 sites on the body: (1) the lateral forearm and (2) the contralateral anterior thigh. Triplicate and average PPT scores by time points will be listed for all study participant at each time point. Mean and change from Baseline in average PPT score will be summarized by assessment site, treatment sequence and period, based on the FAS. If only one or two PPT assessments are collected at a time point, the available assessments will be used for the average PPT score at that time point.

5.10 Biomarkers

Venous blood samples will be collected to measure IgG binding as an exploratory endpoint.

The reporting and analysis of the exploratory biomarker results will be conducted separately from the CSR and will not be covered in this SAP or associated TFL shells.

5.11 Immunological Endpoint

The following blood samples for immunological testing will be collected as specified in the protocol schedule of activities:

- IgA, IgE, IgM (for participants randomized under Protocol Amendments 1 and 2 only)
- Serum complement (C3, C4)
- Plasma complement (C3a, C5a)

A listing of serum immunoglobulin laboratory results will be provided using the SS-r.

Serum and plasma complement results collected at Baseline and at any post-Baseline visits, will be listed using SS-r.

5.12 Early readout analysis and data monitoring

5.12.1 Early Readout Analysis

An Early Readout Analysis is planned to be conducted after all randomized study participants have either completed the BPI-SF assessment at Visit 27, or have withdrawn from the study.

For this Early Readout Analysis, a snapshot of the database will be taken once the BPI-SF data has been entered at Visit 27 (or earlier in the case of withdrawals) for the final randomized participant. The data will be cleaned for the purpose of the analysis. Details regarding the unblinding of individual team members and results dissemination will be provided in a separate unblinding plan. The study team will be unblinded following data cleaning and all study data, including the live random code and any vendor data previously considered unblinding will be provided. Some study team members will remain blinded until database lock. Details of team members who should remain blinded are provided in the unblinding plan. The Investigators and study participants will remain blind to the assigned treatment dosing regimen until the Follow-Up Period is complete and the database is locked.

A subset of key TFLs will be provided which will include the evaluation of the primary efficacy estimand, the secondary efficacy endpoints, PK and PD data, as described in Section 5.8.2, Section 5.8.4 , Section 5.9.1 and Section 5.5.

5.12.2 Data Monitoring

A SMC will regularly review (approximately every 3 months, with the option to adapt the frequency based on recruitment rates) the available blinded safety data. The first SMC review will be conducted approximately 2 months after randomization of the first study participant, or when 25% of the study participants are randomized, whatever comes first. The SMC will decide if the study is safe to continue. Details will be described in a separate charter.

If there are safety concerns during the SMC session an ad hoc closed SMC meeting may be called if revealing treatment allocation would aid decision making. The members of closed SMC sessions will be restricted and specified in the charter.

6 CTR AND DSUR OUTPUTS

6.1 CTR

The following tables outlined in previous SAP sections fulfil the criteria for transparency reporting for clinicaltrials.gov and EudraCT:

- DS_T_03 Disposition and Discontinuation Reasons [RS] as per Section 5.2.1
- DM_T_01 Demographics (all age categories are mandatory) [RS] as per Section 5.3.1
- AE_T_01 Incidence of TEAEs – Overview (mandatory, including both All Deaths and TEAE leading to Deaths)] [SS-t] as per Section 5.6.2

- AE_T_06 Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% of participants [SS-t] as per Section 5.6.2
- DS_T_04 Discontinuation due to AEs [RS] as per Section 5.2.1
- AE_T_04b Incidence of serious TEAEs by Relationship [SS-t]
- AE_T_04b Incidence of fatal TEAEs by Relationship [SS-t]

For results disclosure on public registries (eg. ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be published.

6.2 DSUR

The following tables will be created by the UCB statistical programming team for reporting for DSUR:

- EX_T_03 Cumulative Duration of Exposure. This table will be created for DSUR outputs needed whilst the study is ongoing and also once the study is completed.
- EX_T_03 Cumulative Duration of Exposure by Treatment, Age Group and Gender. This table will be created once the study is completed.
  - EX_T_03 Cumulative Duration of Exposure by Treatment and Race. This table will be created once the study is completed.

7 REFERENCES

Cleeland, Charles S., and K. Ryan. "The brief pain inventory." Pain Research Group 20 (1991): 143-147.

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

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

8 APPENDICES

8.1 Appendix 1: Abnormality Criteria for Laboratory and Vital Sign Parameters

8.1.1 Laboratory Assessments Marked Abnormality Criteria

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. If both high and low criteria are shown for a parameter, the criteria should be summarized separately in tabular or graphical data summaries. A treatment-emergent markedly abnormal assessment is defined as any abnormal assessment obtained on or after the first dose of IMP in Run-In, and on or before the earliest of the following: the last date of infusion (including Run-Out, if applicable) +56 days, final contact date or death and where the corresponding Baseline value does not meet the criteria.

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

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
Bilirubin (Total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal (based on reference range); >3.0 x Baseline value if Baseline is abnormal
Albumin[2]	g/dL	g/L	<2 g/dL; <20 g/L
Creatinine	mg/dL	umol/L	>3.0 x ULN or >3.0 x |Baseline;
Estimated glomerular filtrate rate (eGFR)	mL/min/1.73 m^2	mL/min/1.73 m^2	eGFR ≤29 mL/min/1.73 m^2

PARAMETER	UNIT (conventional)	UNIT (standard)	MARKED ABNORMALITY CRITERIA
C reactive protein (CRP)[3]	mg/L	mg/L	>10 mg/dL; >100mg/L
Calcium	mg/dL	mmol/L	Low: Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L
			High: Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L
Immunoglobulin G	(g/L)	(g/L)	<1.09 g/L (BLQ)
Potassium	mmol/L	mmol/L	Low: <3.0 mmol/L
			High: >6.0 mmol/L
Sodium	mmol/L	mmol/L	Low: <125 mmol/L
			High: >155 mmol/L
Glucose[4]	mg/dL	mmol/L	Low: <40 mg/dL; <2.2 mmol/L
			High: > 250 mg/dL; >13.9 mmol/L
Total Cholesterol	mg/dL	mmol/L	>400 /dL; >10.34 mmol/L
Triglycerides	mg/dL	mmol/L	>500 mg/dL; >5.7 mmol/L

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

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

[1]WBC (Leukocytes) markedly abnormal high criterion is not based on Version 5 CTCAE Grade 3 or higher criteria. Due to the allowance of concomitant steroid medication that by its mechanism of action may elevate WBCs, 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).

[2]Albumin data is classed as unblinding and results will therefore only be available after unblinding.

[3]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/.

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

8.1.2 Vital signs

Abnormality criteria to be applied in the assessment of vital signs parameter values are given below. A treatment-emergent markedly abnormal assessment is defined as any abnormal assessment obtained on or after the first dose of IMP in Run-In, and on or before the earliest of the following; the last date of infusion (including Run-Out, if applicable) +56 days, final contact date or death and where the corresponding Baseline value does not meet the criteria.

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	>38.3 ^{0}C
Body Weight	≥ 10% decrease from Baseline ≥ 10% increase from Baseline

8.2 Appendix 2: Handling of Dates

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

- Classification of AEs as TEAEs
- Durations of AEs
- Classification of medications and medical procedures as prior or concomitant
- Time since diagnosis of FMS and time since first symptoms of FMS.

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

8.2.1 Adverse Events

For the classification of TEAEs, the rules below will be applied for partial or completely missing start dates. In general dates will be imputed conservatively such that if possible an AE will be classified as treatment-emergent. If a TEAE could potentially be assigned to more than one period, based on imputation, the following priority order will be used to impute the dates – Treatment Period 2>Treatment Period 1>Run-In Period:

- If only day is missing:
  - If month and year are the same as the first dose in Treatment Period 2, then use the date of first dose in Treatment Period 2, else;
  - If month and year are the same as the first dose in Treatment Period 1, then use the date of first dose in Treatment Period 1, else;
  - If month and year are the same as the first dose in Run-In (and not the same as the first dose in Treatment Period 1), then use the date of first dose in Run-In.
  - If none of the above apply then use the 1st of the known month or the date of Screening if this is later.

  If any of the above result in an imputed start date after a known end date then use the 1st of the start month or the date of Screening if this is later.

- If day and month are missing:
  - If the year is the same as the first dose in Treatment Period 2, then use the date of first dose in Treatment Period 2, else;
  - If the year is the same as the first dose in Treatment Period 1, then use the date of first dose in Treatment Period 1, else;
  - If the year is the same as the first dose in Run-In (and not the same as the first dose in Treatment Period 1 or Treatment Period 2), then use the date of first dose in Run-In.
  - If none of the above apply then use the 1st of January in the known year or the date of Screening if this is later.

  If any of the above result in an imputed start date after a known end date then use the 1st of January in the known year or the date of Screening if this is later.
- If the start date is completely unknown, then use the date of first dose in Treatment Period 2. If this results in an imputed start date that is after a known end date, then use
  - The date of first dose in Treatment Period 1 (if prior to known end date), else;
  - The date of first dose in Run-In (if prior to known end date), else;
  - 1st of January in the year of the end date or the date of Screening if this is later.

Missing or partially missing dates will be imputed as described in the below table for the calculation of duration of each AE. Adverse event duration is computed in and reported in days.

Calculation rules for AE duration

Data availability	Onset date	Outcome date	Calculation rules
Complete data	D1	D2	Duration = D2 – D1 +1 day
Start date partially or completely missing	--	D2	Duration = D2 – D0 +1 day Notes: D0 is imputed start date per above rules.
End date partially missing or completely missing	D1	--	For ongoing AE: Duration = >Discharge date – D1 For resolved AE: Duration = < Discharge date – D1 Where discharge refers to the date of the SFU/EOS visit, or the date of last contact if the participant did not attend the SFU/EOS visit.

Calculation rules for AE duration

Data availability	Onset date	Outcome date	Calculation rules
Start and end date missing	--	--	For ongoing AE: Duration = >Discharge day – D0 For resolved AE: Duration = <Discharge day – D0 Where discharge refers to the date of the SFU/EOS visit, or the date of last contact if the participant did not attend the SFU/EOS visit.

Days since most recent dose/first dose in Run-In/first dose in Treatment Period 1 are calculated in the following way:

AE start date – date of most recent dose/first dose of treatment in Run-In/first dose in Treatment Period 1 +1 day

This calculation will only be completed for AEs with a known start date.

8.2.2 Medications

For the classification of medications as prior or concomitant, the rules below will be applied for partial or completely missing start dates. In general, dates will be imputed conservatively such that if possible a medication will be classified as concomitant. If a medication could potentially be assigned to more than one period, based on imputation, the medication would be assigned to all possible periods.

- If only day is missing, then use the 1st of the known month or the date of Screening if this is later.
- If day and month are missing, then use the 1st of January in the known year or the date of Screening if this is later.
- If the start date is completely unknown, then use the date of Screening.

For the classification of prior and concomitant medications the following rules will be applied for partial or missing stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the participant dies, then use the date of death;
- If the stop date is completely unknown, do not impute the stop date.

If the stop date of a medication is completely unknown and therefore not imputed, medications are assumed to be concomitant in all periods following the start date, for all periods the participant entered.

8.2.3 Procedures

For the classification of medical procedures as prior or concomitant, the rules below will be applied for partial or completely missing date of procedure.

- If only day is missing, then use the 1st of the known month or the date of Screening if this is later.
- If day and month are missing, then use the 1st of January in the known year or the date of Screening if this is later.
- If the date of procedure is completely unknown, then use the date of Screening.

8.2.4 Time Since Diagnosis / First Symptoms of FMS

For the calculation of time since diagnosis of FMS and time since first symptoms of FMS, the following rules will be applied for partial start dates:

- If only day is missing, then use the 1st of the known start month
- If month and day are missing, then use January 01 in the known start year.

If the date is completely missing, then no imputation is applied and therefore, the time since diagnosis / first symptoms of FMS will not be calculated.

Time since diagnosis of FMS is calculated in the following way:

- Time since diagnosis of FMS (years) = (date of screening – date of FMS diagnosis)/365.25

Time since first symptoms of FMS is calculated in the following way:

- Time since first symptoms of FMS (years) = (date of screening – date of first symptoms of FMS)/365.25

Time since diagnosis and time since first symptoms will be rounded to 1 decimal place for the listings.

8.3 Appendix 3: AEOF

The following events are Adverse Event of Focus for rozanolixizumab:

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

No	Event (also included in Title of TFL output)	Selection criteria
		HLT='Injection site reactions' or HLT='Infusion site reactions' or HLT='Administration site reactions NEC'
7	Infections	TEAE with SOC ="Infections and infestations" **Note:** This was added as a reminder for safety that infections are considered as AE of focus and require assessment. No programming of this topic is required as TEAEs can be found in general AE Tables.
8	Opportunistic infections (Note: also included in AESM)	TEAEs in MedDRA SMQ = 'Opportunistic infections' narrow search
9	Effects on the kidney	TEAEs in SMQ= 'Acute renal failure' narrow search
10	Drug related hepatic disorders	TEAEs in SMQ='Drug related hepatic disorders - comprehensive search' narrow and broad search
11	Effect on lipids	TEAEs with PT= 'Blood cholesterol increased' or PT= 'Low density lipoprotein increased' or PT= 'Blood triglycerides increased' or PT= 'Hypercholesterolaemia' or PT= 'Hypertriglyceridaemia' or PT= 'Hyperlipidaemia' or PT= 'Dyslipidaemia' or PT= 'Lipids increased'

8.4 Appendix 4: Period of Onset Assignment

8.4.1 Adverse Events and IPDs

The period of onset for AEs and IPDs is determined in the following way:

- If the event occurs prior to the date of first dose of IMP in Run-In, then the event is assigned to the Screening Period.
- Events are assigned to the Run-In Period in the following cases:
  - If the event occurs on or after the date of first dose of IMP in Run-In and prior to the date of first dose of IMP in Treatment Period 1.
  - If the study participant withdraws during Run-In (ie prior to the first dose of IMP in Treatment Period 1) and the event occurs on or after the date of first dose of IMP in Run-In and within 6 days after the date of last dose of IMP prior to withdrawal.

- Events are assigned to Treatment Period 1 in the following cases:
  - If the event occurs on or after the date of first dose of IMP in Treatment Period 1 and prior to the date of first dose of IMP in Treatment Period 2.
  - If the study participant withdraws during Treatment Period 1 (ie prior to the first dose of IMP in Treatment Period 2) and the event occurs on or after the date of first dose of IMP in Treatment Period 1 and within 6 days after the date of last dose of IMP prior to withdrawal.
- Events are assigned to Treatment Period 2 in the following cases:
  - If the event occurs on or after the date of first dose of IMP in Treatment Period 2 and prior to the date of first dose of IMP in Run-Out.
  - If the study participant withdraws during Treatment Period 2 (ie prior to the first dose of IMP in Run-Out) and the event occurs on or after the date of first dose of IMP in Treatment Period 2 and within 6 days after the date of last dose of IMP prior to withdrawal.
- Events are assigned to the Run-Out Period in the following cases:
  - If the event occurs on or after the date of first dose of IMP in Run-Out and within 6 days after the date of last dose of IMP in Run-Out.
- Events are assigned to the SFU in the following case:
  - If the event occurs on or after 7 days after the date of last dose of IMP.

For AEs, the above rules are applied after any date imputation.

8.4.2 Medications

Medications are attributed to all study periods where received, using imputed start dates, if required:

- If the medication was received prior to the date of Screening, then the medication is attributed to the Pre-Screening Period.
- If the medication was received on or after the date of Screening and prior to the date of first dose of IMP in Run-In, then the medication is attributed to the Screening Period.
- Medications are attributed to the Run-In Period in the following cases:
  - If the medication was received on or after the date of first dose of IMP in Run-In and prior to the date of first dose of IMP in Treatment Period 1.
  - If the study participant withdraws during Run-In (ie prior to the date of first dose of IMP in Treatment Period 1) and the medication was received on or after the date of first dose of IMP in Run-In and within 6 days after the date of last dose of IMP prior to withdrawal.
- Medications are attributed to Treatment Period 1 in the following cases:
  - If the medication was received on or after the date of first dose of IMP in Treatment Period 1 and prior to the date of first dose of IMP in Treatment Period 2.

  - If the study participant withdraws during Treatment Period 1 (ie prior to the date of first dose of IMP in Treatment Period 2) and the medication was received on or after the date of first dose of IMP in Treatment Period 1 and within 6 days after the date of last dose of IMP prior to withdrawal.

- Medications are attributed to Treatment Period 2 in the following cases:
  - If the medication was received on or after the date of first dose of IMP in Treatment Period 2 and prior to the date of first dose of IMP in Run-Out.
  - If the study participant withdraws during Treatment Period 2 (ie prior to the date of first dose of IMP in Run-Out) and the medication was received on or after the date of first dose of IMP in Treatment Period 2 and within 6 days after the date of last dose of IMP prior to withdrawal.
- Medications are attributed to the Run-Out Period in the following cases:
  - If the medication was received on or after the date of first dose of IMP in Run-Out and within 6 days after the date of last dose of IMP in Run-Out.
- Medications are attributed to the SFU in the following case:
  - If the medication was received on or after 7 days after the date of last dose of IMP.

9 AMENDMENT(S) TO THE STATISTICIAL ANALYSIS PLAN (SAP)

9.1 Amendment 1

The following updates were made in SAP Amendment 1:

- The exploratory endpoints listed in Section 1.1 were updated to align with Protocol Amendment 3
- Section 1.2 was updated to include the inclusion criteria for study participants enrolled under all versions of the protocol.
- Clarifications were made to the definitions of the SS-t and PDS in Section 4
- The definition of Period Day was updated in Section 5.1.1.1 and clarification of study periods was added to Section 5.1.1.2.
- The definitions of Baseline were updated for hematology, serum chemistry, urinalysis, vital signs and ADA assessments in Section 5.1.1.3. The ECG endpoint was removed, and the PD and Pressure Pain Threshold Baseline definitions were added to the table.
- Duplicated text relating to the analysis sets was removed from Section 5.1.1.4
- An additional sub-section (Section 5.1.2) was added detailing the changes to protocol-defined-analyses
- Clarification relating to the reporting of IPDs and details regarding the classification of IPDs and analysis sets for the early readout and final analysis were added to Section 5.1.3.

- Clarification of the handling of early withdrawal events was added to Section 5.1.5.
- The WHO-DD version was updated throughout
- The calculation of total days on study medication was added to Section 5.2.1 and clarification of how the period of discontinuation is to be derived was added.
- Section 5.3.1 was updated to include weight and BMI categories to the list of required categorical demographic summaries.
- Additional sections were added to denote the listing requirements for the History of Headache and Medical History on Pain Management Programs eCRF following Protocol Amendment 3.
- The definitions of prior and concomitant medications were amended in Section 5.3.6 and clarification was added regarding the attribution of medications to study periods. Reference to prior and concomitant medical procedures was removed and a new section was added for the definition and listing requirements of medical procedures (Section 5.3.7).
- Clarification of the TFL requirements for the pharmacokinetics and pharmacodynamics endpoints were added to Sections 5.5.1 and 5.5.2, respectively.
- Section 5.6.1 was updated to ensure the TFL summaries for extent of exposure cover all planned treatment sequences and not exposure to active drug only. In addition, the derivation of study medication duration was split out into 2 calculations for the summaries, and the summary by treatment duration category was removed.
- In Section 5.6.2, the definition of TEAE was amended. The requirements of the table summaries were clarified, the requirement of exposure adjusted analysis was removed, and the data required in the AE listings was clarified. In addition, the summaries of drug-related TEAEs and serious drug-related TEAEs by preferred term were added.
- The definition of treatment-emergent was updated in Section 5.6.6 and Appendix 1.
- The requirements of the clinical laboratory tables and listings were updated in Section 5.6.6
- The requirements of the time points to summarise for the vital signs tables were updated in Section 5.6.7
- ECG assessments at Visit 15, 27, and EOT/EW were removed from the schedule of assessments in Protocol Amendment 3. Therefore, the description of the summary tables were removed from Section 5.6.8.
- The requirements of the immunogenicity analysis were re-defined in Section 5.7.
- Section 5.8 was updated to clarify the table summary requirements of the efficacy endpoints, as well as the Forest plot requirements, and to clarify how multiple daily pain and fatigue NRS scores should be handled.
- The model to be used for the secondary analysis was updated to align with the model for the primary efficacy analysis in Section 5.8.2.2
- Section 5.8.3 was updated to clarify the requirements of the supportive and sensitivity analyses.

- Clarifications of the secondary and exploratory efficacy endpoints were added to Section 5.8.4
- Clarification that no imputation of efficacy variables will be conducted was added to Section 5.8.5
- The analysis requirements of the immunological endpoints were updated in Section 5.11
- Reference to the Interim Analysis was removed throughout.
- Section 5.12.1 was updated with a description of the Early Readout Analysis.
- Section 6.2 was updated to clarify that the DSUR tables will be completed by the UCB statistical programming team.
- Appendix 1 and 2 (Schedule of Activities and Changes to Protocol Planned Analyses) were removed and subsequent appendices were re-numbered accordingly.
- Minor amendments were made to the TEMA criteria for WBC, glucose and IgG laboratory assessments marked abnormality criteria in Section 7.1
- Section 7.2 was updated to add reference to partial times when classifying TEAEs and prior and concomitant medications, and calculating AE durations and time to onset of AEs. Rules were also added for handling partial dates of medical procedures and diagnosis and first symptoms of FMS.
- Section 7.3 was updated to align with the AEOF criteria listed in the FM0001 PSAP.
- Section 7.4 was added to clarify the assignment of period of onset for AEs, IPDs, and medications

  Additional minor clarifications and cosmetic updates were made throughout.

Approval Signatures

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