TP0003

STATISTICAL ANALYSIS PLAN

AMENDMENT 3

Study: TP0003

Product: Rozanolixizumab

A PHASE 3 MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ROZANOLIXIZUMAB IN ADULT STUDY PARTICIPANTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

SAP/Amendment Number	Date
Final SAP	10 Jul 2020
SAP Amendment 1	27 Jan 2021
SAP Amendment 2	22 Feb 2021
SAP Amendment 3	16 Aug 2022

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List of Abbreviations

ADAs	Antidrug antibodies
AEOF	Adverse event of focus
BLQ	Below the limit of quantification
BP	Blood pressure
CP	Confirmed positive
CSR	Clinical Study Report
CV	Coefficient of variation
DEM	Data Evaluation Meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EQ-5D-5L	European Quality of Life-5 Dimension 5 Level Assessment
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EW	Early withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
geoCV	Geometric coefficient of variation
geoMean	Geometric mean
hCG	Human chorionic gonadotropin
HLT	High level term
HRQoL	Health-related quality of life
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IPD	Important protocol deviations
ITP	Primary immune thrombocytopenia
ITP-BAT	ITP- Bleeding Assessment Tool
ITP-PAQ	ITP-Patient Assessment Questionnaire
LLOQ	Lower limit of quantification
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities

n	Number of participants
NCP	Not confirmed positive
OLE	Open Label Extension
PCS	Physical Component Summary
PD	Pharmacodynamic
PDILI	Potential drug-induced liver injury
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PROs	Patient reported outcomes
PT	Preferred term
RNA	Ribonucleic acid
RLZ	Rozanolixizumab
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SF-36	Short-Form 36-Item Health Survey
SFU	Safety Follow-up
SOC	System organ class
SS	Safety Set
TEAE	Treatment-emergent adverse event
TEMA	Treatment-emergent markedly abnormal
TFLs	Tables, figures and listings
TPO	Thrombopoietin
TPO-RAs	Thrombopoietin-receptor agonists
ULN	Upper limit of normal

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the statistical analyses of the study TP0003, including the final analyses. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

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

Protocol Amendment 3: 03 Dec 2021 and all previous protocol versions
DMC Charter 2: 14 Jun 2021

At the time this SAP, that is based on Protocol Amendment 3, was written, the sponsor had decided to terminate this study. No study participant was randomized under Protocol Amendment 3 and hence all analyses that are described in this SAP will be run on data from study participants that were randomized according to previous versions of the protocol. These study participants did all receive a starting dose of [redacted] equivalent rozanolixizumab and continued dosing on a bi-weekly basis. None of the study participants were switched to weekly dosing prior to termination of the study.

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

UCB is the Sponsor and Parexel is the Contract Research Organization (CRO) for this study.

Note: The terms Investigational Medical Product (IMP) and study medication are used interchangeably in this document.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To demonstrate the clinical efficacy of rozanolixizumab in maintenance treatment in study participants with primary ITP.

2.1.2 Secondary objective

To assess the safety and tolerability of rozanolixizumab

2.1.3 Exploratory objectives

- To evaluate the clinical efficacy as measured by the ITP bleeding score
- To assess the effect of rozanolixizumab on health-related quality of life (HRQoL)
- To assess hospitalizations due to ITP
- To assess the effect of rozanolixizumab on patient reported outcomes (PROs)
- To assess the pharmacokinetics of rozanolixizumab administered by subcutaneous (sc) infusion

- To evaluate the incidence and emergence of antidrug antibodies (ADAs) of rozanolixizumab
- To assess the pharmacodynamic (PD) effects of rozanolixizumab
- To assess the influence of rozanolixizumab treatment on vaccination titers
- To assess the effect of rozanolixizumab on response to vaccination in study participants who received COVID-19 vaccine

2.2 Study endpoints

2.2.1 Efficacy endpoints

2.2.1.1 Primary efficacy endpoint

Durable Clinically Meaningful Platelet Response of $\geq 50x10^9$/L for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to 25)

2.2.1.2 Secondary efficacy endpoints

- Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50x10^9$/L over the 24-week treatment period
- Time to first Clinically Meaningful Platelet Response of $\geq 50x10^9$/L: time from starting treatment to achievement of first response of $\geq 50x10^9$/L
- Clinically Meaningful Platelet Response of $\geq 50x10^9$/L by Day 8
- Response defined as platelet count $\geq 30x10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit[a,b]
- Time to first rescue therapy
- Change from Baseline to Week 25 in ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score

Notes:

[a] Absence of bleeding indicated by Grade 0 for all domains of the skin, mucosae, and organs (SMOG), or a Skin Grade of 0 or 1.

[b] Nominal visits are on-site visits where ITP bleeding scale assessment is performed.

2.2.1.3 Other efficacy endpoints

- Duration of first Clinically Meaningful Platelet Response of $\geq 50x10^9$/L: measured from achievement of first Response to loss of Response (loss of Response defined as platelet count $<50x10^9$/L)
- Time to first Response: time from starting treatment to achievement of Response
- Usage of rescue therapy (Yes/No) by visit
- Complete Response (platelet count): defined as platelet count $\geq 100x10^9$/L confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit

- Cumulative number of weeks over the planned 24-Week treatment period with platelet counts of $\geq 100 \times 10^9$/L
- Cumulative number of weeks over the planned 24-Week treatment period with platelet counts $\geq 30 \times 10^9$/L and at least doubling from Baseline
- Mean change from Baseline in platelet count by visit
- Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L, for at least 4 out of 6 weeks during the last 6 weeks (Week 19 to 25)
- Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L, for at least 6 out of 8 weeks during the last 8 weeks (Week 17 to 25)

2.2.1.4 Exploratory endpoints

- ITP-specific Bleeding Assessment Tool (ITP-BAT) bleeding events and severity by visit
- Change from Baseline in European Quality of Life-5 Dimension 5 Levels (EQ-5D-5L) item responses
- Change from Baseline in Short form 36-item (SF-36) domain and composite scores
- Change from Baseline in the ITP-PAQ V1 domain Scores
- Number and length of hospitalizations
- Change from Baseline in FATIGUE-PRO Physical Fatigue Score by visit
- Change from Baseline in Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C) at all available post-baseline assessments
- Plasma concentration of rozanolixizumab
- ADAs at each scheduled assessment

2.2.1.4.1 Exploratory pharmacodynamic endpoint:

- Total serum IgG (absolute value) and change from Baseline (absolute values and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment
- Absolute values and change from Baseline (absolute values and percentage) in serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment

2.2.1.4.2 Other exploratory endpoints

- Percent change from Baseline in vaccination titers against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants
- Percent change from Baseline in vaccination titers against tetanus in all study participants
- Change in biomarkers of COVID-19 vaccine response over time

2.2.2 Safety endpoints

Secondary Safety Endpoints:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Occurrence of TEAEs leading to withdrawal of investigational medicinal product (IMP) (ie, study discontinuation)

2.2.2.1 Other safety endpoints

- Occurrence of serious TEAEs
- Occurrence of treatment related TEAEs
- Occurrence of adverse events of special monitoring (AESM)

2.3 Study design and conduct

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study with rozanolixizumab in study participants with persistent or chronic primary ITP defined as more than 3 months, or 12 months of duration, respectively, since diagnosis.

The study participants will be male and female adults with persistent or chronic primary ITP, a platelet count measurement at Screening and at Baseline with an average of the two <$30x10^9$/L (no single count may be >$35x10^9$/L) and a documented history of low platelet count prior to Screening.

The primary objective of TP0003 is to evaluate the clinical efficacy of rozanolixizumab as a maintenance treatment in participants with persistent or chronic primary ITP.

The study will assess whether multiple sc infusions of rozanolixizumab will result in a durable Clinically Meaningful Platelet count increase of ≥$50x10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks of the Treatment Period (Week 13 to 25). On Day 1 (Baseline Visit), study participants will be randomized 2:1 to receive a fixed-unit dose of rozanolixizumab [redacted] or placebo QW until Week 24, with randomization stratified by the degree of thrombocytopenia (platelet count < or ≥$15x10^9$/L) and history of splenectomy (yes or no). The last assessments prior to the SFU Visit will be done at Week 25. Study participants will be observed during the 8-week SFU Period after the final administered dose.

Note: As all study participants for the analysis were enrolled under previous protocol versions, they were randomized to receive a fixed-unit starting dose of rozanolixizumab [redacted] or placebo. Following the initial dose, study participants were receiving a fixed unit dose [redacted] rozanolixizumab or placebo Q2W until Week 23.

The total maximum study duration per study participant is up to 35 weeks, including a Screening Period (up to 4 weeks), a Dose Adaptation Period (12 weeks), a Maintenance Period (12 weeks) and an SFU Period (8 weeks after final dose administered). Splenectomized participants will be required to attend a Prolonged Screening Period prior to the Screening Visit in order to receive, if applicable, the required vaccinations, which will extend the total study duration by up to 20 weeks.

The eligibility of study participants to participate in the study will be determined during the Screening Period. Once eligibility is confirmed, the study participants will come to the site on Day 1 (Baseline Visit) and receive a single fixed-unit dose of rozanolixizumab or placebo administered sc (based on randomization).

Rozanolixizumab or placebo will be administered as a sc infusion with an infusion pump at a [redacted]. A fixed-unit dose across different body weight tiers, as presented in Table 1-2 in the study protocol will be applied.

[redacted]

The placebo arm will use 0.9% sodium chloride aqueous solution (physiological saline, preservative-free) for sc administration, matching the volumes of the rozanolixizumab arm. Dosing will be followed by a series of postdose study assessments on Day 1 through Day 169, with a subsequent SFU Period through Day 218. On dosing days, for the first 2 weeks, a 4-hour post-dose observation will be in place. Assuming the first 2 doses were well tolerated, on dosing days in Week 3, 4, and 5, a 1-hour post dose observation will be in place. Assuming the first 5 doses were well tolerated, on subsequent weeks, a 15-minute post-dose observation will be in place. However, if the dose needs to be decreased due to a TEAE(s) or dose needs to be increased, post dose observation will be extended to 1 hour after the end of infusion for the next 2 infusions. The post-dose observation time frame may be extended at the discretion of the investigator. These recommendations are applicable for dosing at site and at home. Approval from the investigator and sponsor is required prior to the start of home dosing.

Note: All study participants for the analysis described in this SAP were enrolled under previous protocol versions and randomized to bi-weekly dosing. SFU Period was until Day 211. For the first three infusions, they were expected to stay at the study site for 4 hours after the end of infusion, and 2 hours after the IMP infusion for the remaining visits until W23. If needed, observation time at site could be extended for each study participant.

In exceptional circumstances (eg, pandemic, hurricanes, etc) where study-specific investigations may not be conducted according to study protocol, contingency measures will be in place (see Section 8 in the study protocol for details).

Approximately 150 study participants were planned to be screened at approximately 70 sites from North America, Europe and Asia to achieve the targeted number of approximately 60 evaluable study participants randomized to weekly dosing.

Note: Due to a strategic decision, the study was stopped early after 33 participants were randomized to bi-weekly dosing per previous protocol versions. Thus, no participants were randomized to weekly dosing in the study per Protocol Amendment 3.

All study participants completing the Treatment Period (with or without the need for rescue therapy) and fulfilling the OLE study (TP0004) eligibility criteria will be allowed to enroll into TP0004.

If study participants require rescue therapy during the Treatment Period (Week 1 to Week 25), they were allowed to receive commercially available rescue therapy (Section 6.4.3 in the study protocol).

An external IDMC was established to review the safety data at predefined intervals and ad hoc as needed, should emerging safety concerns arise during the study. The first IDMC meeting for the review of safety data was planned to occur after approximately 15 participants had received 3

doses of IMP in TP0003 or TP0006. The study was to be put on hold if any of the following occurred:

- The IDMC judges it necessary for medical or safety reasons and
- The sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations and Good Clinical Practice.
- Three study participants experience any SAE of same type within the first 15 study participants who have received 3 doses of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug. After Protocol Amendment 3, this rule no longer applied.
  - For US and Canada only: Three study participants experience any SAE within the first 15 study participants who have received at least one dose of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.

The IDMC has the possibility to unblind the data. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter. It is intended to have one IDMC for both of the pivotal studies (TP0003 and TP0006), where the data will be presented unpooled, ie, data from each study will be reviewed separately. Key safety data may be pooled at the discretion of the IDMC for protection of all study participants if warranted.

Based on feedback from the IDMC, weekly dosing was suggested and it was implemented in protocol amendment 3. Study participants being treated with the bi-weekly dosing regimen would switch to the weekly dosing regimen once protocol amendment 3 was approved at the respective study site.

Note: No study participants were actually switched to weekly dosing or started on weekly dosing prior to the termination of the study.

Additionally, a Safety Signal Detection Team performed rozanolixizumab program-wide aggregated safety data reviews at predefined intervals.

2.4 Determination of sample size

Following Protocol Amendment 3, the sample size calculation was amended to reflect the primary objective of assessing the treatment effect on participants who were randomized to weekly infusions. To achieve the study objectives within the sample size cap of the original 2-stage adaptive design, the futility assessment and option for a sample size re-assessment were no longer considered and the sample size calculation was amended as appropriate for a fixed parallel group design.

The observed durable platelet response rates (platelet count $\geq 50 \times 10^9$/L during 6 or more of the last 8 weeks of treatment), from Kuter et al (2008) in splenectomized participants were 38% (16/42) on active and 0% (0/21) on placebo. In non-splenectomized participants the rates were 61% (25/41) and 5% (1/21), respectively.

Using the true response rate of 0.45 versus 0.05, a sample size of 60 participants randomized in a 2:1 ratio (ie, n=40 on rozanolixizumab and n=20 on placebo) receiving weekly infusions would provide >90% power to detect a statistically significant difference between treatment groups using Fisher's Exact Test at an alpha level of 0.025 (1-sided).

By definition participants who dropout of the study are determined as nonresponders and are incorporated in the overall response rate. If the number of dropouts is greater than anticipated by 10%, the impact on the rozanalixizumab response rate would mean that it would drop to a response rate of 0.4. In such cases, the study would still achieve >80% power if the overall response rate on placebo remains at 0.05.

If the response rate on placebo was 0.1 rather than the anticipated 0.05, the rozanolixizumab rate would need to be >0.45 to achieve 80% and >0.5 to achieve 90% power. Table 2-1 provides power estimates for a fixed study design of n=60 participants in a 2:1 randomization ratio.

Table 2-1: Expected sample size

Scenario	Placebo Response Rate of 0.05			Placebo Response Rate of 0.1		
	RLZ	Placebo	Power[a]	RLZ	Placebo	Power[a]
1	0.30	0.05	56%	0.30	0.10	32%
2	0.35	0.05	73%	0.35	0.10	48%
3	0.40	0.05	85%	0.40	0.10	63%
4	0.45	0.05	93%	0.45	0.10	77%
5	0.50	0.05	97%	0.50	0.10	87%
6	0.55	0.05	98%	0.55	0.10	93%

[a] Power for a Parallel Group Design with N=60 in a 2:1 randomization test computed with Fisher's exact test using NQuery Advisor 7.0.

Note: Due to sponsor decision, the study was stopped early after 33 study participants were randomized to bi-weekly dosing per previous protocol versions. Thus, no study participants were randomized to weekly dosing in the study per Protocol Amendment 3 and all analyses will be conducted on the first 33 study participants who had bi-weekly dosing.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, participant data listings, and statistical output will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC, USA).

All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For continuous variables, descriptive statistics will include number of participants with available measurements (n), mean, standard deviation (SD), the median, minimum, and maximum.

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

- For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the analysis set and include a "Missing" category (corresponding to participants with missing data for the variable being summarized) as the last row in the list of categories being summarized.
- For summaries of efficacy and safety variables, unless otherwise specified: summarize percentages based only on those participants with observed data for the variable being summarized. As the denominator may be different from the number of participants in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)."

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

For the purpose of the tabulations the lower and upper confidence limits for the percentages will be truncated at 0 and 100% respectively.

For PK concentrations, summary statistics will include geometric mean, geometric coefficient of variation (CV), 95% confidence intervals (CIs) for geometric mean, arithmetic mean, SD, median, minimum, and maximum. All summaries of PK variables will be based on the observed values. No imputation will be used.

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

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

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

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

3.2 General study level definitions

3.2.1 Analysis time points

All data will be analyzed based on the visits identified per the Schedule of Activities in the protocol.
Note: As no study participants were randomized under Protocol Amendment 3 the visit schedule and associated activities relate to those of earlier protocol versions.

Mapping to visit windows will not be applied. For Early Withdrawal visits refer to Section 3.2.3.

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first sc infusion of study drug as reference.

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

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

The relative day for an event or measurement occurring on or after the reference date to the date of the last infusion is calculated as follows:

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

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

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

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

3.2.2 Study periods

The following study periods are defined for this trial:

- Prolonged Screening Period: splenectomized participants will be required to attend a Prolonged Period prior to the Screening Visit for the assessment of vaccination titers and to receive, if applicable, the required vaccinations, which will extend the total study duration by up to 20 weeks.
- Screening Period (up to 4 weeks): Starts at the time of the informed consent date and ends the day before the first dose administration of study drug (i.e. generally the day before Day 1 visit date).

  Note: after signing the ICF splenectomized participants will go first through the Prolonged Screening Period and then to the Screening Period, while the non-splenectomized will go directly to the Screening Period.
- Dose Adaptation Period (12 weeks): Starts on the day of the first dose administration of study drug (Day 1) and ends after the Week 13 visit assessments.
- Maintenance Period (12 weeks): Starts on the day after the 12-week Dose Adaptation Period (Week 13) and ends after the Week 25 visit assessments (or at the Early Withdrawal (EW) Visit for study participants withdrawn from the study before Week 25 visit).
- Treatment Period: Starts on the day of the first dose administration of study drug (Day 1) and ends after the Week 25 visit assessments (or at the EW Visit for study participants withdrawn from the study before Week 25 visit). It is the combination of the Dose Adaptation Period and the Maintenance Period.
- Safety Follow-up Period (SFU): Starts with last dose administered and ends 8 weeks after final dose administered.

A study participant is considered to have completed the study if he/she has completed all phases of the study including the SFU Period or has successfully been enrolled (completed Visit 1 in TP0004) into TP0004 at Week 25.

A study participant will be said to have completed the SFU period if she/he had completed the last scheduled visit in the SFU period.

Study participants will have an EOS Visit performed 8 weeks after the final dose of IMP (unless they are enrolling in TP0004 at Week 25), or upon discontinuation of the study.

3.2.3 Mapping of assessments performed at Early Withdrawal Visit

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

3.2.4 Dosing Regimen

Because no participants in TP0003 were randomized or treated under Protocol Amendment 3.0, analysis by dosing regimen will not be performed.

3.3 Definition of Baseline values

Baseline will be the last available pre-dose value prior to the first infusion of study drug in the Treatment Period, or if missing, the Screening value. Scheduled or unscheduled measurements can be used as the Baseline value. If an unscheduled measurement occurs after the planned baseline measurement time point but before dosing, then the unscheduled measurement will be used.

3.4 Protocol deviations

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

3.5 Analysis sets

3.5.1 Enrolled Set (ES)

All study participants who have signed the informed consent.

3.5.2 Randomized Set (RS)

The RS will include all enrolled study participants who were randomized. This is equivalent to the Intent-to-Treat Set.

3.5.3 Safety Set (SS)

The SS will include all randomized study participants who received at least one dose of IMP (partial or full). Analysis of this set will be according to the treatment the participants received and will be used for the demographic and safety analyses.

3.5.4 Full Analysis Set (FAS)

The FAS consists of all randomized study participants who have received at least one sufficient sc infusion of IMP, have a valid Baseline, and at least 1 valid post-Baseline platelet count measurement during Weeks 13-25.

Note: Due to the early termination of the study and changes to the analysis, the Full Analysis Set will not be included in the analysis and the clinical study report.

3.5.5 Pharmacodynamic Per-Protocol Set (PD-PPS)

The PD-PPS is a subset of the SS, consisting of those study participants who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a participant from the PD-PPS but may lead to exclusion of specific data.

Note: Due to the early termination of the study and changes to the analysis, the PD-PPS will not be included in the analysis and the clinical study report.

3.5.6 Pharmacokinetic Per-Protocol Set (PK-PPS)

The PK-PPS is a subset of the SS, consisting of those study participants who received at least 1 dose (as described above), had at least 1 valid PK measurement and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock.

3.6 Treatment assignment and treatment groups

If after unblinding it is determined that participants at any time received incorrect treatment from their randomized assignment, then for safety analyses these participants will be reallocated to the appropriate treatment group. For example, if participants randomized to placebo received rozanolixizumab, then for the safety analyses, these participants will be reallocated to rozanolixizumab.

Participants randomized to rozanolixizumab will only be reallocated to the placebo treatment group if they never received rozanolixizumab.

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

- Placebo
- RLZ

Safety data will also be summarized based on the two groups and dose will not be shown in the header. Dose will be captured in the listings.

3.7 Center pooling strategy

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

3.8 Coding dictionaries

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

Medications will be coded according to version Mar 2021 or later of the World Health Organization Drug Dictionary (WHODD). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

(1) Analysis sets

(1.2) The FAS was removed from analysis
(1.3) The PD-PPS was removed from analysis

(2) Added COVID-19 as an intercurrent event to all endpoints

(3) Note: The study was terminated early after 33 participants were randomized to bi-weekly infusions per Protocol Amendment 2; no participants were randomized to weekly infusions in the study per Protocol Amendment 3.

(4) No formal statistical analyses of efficacy endpoints were conducted. Only the primary and secondary efficacy endpoints were summarized descriptively and listed. Protocol-defined analyses for efficacy endpoints are described below.

The primary efficacy analysis of the study was planned to conduct a Stratified Cochran-Mantel-Haenszel test statistic. Sensitivity, supplemental and subgroup analyzes were planned to test the robustness of the assumption. The secondary efficacy analyses were planned to conduct a sequential hierarchical test procedure to protect the overall significance level for the multiplicity of endpoints.

Primary and secondary efficacy endpoints listed below will be listed and summarized descriptively for study participants randomized to bi-weekly dosing according to previous protocol versions.

- Durable Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to 25)
- Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L over the 24-week treatment period (Week 1 to Week 25)
- Time to first Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L: time from starting treatment to achievement of first response of $\geq 50 \times 10^9$/L
- Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L by Day 8

- Response defined as platelet count ≥30x10^9/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit
- Time to first rescue therapy
- Change from Baseline to Week 25 in ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score

Other efficacy endpoints listed below will be listed and summarized descriptively as well.

- Cumulative number of weeks over the planned 24-Week treatment period with platelet counts ≥30×10^9/L and at least doubling from Baseline
- Mean change from Baseline in platelet count by visit

The data collected for all other efficacy endpoints will be listed only.

(5) All sensitivity and supplemental analysis to the primary endpoint and to the secondary efficacy endpoints will not be performed

(6) Subgroup analyses to the primary efficacy analysis will not be performed

(7) Analysis for the PMDA on the Japanese subset of participants will not be performed

(8) Change from baseline will not be calculated for the following endpoints. Only item responses will be listed.

- Change from Baseline in European Quality of Life-5 Dimension 5 Levels (EQ-5D-5L) item responses
- Change from Baseline in Short form 36-item (SF-36) domain and composite scores
- Change from Baseline in the ITP-PAQ V1 domain Scores
- Change from Baseline in FATIGUE-PRO Physical Fatigue Score by visit
- Change from Baseline in Patient Global Impression of Severity (PGI-S)

(9) Percent change from Baseline will not be calculated for the following endpoint. Titers will be listed.

- Percent change from Baseline in vaccination titers against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants

(10) The following endpoint will not be analyzed because no samples were collected:

- Change in biomarkers of COVID-19 vaccine response over time

(11) Change from Baseline will not be calculated for the following safety endpoints. Only raw data will be listed.

- Vital signs change from Baseline (blood pressure [BP], pulse rate, body temperature) at each scheduled assessment during Treatment and SFU Periods
- 12-lead echocardiogram (ECG) change from Baseline at each scheduled ECG visit
- Laboratory change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods

- Change from Baseline in concentrations of total protein and albumin
- Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)
- Absolute values and change from Baseline (absolute values and percentage) in serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates/factors

No statistical analysis will be performed adjusting for covariates/factors.

4.2 Handling of dropouts or missing data

4.2.1 Handling missing data for the primary and secondary efficacy endpoints

Study participants who have not met the threshold for clinically meaningful response will be imputed as non-responders for the analysis. Missing platelet data at any visit will be considered "worst case" and set to zero ("no response") for that specific visit.

Missing data for ITP Patient Assessment Questionnaire (ITP PAC) instrument will not be imputed.

Missing efficacy data encountered due to permanent treatment discontinuation due to TEAEs, or the receipt of rescue therapy will be considered as intercurrent events. For the primary efficacy analysis, patients with intercurrent events will be considered as non-responders.

Missing data strategy for PRO related endpoints will follow instructions indicated in each instrument.

4.2.2 Missing Data due to COVID-19

Unless specified otherwise, study participants who have visits impacted by COVID-19 for any reason will be considered non-responders at the corresponding visit, and missing platelet count data due to COVID-19 will be considered worst case and set to zero (“no response”) for that particular visit.

4.2.3 Dates and times

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

- Classification of Adverse events (AEs) as treatment-emergent
- Classification of medications as past, prior, or concomitant
- Durations of AEs.

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

The following rules will be applied for partial start dates:

- If only start month and year are specified and are not the same as month and year of first dosing, then use the 1st of the month
- If only the month and year are specified and the month and year of first dosing is the same as the month and year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the start month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month).
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date.
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the start date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).
- If the start date is completely unknown, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01).

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

The following rules will be applied **for partial stop dates**:

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of the known year

If the stop date is completely unknown, do not impute the stop date, except for ITP medications where end date is missing and ongoing is ticked as "no", which will be imputed as "Past" medications.

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

Table 4-1: Calculation rules for duration of AEs

Data availability	Onset date	Outcome date	Calculation rules
Complete data	Analysis Start Date (D1)	Analysis End Date (D2)	Duration = D2 – D1 + 1 day
Start date partially or completely missing	--	D2	Duration = < D2 – D0 + 1 day Notes: D0 = imputed dose start date per partial stop dates.

Data availability	Onset date	Outcome date	Calculation rules
End date partially or completely missing	D1	--	**If end date is completely missing, then:** **For ongoing AE** Duration ≥ (Discharge day – D1) + 1 day or Duration ≥ (Data cut-off day – D1) + 1 day **For resolved AE:** Duration ≤ (Discharge day – D1) + 1 day or Duration ≤ (Data cut-off day – D1) + 1 day Note: Where discharge refers to the date when the participant rolls over TP0004, or the date of EOS visit for study completers, or date of discontinuation for participants that were withdrawn from the study. **If end date is partially missing**, then: Duration = D3 – D1 + 1 day, where D3 is imputed end date using partial stop dates (see above). For any AEs with known start date, if the end date is missing, the date of last contact will be used as the discharge day. For participants still ongoing in the study at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

Data availability	Onset date	Outcome date	Calculation rules
Start and end date partially or completely missing	--	--	**For ongoing AE:** Duration ≥ (Discharge day – D0) + 1 day or Duration ≥ (Data cut-off day – D0) + 1 day **For resolved AE:** Duration ≤ (Discharge day – D0) + 1 day or Duration ≤ (Data cut-off day – D0) + 1 day For a participant in the SS, D0 is the date of first administration of IMP, and for screen failures, D0 is the date of the screening visit. Note: Discharge refers to the date of the end of study visit or the date of discontinuation from the study for participants that withdraw. For any AEs with known start date if the end date is missing, the date of last contact will be used as the discharge day. For participants still ongoing in the study at the time of the data cut-off, and for whom no discharge date is available, the date of the data cut-off will be used instead of the discharge date.

4.3 Handling of repeated and unscheduled measurements

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

- For repeated or unscheduled measurements obtained prior to the first dose of IMP the latest reliable value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics (ie, Screening and/or Baseline)
- For repeated or unscheduled measurements obtained at the designated Baseline visit, the latest reliable value (which may be scheduled or unscheduled) will be defined as the Baseline record if occurred prior to the first dose of IMP
- If any scheduled measurement obtained at any time point after the first dose of IMP is missing, unscheduled measurements will not be used for any missing assessment.
- See Section 10.4 for the rules applied to ECG triplicate measurements.

4.4 Handling and definition of the Corticosteroid (CS) prednisone equivalent dose

For the purposes of further analysis and tabulations, all corticosteroid doses (including both prior and concomitant corticosteroids taken for any indication) will be converted to prednisone equivalent doses. The conversion table for systemic corticosteroids is presented in Table 4-2.

Systemic corticosteroids are those with a route of administration of oral, intravenous, or intramuscular. All others (including topical, ocular, nasal, subcutaneous, intraarticular, etc.) will be considered non-systemic steroids which will have a prednisone equivalent dose = 0mg/day.

Budenoside is considered non-systemic even if taken orally and will always be assigned a prednisone equivalent dose = 0mg/day.

The prednisone equivalent dose will be included in the listing.

For example, if the total daily dose of triamcinolone is 8mg, the equivalent total daily dose of prednisone will be 10mg. If a new corticosteroid is reported that is not in Table 4-2, the appropriate prednisone equivalent conversion will be determined and the prednisone equivalent dose will be included in a separate systemic corticosteroids concomitant medication listing.

If medications are available in [redacted] which are not in table below, then the dose equivalent to 5mg/day Prednisone will be provided by the physician for this new system CS and the TFL footnote will be updated with this information for the newly identified CS

Table 4-2: Prednisone equivalent doses of systemic corticosteroids/steroids

Corticosteroids /Steroids	Dose equivalent to 5mg/day Prednisone
Cortisone	25
Hydrocortisone	20
Deflazacort	6.5
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Dexamethasone	0.75
Betamethasone	0.6

Notes:

- All non-systemic corticosteroids (including topical, ocular, nasal, subcutaneous, intra articular, etc.) will be assigned a prednisone equivalent dose = 0 mg/day.
- ATC2 Term = "CORTICOSTEROIDS FOR SYSTEMIC USE, [redacted]"

4.5 Interim analysis and data monitoring

4.5.1 Data Monitoring

An external IDMC will be established to review the safety data at predefined intervals and ad hoc as needed, should emerging safety concerns arise during the study. The IDMC will consist of members independent from UCB. Study enrollment will not be halted during planned IDMC review of the safety and efficacy data. The IDMC will have the possibility to unblind the data. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter. One IDMC is planned for both pivotal studies (TP0006 and TP0003), where the safety data will be initially presented unpooled, ie, data from each study will be reviewed separately. Key safety data may be pooled at the discretion of the IDMC for protection of all study participants if warranted. The first IDMC meeting for the review of safety data is planned to occur after approximately 15 participants have received 3 doses of IMP in TP0003. The

intervals for planned IDMC meetings are included in the section 4.1.2.1 in the TP0003/TP0006 Independent Data Monitoring Committee Charter. The study will be put on hold if any of the following occurs:

- The IDMC judges it necessary for medical or safety reasons and
- The sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations and Good Clinical Practice.
- An ad hoc IDMC meeting for the review of safety data is planned to occur if one of the stopping rules is met:
  - **US & Canada Rule**: Three participants experience any serious adverse event (SAE) within the first 15 study participants who have received at least one dose of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.
  - **Rest of World Rule**: Three participants experience an SAE of the same type within the first 15 study participants who have received 3 doses of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.

4.5.2 Interim analyses:

The interim analysis planned for this study under previous protocol versions was removed from Protocol Amendment #3.

4.6 Multicenter studies

This is a multicenter study however individual center's results will not be presented.

4.7 Multiple comparisons/multiplicity

As inferential statistical analyses will no longer be performed this section is not applicable.

4.8 Use of an efficacy subset of participants

Subset analyses will no longer be performed.

4.9 Active-control studies intended to show equivalence

Not applicable

4.10 Examination of subgroups

Subgroups will no longer be examined.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The following outputs will be created.

Summaries:

- **Reasons for screen failures** (as collected on the Study Termination Screen Failure CRF page) will be summarized using the ES for overall for all screened study participants who failed to be randomized.

- **Disposition of study participants screened** will be summarized using the ES for overall, by region and by site. In this summary, the site number, principal investigator name, first subject in date, last subject out date, will be captured by randomized treatment, and by each analysis set (ES, RS, SS, PK-PPS).
- **Disposition of Analysis Sets:** summary of disposition of study participants by treatments group, by analysis sets (ES, RS, SS, and PK-PPS) using the RS.
- **Disposition and Discontinuation Reasons**, using the RS, will contain the number and percentage of study participants who:
    - Started study and started each study period (Dose Adaptation Period, Maintenance Period and SFU Period)
    - Completed the study and completed each study period study period (Dose Adaptation Period, Maintenance Period and SFU Period)
    - Discontinued study and discontinued in each study period (Dose Adaptation Period, Maintenance Period and SFU Period)
    - Primary Reason for discontinuation (premature study termination as collected in the Study Termination CRF)
- **Discontinuation due to AEs**, using the RS to tabulate the total number of study participants who discontinued the study due to AEs by treatment group, and the categories: AE serious, fatal, AE non-fatal and other (AE non-serious, fatal).
- **COVID-19 Disposition:** Disposition and discontinuation reasons using the RS will contain the number and percentage of study participants who started, completed and permanently discontinued Treatment Period / Observation Period overall and by pre-, and during the COVID-19 pandemic based on the start, completed and discontinuation date relative to the pandemic cut-off date. The pandemic start date is March 20, 2020. The discontinuation reason in each period will also be summarized. Discontinuation due to COVID-19 pandemic will be listed as sub-category under “Other” reason.

5.2 Protocol deviations

Important Protocol deviations will be summarized by treatment group, using the RS to include the number and percentage of participants with:

a. No important protocol deviations

b. At least one important protocol deviation and the
   - Inclusion criteria deviation
   - Exclusion criteria deviation
   - Withdrawal criteria deviation
   - Prohibited concomitant medication use
   - Incorrect treatment or dose
   - Treatment non-compliance

- Procedural non-compliance

c. Number of Participants excluded from the PK-PPS (and all categories in item b above).

d. A summary of number and percentage of participants with an important protocol deviation by relationship to COVID-19 and treatment group will be provided for the RS. Additionally, the summary will be repeated by pre- and during the COVID-19 pandemic based on the deviations start date relative to the pandemic cut-off date. The pandemic start date is March 20, 2020.

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

Note: The criteria for exclusion of study participants and/or study data from the PK-PPS will be defined in the Protocol Deviation Specification document.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

6.1 Demographics

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

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

- Age (years) - at the time of study entry.
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) calculated as: $BMI = \frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$

Categorical variables (using frequency counts and percentages):

- Age (18 - <65, 65 - <85, ≥85 years)
- Age (≤18, 19 - <65, ≥65 years)
- BMI (<25, 25 to <30, ≥30 kg/m^2)
- Weight (<50kg, 50kg-<70 kg, 70-<100kg, ≥100kg)
- Gender (Male, Female)
- Race (American Indian or Alaska native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (North America, Europe, Asia [excluding Japan], Japan)
- Country

By-study participant listings of demographics will be provided.

Childbearing potential will be listed for the RS.

6.2 Other Baseline characteristics

6.2.1 Baseline disease characteristics

Baseline disease variables will be summarized using the RS, using descriptive statistics by treatment group and overall:

- Age at first ITP diagnosis (years)
- Time since first confirmed diagnosis of ITP (as collected in the eCRF)
- Splenectomy (Yes/No)
- IgG level (g/L) for
  - Non-splenectomized participants
  - Splenectomized participants
- Platelet count ($x10^9$/L) (as collected in the eCRF)
- Degree of thrombocytopenia (platelet count < or ≥$15x10^9$/L) (using data collected in the eCRF)
- ITP Duration (persistent or chronic primary ITP as defined in Section 2.3)
- Total number of prior unique ITP medications (continuous)
- Total number of prior ITP medications (continuous)
- Number of prior unique ITP medications (1, 2 and ≥3)
- Concomitant use of TPO-RAs (eg, Eltrombopag and/or Avatrombopag) (Yes/No)

Notes:

- Persistent or chronic primary ITP as defined in Section 2.3
- In addition, the number and percentages of study participants in each stratum for each stratification factor (splenectomy (yes/no), degree of thrombocytopenia (platelet count < or ≥$15x10^9$/L) will be presented.
- Data will be summarized using data captured or derived from eCRF.
- The duration of ITP for chronic ITP participants will be computed in years and it will be calculated as follows:

  $\frac{\text{Date of Screening} - \text{Date of Diagnosis}}{365.25}$, where the date of diagnosis will be obtained from the ITP history eCRF page.
- The duration of ITP – for persistent ITP participants will be computed in months and it will be calculated as:

  $\frac{\text{Date of Screening} - \text{Date of Diagnosis}}{30.5}$, where the date of diagnosis will be obtained from the ITP history eCRF page.

- Age at diagnosis (years) will be calculated as: $\frac{\text{Date of first diagnosis} - \text{Date of birth}}{365.25}$
- If the date of diagnosis is missing, the duration of disease and age at first diagnosis will not be calculated. In the case of the day (of the date of first diagnosis) being missing, then the day will be imputed with the last of the month. In the case day and month being missing (for the date of first diagnosis), the date will be imputed with 31st December.

  Note: if the imputation results in an imputed diagnosis date that is after screening date, then the diagnosis date will be imputed to the screening date.
- The duration of ITP will be presented in the listings as follows:
  - In years to 1 decimal place for chronic primary ITP participants
  - In months (3-12) for persistent primary ITP participants
- Unique Prior ITP is derived as follows:
  - To derive prior ITP medications, see Section 6.5
  - To derive unique: count all medications with [redacted] as one, count all medication with [redacted] as one, for remaining prior ITP medications count all unique standardized medication names (CMDECOD)

6.2.2 Lifestyle

A listing for DILI CRFs (DILI patients only) data (alcohol use and illicit drug use in the past six months (yes/no)) will be created using the RS.

6.3 Previous and ongoing medical history

Previous and ongoing medical history will be summarized by treatment group and overall system organ class (SOC), high level group term (HGLT), high level term (HLT) and preferred term (PT). Medical procedures are not coded.

Previous and ongoing medical history will be listed (separated) for the RS by treatment group and will include the MedDRA SOC, high level group term (HGLT), high level term (HLT) and PT.

6.4 Procedure history and concomitant medical procedures

Procedure history and concomitant medical procedures will be listed using the RS.

6.5 Concomitant medications

Definitions:

Past Medications: defined as any medications that started and stopped before first administration of IMP.

This includes medications reported in the following eCRF pages:

- "ITP Treatment history"
- "Prior and Concomitant Medications", if end date before first IMP date

- "Prior and Concomitant Medications ITP Treatment", if end date before first IMP date.

Prior Medications: defined as any medications that started before the first administration of IMP.

This includes medications reported in the following eCRF pages:

- "ITP Treatment History",
- "Prior and Concomitant Medications", if start date before first IMP date.
- "Prior and Concomitant Medications ITP Treatment", if start date before first IMP date.

Baseline Medications: defined as any medications that started prior to first administration of IMP and stopped after the first administration of IMP (classified as prior and concomitant medications). This includes medications reported in the following eCRF pages:

- "Prior and Concomitant Medications", if start date before first IMP date and end date after first IMP date or ongoing
- "Prior and Concomitant Medications ITP Treatment", if start date before first IMP date and end date after first IMP date or ongoing

Concomitant medications: defined as any medication that has been taken at least once after the first administration of IMP.

This includes medications reported in the following eCRF pages:

- "Prior and Concomitant Medications", if end date after first IMP date or ongoing
- "Prior and Concomitant Medications ITP Treatment", if end date after first IMP date or ongoing

Concomitant only medication: defined as any medication that started after first administration of IMP

This includes any medication reported in the following eCRF pages:

- "Prior and Concomitant Medications", if start date after first IMP date
- "Prior and Concomitant Medications ITP Treatment", if start date after first IMP date

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

Table 6-1: Concomitant Medications Classification

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

All the categories mentioned above will be summarized separately for ITP medications; Non-ITP medications will be listed only (using the RS) to display the number and percentage of participants in each category by treatment group, overall and by Anatomical Therapeutic Chemical classification (ATC) class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term.

Any medications with missing dates will be handled as described in Section 4.2.2 in order to classify them as prior and/or concomitant.

Listings for ITP medications will be also produced using the RS.

Notes:

- WHODD Mar2021 will be used for ATC terms.

6.5.1 Assignment of medications to treatment period

- **Treatment Period**: The treatment period will include medications taken at least once between the first administration of IMP on Day 1, up to the earliest of:
  - Week 25 (for participants who roll over to TP0004)
  - [redacted] after the last dose of IMP
  - The early withdrawal visit.
- **Safety Follow-Up Period:** A medication will be assigned to the Safety Follow Up Period if it has been taken at least once from the day after the end of the Treatment Period up until the EOS visit.

6.6 Prohibited concomitant medications and rescue medication

6.6.1 Prohibited concomitant medication

All prohibited concomitant medication listed in section 6.4.2 in the protocol will be summarized on the RS using the number and percentage of study participants who received prohibited concomitant medication by ATC class, presenting ATC Level 1, ATC level 3, and PT, ordered

alphabetically for the ATC class and in terms of decreasing frequency for PT within ATC class by treatment group. In the event of ties, PT will be ordered alphabetically.

6.6.2 Rescue Therapy

All rescue therapies mentioned in section 6.4.3 in the protocol, identified if Rescue Medication is ticked as yes on CRF will be summarized using the RS.

The number and percentage of study participants who received rescue medication will be displayed by ATC class, presenting ATC Level 1, ATC level 3, and PT (ordered alphabetically for the ATC class and in terms of decreasing frequency for PT within ATC class by treatment group. In the event of ties, PT will be ordered alphabetically).

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable. The number of infusions will be recorded as detailed in Section 10.1.

8 EFFICACY ANALYSES

All efficacy variables will be listed for all participants by treatment group and visit, and analyses performed using the RS unless specified otherwise.

8.1 Statistical analysis of the primary efficacy endpoint

8.1.1 Primary analysis of the primary efficacy endpoint

The primary efficacy endpoint will be analyzed according to the following estimands' attributes:

(1) Treatment conditions: Placebo and rozanolixizumab (please refer to section 6 Study treatments in the protocol for details)

(2) Population: Adult Study Participants with Persistent or Chronic Primary Immune Thrombocytopenia (ITP) who fulfill the inclusion / exclusion criteria according to the protocol.

(3) Endpoint: Durable Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)

This endpoint includes the platelet count recorded at Week 14 to Week 25 corresponding to the response achieved following dosing at Week 13 to Week 24)

(4) Intercurrent Events: see below.

Table 8-1: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of the primary endpoint

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Use of Rescue therapy from Baseline prior Week 25	A composite strategy Participants impacted by any ICE (a, b, c and d) will be considered as non-responders after the time of event.	Not applicable Section 4.2.2
b) Participants who experience any TEAEs leading to permanent treatment discontinuation		
c) Participants who discontinue prior to receiving IMP		
d) Participants who do not have any post-treatment assessment		
e) COVID-19*	A composite strategy Participants impacted by ICE (e) will be considered as non-responders at the time of event.	

* COVID-19 Impact category: Temporary discontinuation of study drug, Permanent discontinuation of study drug, Termination of study participation and Relationship to COVID-19: confirmed, suspected, general or other as recorded in the COVID-19 impact eCRF form.

(5) Population-level summary: Owing to early termination of the study, the population-level summary will be provided using descriptive statistics.

8.2 Statistical analysis of the secondary efficacy endpoints

8.2.1 Cumulative number of weeks with Clinically Meaningful Platelet Response of ≥50x10^9/L over the 24-Week treatment period (Week 1 to Week 25)

The secondary efficacy endpoint: Cumulative number of weeks with Clinically Meaningful Platelet Response of ≥50x10^9/L over the 24-week treatment period will be analyzed on the RS, under the same treatment conditions and population of interest as for the primary endpoint. Note: if platelet count was assessed multiple times in a given week, Clinically Meaningful Platelet Response only needed to be observed at one timepoint during the week. ICE, ICES and population level summary will be handled as described below:

Table 8-2: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of the Cumulative number of weeks with Clinically Meaningful Platelet Response of ≥50x10^9/L over the 24-Week treatment period

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Use of rescue therapy	A while on-treatment strategy: Participants impacted by	Participants impacted by any of the ICE will be considered as having a loss
b) Withdrawal from the study due to treatment emergent AE		

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
c) Permanent treatment discontinuation	any of the ICE will be considered as having a loss of durable platelet response at the time of the ICE occurring.	of durable platelet response at the time of the ICE occurring. Platelet data up to the start date of this ICE will be utilized in statistical analysis.
d) COVID-19*	A composite strategy: data impacted by COVID-19 will be considered as having a loss of durable platelet response at the time of the ICE occuring.	Section 4.2.2

* COVID-19 Impact category: Temporary discontinuation of study drug, Permanent discontinuation of study drug, Termination of study participation and Relationship to COVID-19: confirmed, suspected, general, or other as recorded in the COVID-19 impact eCRF form.

Population-level summary: Owing to early termination of the study, the population-level summary will be provided using descriptive statistics.

8.2.2 Time to first Clinically Meaningful Platelet Response of ≥50x10^9/L: time from starting treatment to achievement of first response of ≥50x10^9/L.

8.2.2.1 Definition

Time to first Clinically Meaningful Response of ≥50x10^9/L: time from starting treatment to achievement of first response of ≥50x10^9/L (computed as time from starting treatment to achievement of first response of ≥50x10^9/L. Date of first clinically meaningful response - Date of first treatment + 1)

The visit date when the first clinically meaningful response was recorded will be considered as the date of first clinically meaningful response.

8.2.2.2 Estimand's attributes

This secondary efficacy endpoint will be analyzed using the RS, under the same treatment conditions and population as for the primary endpoint while using the ICE, ICES described in Table 8-3 and the population level summary described below:

Table 8-3: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of Time to first Clinically Meaningful Response of ≥50x10^9/L

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Use of rescue therapy prior to Week 25	A while on-treatment strategy: For participants impacted by any of the ICE (a, b and c). Impacted data will be excluded from the time at risk.	Available platelet data up to the start date of this ICE will be utilized in statistical analysis.
b) Withdrawal from the study due to treatment emergent AE		
c) Permanent treatment discontinuation		
d) COVID-19*	Composite Strategy: data impacted by COVID-19 will	Section 4.2.2

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
	be excluded from the time at risk.	

* COVID-19 Impact category: Temporary discontinuation of study drug, Permanent discontinuation of study drug, Termination of study participation and Relationship to COVID-19: confirmed, suspected, general or other as recorded in the COVID-19 impact eCRF form.

Population-level summary: Owing to early termination of the study, the population-level summary will be provided using descriptive statistics. Median time to event will be estimated as median of observed values and also using the Kaplan-Meier estimate.

8.2.3 Clinically Meaningful Platelet Response by Day 8, defined as platelet count ≥50x10^9/L

This secondary efficacy endpoint will be analyzed using the RS, under the same treatment conditions and population as for the primary endpoint while using the ICE, ICES described in Table 8-4 and the population level summary described below:

Table 8-4: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of Clinically Meaningful Response by Day 8

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Use of rescue therapy up to Day 8	Composite strategy: Participants impacted by any of these ICE will be considered as non-responders.	Participants with missing data due to any of these ICE will be considered as non-responders.
b) TEAEs leading to permanent treatment discontinuation		
c) Discontinue prior to receiving IMP		
d) Study participant do not have a post-treatment assessment up to day 8		
e) COVID-19*	Composite Strategy: Participants impacted by ICE (e) will be considered as non-responders at the time of event.	Section 4.2.2

* COVID-19 Impact category: Temporary discontinuation of study drug, Permanent discontinuation of study drug, Termination of study participation and Relationship to COVID-19: confirmed, suspected, general or other as recorded in the COVID-19 impact eCRF form.

Population-level summary: Owing to early termination of the study, the population-level summary will be provided using descriptive statistics.

8.2.4 Response defined as platelet count ≥30x10^9/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding

Definitions:

a) Two adjacent nominal visits are defined as on-site visits where ITP bleeding scale assessment is performed

b) Absence of bleeding indicated by Grade 0 for all domains of the SMOG, or a Skin Grade of 0 or 1 by visit

8.2.4.1 Estimand's attributes

Estimated on the RS. The same considerations mentioned in Section 8.2.3, except the endpoint which in this case is considered: Response defined as platelet count $\geq 30x10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding. Endpoint will be descriptively summarized.

8.2.4.2 Sensitivity analysis

Sensitivity analysis will no longer be performed.

8.2.5 Time to first rescue therapy

Definitions:

Time to first rescue therapy (in days) is defined as: Date of first rescue therapy use - Date of first treatment + 1.

Participants who are withdrawn due to TEAEs will be censored at the start date of the TEAE, and participants who do not take rescue therapy will be censored at the date of withdrawal/study completion. Where there are several AEs which led to drop out, consider the earliest starting AE.

8.2.5.1 Estimand's attributes

The same considerations for treatment conditions and population of interest as mentioned in items 1 and 2 in Section 8.1.1, except the endpoint which is described above and the following approach for ICE (see Table 8-5) and the population level summary:

Table 8-5: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of Time to first rescue therapy

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Withdrawal from the study due to TEAE	A composite strategy: Participants will be considered censored at the time of the ICE.	Not applicable
b) COVID-19*	A composite strategy:	Section 4.2.2

* COVID-19 Impact category: Temporary discontinuation of study drug, Permanent discontinuation of study drug, Termination of study participation and Relationship to COVID-19: confirmed, suspected, general or other as recorded in the COVID-19 impact eCRF form.

Population level summary: Endpoint will be descriptively summarized. Median time to event will be estimated using the Kaplan-Meier estimate.

8.2.6 Change from Baseline to Week 25 in ITP-PAQ Symptom score

Change in ITP-Patient Assessment Questionnaire (ITP-PAQ, see section 8.1.3.1 in the protocol for details) Symptom score will be calculated at week 25 relative to the Baseline and will be

limited to the participants with a Baseline ITP-PAQ score available. Endpoint will be descriptively summarized. Please see Section 13.5 for details about ITP-PAQ scoring and ITP-PAQ scales.

8.3 Statistical analysis of other efficacy endpoints

8.3.1 Cumulative number of weeks over the planned 24-Week treatment period with platelet counts ≥30×10^9/L and at least doubling from Baseline.

Cumulative number of weeks over the planned 24-Week treatment period with platelet counts ≥30×10^9/L and at least doubling from Baseline will be summarized descriptively using the RS and listed.

The same considerations for treatment conditions and population of interest as mentioned in items 1 and 2 in Section 8.1.1, except the endpoint which is described above and the following approach for ICE (see Table 8-6) and the population level summary:

Table 8-6: Intercurrent Events (ICE), Intercurrent Events Strategies (ICES) and Missing data Strategies for the analysis of cumulative number of weeks over the planned 24-Week treatment period with platelet counts ≥30×109/L and at least doubling from Baseline..

Intercurrent Events (ICE)	ICE Strategy	Missing data strategy
a) Use of rescue therapy prior to Week 25	Composite strategy: Participants impacted by any of these ICE of interest will be considered as non-responders.	Participants with missing values due to any of these ICE of interest will be considered as non-responders.
b) TEAEs leading to permanent treatment discontinuation		
c) Discontinue prior to receiving IMP		
d) Study participant do not have a valid Baseline assessment		
e) COVID-19*	Composite Strategy: Participants impacted by ICE (e) will be considered as non-responders at the time of event.	Section 4.2.2

8.3.2 Mean change from Baseline in platelet count by visit

Mean change from Baseline in platelet count will be summarized descriptively using the RS at each timepoint.

8.4 Statistical analysis of exploratory endpoints

All exploratory variables will be listed only by treatment group and visit. No inferential assessments / testing will be performed.

8.4.1 ITP Bleeding Score

8.4.1.1 ITP-specific Bleeding Assessment Tool (ITP-BAT) bleeding events and severity by visit

ITP-BAT bleeding events by visit, will be listed using the RS.

Table 8-7: ITP-specific Bleeding Assessment Tool (ITP-BAT) Domains and categories

Skin	Mucosal	Organ
- Petechiae - Ecchymoses - Subcutaneous Hematomas - Bleeding from Minor Wounds	- Epistaxis - Oral cavity [a] - Subconjunctival Hemorrhage	- Gastrointestinal Bleeding Not Explained by Visible Mucosal Bleeding or Lesion - Lung Bleeding - Hematuria - Menorrhagia - Intramuscular Hematomas - Hemarthrosis - Ocular Bleeding - Intracranial Bleeding - Other Internal Bleedings

[a] Includes gum bleeding, hemorrhagic bullae or blisters, bleeding after bites to lip & tongue or after deciduous teeth loss

Notes:

- Presence of bleeding will be indicated by a Mucosae or Organs Grade ≥1, or Skin Grade ≥2.
- Bleeding reported by the participant without medical documentation will be graded 1.
- Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact.
- The "worst" bleeding manifestation since the last visit will be graded, and the highest grade within each domain will be recorded.

Please see Section 13.6 ITP bleeding score for more details.

8.4.1.2 ITP bleeding at Screening

Data collected in the Bleeding Assessment Tool – Screening eCRF will be listed using the RS.

8.4.1.3 Presence/Absence of ITP bleeding

The number and percentage of participants with absence/presence of bleeding (see definitions below) will be summarized, and individual participants will be listed at each visit.

- Presence of bleeding is indicated by a Grade of 1 or above, for at least one domain of the SMOG (except for Skin, where it is Grade 2 or above).
- Absence of bleeding is indicated by Grade 0 for all domains of the SMOG, or a Skin Grade of 0 or 1

8.4.2 Effect of Rozanolixizumab on Health-Related Quality of Life (HRQoL)

8.4.2.1 European Quality of Life-5 Dimensions, 5 Levels (EQ-5D-5L) item responses

As described in section 8.1.3.4 in the protocol, the EQ-5D-5L health questionnaire consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

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

Observed values in the European Quality of Life 5 Dimension 5 Levels (EQ 5D 5L) item responses and VAS scores will be listed only.

8.4.2.2 Short form 36-item (SF-36) domain and composite scores

The SF-36v2, standard recall, measures the following eight health domains as rated by the subjects over the past four weeks: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The classification of the questionnaire items to the health domains is shown in Section 13.7.

The SF-36 PCS and MCS scores are used to measure the two broad components, or aspects, of health-physical and mental. PCS and MCS are based on the aggregate of the eight health concepts described above and all of the eight health domain scales are used to score both components summary measures.

One additional item asks responders about health change over the past year.

The SF-36 will be used using QualityMetric's Health Outcomes™ Scoring Software. The software uses updated 2009 U.S. population norms and applies a Full Missing Score Estimation (Full MSE) method as follows:

- A health domain score (except the PF domain) will be estimated provided that at least one non-missing response is available within that domain
- For the PF domain item, response theory will be used to develop a model for estimates of the missing score
- Regression methods are then applied to estimate the PCS and the MCS on the basis of the available domains.

A by-participant listings of SF-36 item responses will be provided. Missing data will not be imputed.

8.4.2.3 ITP-PAQ Domain Scores

The ITP-PAQ V1 consists of 44 items that comprise 10 scales. Each of the 10 scales is scored 0 to 100 according to formula shown in section 13.5, with higher scores indicating better quality of

life. Four of the scales measure physical health: Symptoms, Bother, Fatigue, and Activity. Two of the scales measure emotional health: Fear and Psychological Health. The remaining four scales measure other aspects of QOL: Work QOL, Social QOL, Women's Reproductive QOL, and Overall QOL.

A by-subject listing of the ITP-PAQ V1 questionnaire, ITP-PAQ V1 item responses will be provided by treatment group.

8.4.3 Hospitalization due to ITP / Number and length of hospitalizations

Hospitalizations will be listed.

8.4.4 Effect of Rozanolixizumab on Patient Reported Outcomes (PRO)

8.4.4.1 FATIGUE-PRO physical fatigue score

The Fatigue Patient Reported Outcome (PRO) physical fatigue scale consists of 9 items. The scale is 1 out of the 3 scales composing the broader Fatigue instrument developed by UCB. Items are rated within a 7-day recall period on a 5-point Likert frequency scale ranging from "none of the time" to "all of the time."

A by-subject listing of the FATIGUE-PRO items will be provided by treatment group.

8.4.4.2 Patient Global Impression of Severity (PGI-S)

The PGI-S consists of a single-state, self-report measure that rates a study participant's severity of specific condition, depicting a study participant's rating of overall symptoms ("none", "mild", "moderate", "severe", or "very severe").

A by-subject listing of PGI-S will be provided by treatment group.

8.4.4.3 Patient Global Impression of Change (PGI-C)

The PGI-C is a single-state, self-report measure that reflects a study participant's belief about the efficacy of treatment for a specific condition. The PGI-C is a 7-point scale depicting a study participant's rating of overall improvement ("very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse"), was planned to be summarized at all available post-baseline visits using descriptive statistics by treatment groupon the RS.

A by-subject listing of PGI-C will be provided by treatment group.

The PGI-C sample questionnaire is available in the protocol, Appendix 18, Section 10.18.

9 PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

9.1 Pharmacokinetics

Individual plasma concentration of rozanolixizumab will be summarized by scheduled sampling day for the PK-PPS using n, arithmetic mean, median, SD, minimum, maximum, geometric mean (geomean), geometric coefficient of variation (geoCV) and 95% CI (assuming log-normally distributed data) up to week 4.

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

- Values below the LLOQ will be reported as below the limit of quantification (BLQ)
- Descriptive statistics of concentrations will be calculated if at most 1/3 of the individual data points at a timepoint are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance.
- The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geoCV) is 0
- The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data

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

Individual concentrations of rozanolixizumab will be listed for the RS for each individual with the actual time and will include the equivalent dose and actual dose being administered previous to the pk sample, the sampling time in days relative to the previous dose, the IgG observed at the same visit, the ADA titer observed for the binding assay and the NAb titer for the same visit and platelet count for the corresponding visit.

9.2 Antidrug antibodies (ADA)

The immunogenicity analysis should be done on the safety set SS. Samples from study participants on placebo will not be tested for anti-drug antibodies.

Anti-rozanolixizumab antibodies will be measured using a three-tiered assay approach: screening assay, confirmatory assay and titration assay. 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)). Any sample confirmed positive for ADA within the confirmatory assay will be further evaluated for the presence of neutralizing anti-rozanolixizumab antibodies.
Screening, confirmatory, and titer cut points of the respective assays will be determined by the bioanalytical laboratory. The relevant statistical reports will be provided as part of the bioanalytical reports. Rozanolixizumab has the potential to interfere with the antibody assay at concentrations above the drug tolerance limit (DTL); therefore, an integrated evaluation of anti-rozanolixizumab antibody results and rozanolixizumab plasma concentration will be used to enable the interpretation of immunogenicity results.The ADA sample status will be determined for each visit where samples were taken for ADA analysis:

- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immunodepletion', will be defined as ADA negative if corresponding rozanolixizumab concentrations are equal or below the validated drug tolerance limit of the ADA assay ([redacted] rozanolixizumab) allowing detection of 100ng/mL ADA
- Sample values that are either 'negative screen' or the combination of 'positive screen' and 'negative immuno-depletion', but with corresponding rozanolixizumab

concentrations above the validated drug tolerance limit of the ADA assay, will be defined as ADA inconclusive

- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as ADA positive
- Samples that could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc., will be defined as Missing
- Neutralizing antibody (NAb) sample status (positive/negative/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.

The ADA participant status will be classified on individual and group level as outlined below (Shankar et al. 2014; Rup et al, 2015). A description of how study participants will be categorized for the immunogenicity assessment is provided in Table 9-1.

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

Study participants who are identified as being treatment-induced or treatment-boosted ADA-positive will be grouped as treatment emergent (TE)-ADA positive participants. Study participants who are identified as being treatment-reduced or treatment-unaffected ADA-positive will be grouped as non-TE-ADA positive participants. Both TE-ADA positive and non-TE–ADA positive participants will be further classified as NAb negative or NAb positive.

The individual and combined ADA participant categories will be summarized overall through the SFU sample if applicable (timepoint of interest). The ADA categories are defined in Table 9-1 below.

Notes:

– The ADA sample status should be determined for each visit where samples were taken for ADA analysis.

ADA Baseline

By default, the Day 1 will be the Baseline value if the ADA status at screening is ADA negative or missing. If the ADA status at screening is ADA positive and ADA status at Day 1 is ADA negative or missing, the screening will be the Baseline value. If the ADA status at screening and Day 1 are same, Day 1 will be the Baseline value.

Table 9-1: Terms and Definitions for ADA Status Evaluation in Study Participants

Term	Definition	Category
Individual participant categories		
Pre-ADA negative – treatment induced ADA negative (ADA-NEG)	Study participants who have an ADA negative sample at Baseline and at all sampling points post-Baseline up to the timepoint of interest.	1
Inconclusive	Study participants who have an ADA positive or negative Baseline sample and some post-Baseline samples are missing or inconclusive, while other post-Baseline samples are ADA negative up to the timepoint of interest.	2
Pre-ADA negative – treatment induced ADA positive (TI-POS)	Study participants who have an ADA negative sample at Baseline and at least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest	3
Pre-ADA positive – treatment boosted ADA positive (TB-POS)	Study participants who have an ADA positive sample at Baseline and at least one ADA positive sample at any sampling point post-Baseline up to the timepoint of interest with increased titer values compared to Baseline (greater than a predefined fold difference increase from Baseline value which will be defined within the validation of the assay ie MSR of the assay[1])	4
Pre-ADA positive – treatment reduced ADA positive (TR-POS)	Study participants with an ADA positive sample at Baseline, and ADA negative samples at all sampling points post-Baseline up to the timepoint of interest	5
Pre-ADA positive – treatment unaffected ADA positive (TU-POS)	Study participants with an ADA positive sample at Baseline and an ADA positive sample at any sampling point post-Baseline up to the timepoint of interest, with titer values of the same magnitude as Baseline (less than a predefined fold difference from the Baseline value which will be defined within the validation of the assay, ie MSR of the assay[1])	6
Combined participant categories		
Treatment emergent ADA positive (TE-POS)	Includes study participants who are treatment induced ADA positive (category 3) or treatment boosted ADA positive (category 4).	7
Non-treatment emergent ADA positive (Non-TE-POS)	Includes study participants who are treatment reduced ADA positive (category 5) or treatment unaffected ADA positive (category 6).	8

Table 9-1: Terms and Definitions for ADA Status Evaluation in Study Participants

Term	Definition	Category
Treatment emergent ADA positive – NAb positive (TE-POS, NAb-POS)	Includes study participants who are treatment emergent positive (category 7) and have at least one NAb positive sample	9
Treatment emergent ADA positive – NAb negative (TE-POS, NAb-NEG)	Includes study participants who are treatment emergent positive (category 7) and have no NAb positive samples	10
Non-treatment emergent ADA positive - NAb positive (Non-TE-POS, NAb-POS)	Includes study participants who are non-treatment emergent positive (category 8) and have at least one NAb positive sample	11
Non-treatment emergent ADA positive - NAb negative (Non-TE-POS, NAb-NEG)	Includes study participants who are non-treatment emergent positive (category 8) and have no NAb positive samples	12

[1] 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.

The following outputs will be created:

Summaries on the SS:

Tables:

- Number and percentage of participants in the RLZ arm with positive, negative, inconclusive or missing sample ADA status at the time of each visit will be summarized overall. Denominator is the number of study participants having a non-missing result at that visit.
- Number and percentage of participants in the RLZ arm in each of the ADA individual categories (1 to 6) and combined (7-12) presented above will be summarized overall. Denominator will be the total number of study participants having an individual ADA participant category defined.
- Summary tables displaying the total prevalence of pre-existing ADA and NAb, and persistent ADA positivity in the RLZ arm, as defined below:
  - Total prevalence of pre-existing ADA and NAb: number and percentage of participants having an ADA positive sample status at baseline, with the denominator being the total number of study participants having a non-missing sample result at baseline. The same will be repeated for NAb.
  - Persistent ADA positivity: Number and percentage of study participants with treatment-induced ADA positive samples detected at 2 or more sequential sampling time points during the treatment (including observation and off-treatment periods), where the first and last ADA positive samples are separated by at least 16 weeks (equal to 5 half-lives of human IgG [22 days], as per Rup et al., 2015).

Listings:

Listings by timepoint using the SS will be created. The following datapoints will be included:

- Rozanolixizumab concentration
- Total IgG, and absolute platelet counts
- ADA screening results (with the confirmatory result, the ADA titer result if applicable and the ADA sample status)
- NAb result titer (when performed)
- Time since administration of IMP (in days)
- Individual ADA participant classification that apply (as defined above)
- Previous visit actual dose (mg/kg equivalent) and actual dose (mg)
- By-subject listing of immune-Related TEAEs, TEAEs of hypersensitivity reaction, anaphylactic reaction, injection site reaction, or autoimmune disorder anti-drug antibodies, the time of onset, the ADA and NAb sample status and ADA and NAb titers at the closest sampling time point prior to and subsequent to the TEAE, and time since last administration of IMP (in days).
- Notes: Study physician/safety physician/safety lead will mark the Preferred Term of immune related AEs based on an excel output of all TEAEs (blinded) after database lock. The marked AEs will be used for the summary.

9.3 Pharmacodynamic endpoints (PD)

The following pharmacodynamic endpoints will be based on the SS.

9.3.1 Total serum IgG (absolute value) and change from Baseline (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment

Total serum IgG concentrations will be summarized and listed on the SS by time point for absolute values, change from Baseline, and percentage change from Baseline overall and stratified by body weight tier.

IgG subclasses will be listed on the SS by treatment group, and time point for absolute values, change from Baseline and percentage change from Baseline overall

9.3.2 Serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment

Immunoglobulins (IgE, IgA and IgM) will no longer be summarized; IgE, IgA and IgM concentrations will be listed only.

9.4 Influence of Rozanolixizumab on vaccination titers

9.4.1 Vaccination titers against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae in splenectomized study participants

Vaccine specific antibodies concentrations will be listed to capture absolute values in vaccination titers against *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants by visit using the SS.

9.4.2 Percent change from Baseline in vaccination titers against tetanus in all study participants

Anti-tetanus toxoid serum titers will be listed to capture absolute values and the percent change from baseline in vaccination titers against tetanus in all study participants by visit using the SS.

10 SAFETY ANALYSES

All safety analyses will be presented using the SS. Listings will be presented by period, treatment group and participant; tabulations will be presented by period (treatment and safety FU Period) and treatment group.

Unless otherwise specified, safety analyses will be presented by safety treatment group as defined in Section 3.6.

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

10.1 Extent of exposure

The following summary will be created using the SS by treatment group:

a) Study IMP duration and Subject-Years of Time at Risk will be summarized using descriptive statistics.

- The number of days on IMP (extent of exposure), will be summarized using descriptive statistics for the overall treatment period.

  The number of days on IMP will be calculated as follows:

  Number of days on IMP = [(Date of Last Dose Received) - (Date of First Dose Received)] + 1

  In all calculations, if a patient dies and the date of death is missing, the date of death can be imputed as the date of last infusion of the treatment the participant was taking.

- Subject-Years of Time at Risk:
  - For study participants who complete the study as planned and continue into an open label study (and, therefore, do not have the SFU visit in the parent study)

    Date of last visit – Date of first dose + 1

  - For study participants who die prior to the final visit

Date of death – Date of first dose + 1

- For all other study participants, use the minimum of the following:

  Date of last dose – Date of first dose + 56

  Date of last clinical contact – Date of first dose + 1

- This last group could include study participants who discontinue early, study participants who complete the study as scheduled but choose not to continue into an open label study, or study participants who are ongoing in the SFU period at the time of the data snapshot.

- The total time at risk is calculated as the sum of the person-time at risk (days) across all participants in the population divided by 365.25.

As described in the protocol, a fixed-unit doses across body weight tiers and treatment arms will be employed in this study according to the following scheme, as presented in Table 10-1 below

Table 10-1: TP0003 dose levels and weight tiers of rozanolixizumab

Bodyweight	Starting dose	Maintenance dose level 1	Maintenance dose level 2	Maintenance dose level 3
>35 to <50kg	[redacted]	[redacted]	[redacted]	No weight adjustment
≥50 to <70kg	[redacted]	[redacted]	[redacted]	
≥70 to <100kg	[redacted]	[redacted]	[redacted]	[redacted]
≥100kg	[redacted]	[redacted]	[redacted]	

Note: the starting dose of [redacted] is not applicable in Protocol Amendment 3, but is applicable in earlier protocol versions.

If a study participant is in the lowest body weight tier (below 50kg) and is on the lowest dose level with a platelet count between $\geq 150\times10^9$/L and $<400\times10^9$/L, the investigator might decide to temporarily stop treatment according to medical judgement based on the observation of platelet variability. If the platelet count increases above 400×10^9/L then treatment must be stopped anyway.

The placebo arm will use 0.9% sodium chloride aqueous solution (physiological saline, preservative-free) for IV administration, matching the volumes of the rozanolixizumab arm.

A listing with all drug administration details including date, start and stop time of infusion, interruptions, discontinuations, dose, volume delivered, percent of planned dose and reasons for any interruptions or discontinuations will be created using the SS.

10.2 Adverse events

10.2.1 Data considerations

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 3.8).

In addition, AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 or later for severity. For any AEs where it is not possible to provide

a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe). For the purpose of the tabulations all CTCAE severity classifications will be mapped to a mild/moderate/severe grade as described below:

CTCAE Toxicity Grade: Severity

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3, 4, 5: Severe
- Not gradable

In summaries including intensity, the categories will be summarized according to the following:

Grade: Intensity

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe

For AEs that were not classified according to the CTCAE Toxicity (Severity) criteria, the standard intensity Grade will be applied. In case there are mismatches between Severity and Intensity Grade, the worst case (i.e., the most severe grade) will be applied.

Treatment-emergent AEs are defined as AEs starting after the time of first IMP administration up to and including 8 weeks (56 days) after the final dose.

AEs before first dosing and AEs after 8 (56 days) weeks following the final dose will be combined in one category and listed.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless evidence exists that does not allow the AE to be treatment-emergent. Handling of missing dates for classification of AEs as TEAEs is described in Section 4.2.2 .

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

TEAE-Treatment Period: a TEAE will be assigned to the Treatment Period for the tabulations if the start date of the event is on or after the date of the first administration of IMP on Day 1, up to 7 days following the final dose of IMP.

TEAE-Safety Follow up Period: a TEAE will be assigned to the Safety Follow up Period for the tabulations if the start date of the event is greater than 7 days after the date of the final dose of IMP until 8 weeks following the final dose; events starting later than 8 weeks following the final dose of IMP are not considered TEAEs.

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

A TEAE will be counted as a TEAE related to IMP if the response to the question “Relationship to Study Medication” is “Related”.

AEs will be presented as “number of participants (percentage of participants) [number of events]”. In this style of output, “[number of events]” will include all cases of an AE including repeat occurrences in individual participants, while “number of participants” will count each participant only once. AE analysis will be summarized by Treatment and follow up periods.

10.2.2 Adverse Event Summaries

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

(1) Incidence of TEAEs (defined as the number and percentage of participants with at least one TEAE (incidence proportion)) – Overview. The following categories will be included by treatment arm:
- Any TEAEs
- AESMs
- AESIs
- Serious TEAEs
- TEAEs leading to Study Discontinuation
- Permanent withdrawal from IMP due to TEAEs
- Drug-related TEAEs
- TEAEs with CTCAE Grade 3 and above [or rated as 'severe' for events with no CTCAE classification]
- All Deaths (AEs leading to death)
- All Deaths (TEAEs leading to death)
- TEAEs leading to dose modification (defined as TEAEs with an action taken with study medication of "dose increased" or "dose decreased")
- TEAEs resulting in temporary treatment interruption

The following summaries will be created by SOC, HLT and PT

(2) Incidence of fatal TEAEs by relationship
(3) Incidence of Serious TEAEs by Relationship
(4) Incidence of TEAEs leading to permanent discontinuation of IMP
(5) Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% of participants by System Organ Class and Preferred Term

– AESIs are Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality.

– AESMs are severe headache, severe GI disturbance (ie, diarrhea, abdominal pain, vomiting), opportunistic infections, arterial and venous thrombotic and thromboembolic events.

– AESMs and AESIs will be identified based on the assessment by the Investigator as recorded in the CRF. An AE will be counted as an AESM if there is a 'yes' response to the question "Is this an event of Special Monitoring?" and not otherwise. An AE will be counted as an AESI if there is a 'yes' response to the question "Adverse Event of Special Interest?" and not otherwise.

Listing will be presented by treatment group, most recent dose and participant for all AEs. This will include the onset date/time and outcome date/time of the event (including relative days), the AE duration, days since first dose of IMP, days since most recent dose of IMP, most recent dose, pattern of event, severity/intensity, relationship, action taken

and outcome. In addition, the listing will flag AEs that led to discontinuation, TEAEs, serious adverse events (SAEs), AESMs, and AESIs.

AEs of Focus:

AEs of Focus (AEOF) will be defined using Version 3.0 or later of "Adverse Events of Focus for the Rozanolixizumab program". In addition, worsening thrombocytopenia and haemorrhagic events will be included as AEOF as described in AEOF Version 1.4. The following AEs are defined in the rozanolixizumab program as AEs of focus (please see Section 13.1 for more details)

- Headaches
- Gastrointestinal Disturbances
- Hypersensitivity Reactions
- Anaphylactic Reactions
- Injection Site Reactions
- Infusion Reactions
- Opportunistic Infections
- Reductions in Albumin and Plasma Proteins
- Effects on the Kidney
- Drug Related Hepatic Disorders
- Thromboembolic Events
- Hemorrhagic Events
- Worsening of Thrombocytopenia

AEOFs will be listed only.

10.3 Vital Signs, Physical Findings, and Other Observations Related to Safety

10.3.1 Vital Signs and Physical Findings

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Temperature (oral, tympanic, or axillary)

A summary of participants who meet each of the Marked Abnormality (MA) Criteria (Appendix 13.3) will be summarized by treatment group at each timepoint.

A by-participant listing of all vital sign measurements and change from Baseline will be presented by treatment group and timepoint. The listing will include a flag for values identified as MA criteria (Appendix 13.3).

Repeated and unscheduled measurements will be handled as described in Section 4.3.

10.4 12-lead Electrocardiograms (ECG)

12-Lead ECG data (measured values and changes from Baseline) will be listed only. The following variables will be reported:

- Heart rate
- PR interval
- RR interval
- QRS duration
- QT interval
- QT corrected for heart rate using Bazett's formula (QTcB = QT/RR1/2)
- QT corrected for heart rate using Fridericia's formula (QTcF = QT/RR1/3)

A summary of participants who meet each of the Market Abnormally (MA) criteria outlined in Appendix 13.4 will be summarized by treatment group at each timepoint and overall.

All calculations of changes from Baseline will be based on the mean of triplicate assessments at each timepoint. If there are not 3 available measurements at a given timepoint, the mean will be calculated based on the number of measurements for which data are provided.

Electrocardiogram findings for the individual triplicate measurements will be listed separately.

Repeated and unscheduled measurements will be handled as described in Section 4.3.

10.5 Clinical Safety Laboratory Assessments

Laboratory data (as specified in Table 10-2 Protocol-required safety laboratory assessments in the protocol) and changes from Baseline (if applicable) for numeric variables will be listed by treatment group and timepoint. Values outside the reference range for the numeric variables will be flagged in the listings. The reference ranges will also be reported in the listings. In addition, the listings will include a flag for values identified as Laboratory assessments – MA Criteria (Appendix 13.2).

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change from Baseline. Measurements ALQ, if applicable, will be imputed to the upper quantification limit. These rules will be applied to all safety laboratory data including clinical chemistry and urinalysis.

Descriptive statistics will be calculated if at most 1/3 of the individual data points at a time point are missing or are either not quantifiable (<LLOQ) or ALQ. Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance and values that are ALQ will be imputed to the value of the upper quantification limit. If more than two-thirds of the individual data points at a timepoint are missing or not quantifiable (BLQ and/or ALQ), no descriptive statistics will be calculated.

The following summaries/tables will be created:

- A summary of participants who meet each of the Laboratory assessments – MA criteria (Appendix Section 13.2) will be summarized by treatment group at each timepoint.

A listing for laboratory assessments will be also created using the SS.

10.5.1 Potential Drug-Induced Liver Injury

Data from subjects with any of the laboratory results meeting the criteria for potential drug-induced liver injury (PDILI) (below) was planned to be summarized by treatment arm and visit using the SS to include:

- Subjects with at least one post-Baseline liver laboratory assessment
- Incidence of potential hepatotoxicity with symptoms potentially associated with hepatitis or hypersensitivity, which will account for the number and percentage of subjects meeting laboratory criteria for PDILI for at least 1 visit and reporting at least 1 symptom potentially associated with hepatitis or hypersensitivity according to the Investigator on the PDILI CRF)
- Incidence of potential hepatotoxicity with no symptoms potentially associated with hepatitis or hypersensitivity, which will account for the number and percentage of subjects meeting laboratory criteria for PDILI for at least 1 visit and not reporting any symptom potentially related to hepatitis or hypersensitivity according to the Investigator on the PDILI CRF
- Number and percentage of study participants who meet the Laboratory criteria for PDILI (see table below)

Table 10-2: Laboratory criteria for PDILI

Laboratory Criteria	Comments
(AST or ALT > 3 x ULN) and TBL > 1.5 x ULN	- All values must be met at the same sample taken from the same visit
(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	- All values must be met at the same visit - Subjects who potentially meet Hy's law criteria at least 1 time during exposure. To be counted as potential Hy's Law, all criteria must be met at the same sample taken at the same visit.

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal range.

A listing will be created only for visits for which at least one of the above criteria was fulfilled for a given participant and will display all results obtained at that visit for the specified parameters. The listing will specify AST, ALT, TBL, and ALP.

10.6 Concentrations of Total Protein and Albumin

Concentrations of total protein and albumin for each visit (as described in the schedule of events in the protocol) will be listed using the SS.

10.7 Serum and Plasma Complement Levels

Serum (C3 and C4) and plasma (C3a and C5a) complement variables will be listed by treatment group and time point.

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ). Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper limit of quantification.

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

10.8 Other Safety Variables

10.8.1 Physical examination

Results of physical examination abnormalities will be listed.

10.8.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening. The pregnancy test will be urine at all other visits.

A by-participant listing of the pregnancy test data will be provided by treatment group.

10.8.3 Childbearing potential

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

10.8.4 Assessment and management of Tuberculosis

Results of the interferon-gamma release assay tuberculosis (TB) test will be listed.

Results of the chest X-ray for TB will be listed.

Results of TB signs and symptoms questionnaire will be listed.

11 OTHER ANALYSES

11.1 Specific analyses for Pharmaceuticals and Medical Devices Agency (PMDA)

Separate summaries will not be presented for Japanese participants.

11.2 Headache questionnaire

The results of the headache questionnaire will be listed for each participant. No summary tabulations will be provided for these assessments.

12 REFERENCES

Chow SC, Lin M. Analysis of two-stage adaptive seamless trial design. Pharm Anal Acta. 2015;6(341):2.

Hedges, Larry V., and Ingram Olkin. "Statistical methods for meta-analysis." (1985).

Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371(9610):395-403.

Lehmacher W and Wassmer G. Adaptive Sample Size Calculations in Group Sequential Trials. Biometrics. 1999;55:1286-90.

Levey et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009; 150: 604-612.

Mantel, N., Fleiss, J.L. (1980). Minimum expected cell size requirements for the Mantel-Haenszel one-degree-of-freedom chi-square test and a related rapid procedure. American Journal of Epidemiology 112, 129-134

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.

13 APPENDICES

13.1 AE of focus (AEOF) for the Rozimab Program

AEOF Version: 3.0 or later, Date: 13Dec2021 will be used in this SAP as described below. In addition, worsening thrombocytopenia and haemorrhagic events will be included as AEOF as described in AEOF Version 1.4:

ARTICLE I. MedDRA 22.0 and 22.1 and 23.0 and 23.1 AND 24.0

The purpose of this document is to detail the approach to identifying TEAEs meeting criteria for AEs of focus (AEOF) for the Rozanolixizumab (also called Rozimab) program.

The document is organized by MedDRA version. At the time of writing this document, MedDRA version 22.0 was planned to be used for all indications under investigation (MG, ITP, CIDP, HV). As there is no change between 22.0 and 22.1 and 23.0 and 23.1 and 24.0 regarding terms used in below selection criteria, all below specified algorithms apply to these Meddra versions. If future studies are planned which use a different (more recent) version of MedDRA, this document will be updated.

The MedDRA SMQ files version 22.0, 22.1, 23.0 and 23.1 are attached in the original document.

MedDRA SMQ file 24.0:

SMQ_spreadsheet_ 24_0_English.xlsx

Following Events are Adverse Event of focus For Rozanolixizumab for all indications:

No	Event (also included in Title of TFL output)	Selection criteria	Purpose CSR/ SSD/ IB
1	Headache (Note: also included in AESM if severe)	TEAE with HLGT='Headaches'	CSR/ SSD/ IB
2	Gastrointestinal disturbances (Note: also included in AESM if severe)	TEAE with HLT='Gastrointestinal and abdominal pains (excl oral and throat)' or HLT='Gastrointestinal signs and symptoms NEC' or HLT='Nausea and vomiting symptoms' or HLT='Diarrhoea (excl infective)' or HLT='Gastritis (excl infective)'	CSR/ SSD/ IB
3	Hypersensitivity reactions	SMQ='Hypersensitivity'	CSR/ SSD/ IB
4	Anaphylactic reactions	SMQ='Anaphylactic reaction' and	CSR/ SSD/ IB

		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 <u>any</u> of the following 3 criteria should be included in the summary table: 1. If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. 2. If a subject reports any TEAE which codes to a PT included in Category B **AND** reports any TEAE which codes to a PT included in Category C, **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions. 3. If a subject reports any TEAE which codes to a PT included in Category D **AND** reports (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.	
5	Injection site reactions	TEAE with HLT='Injection site reactions' or HLT='Infusion site reactions' or HLT='Administration site reactions NEC'	CSR/ SSD/ IB
6	Infusion Reactions	Infusion reaction marked on AE CRF page	CSR/ SSD/ IB
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	Opportunistic infections (including tuberculosis) will be summarized in a stand-	CSR/ SSD/ IB

	(Note: also included in AESM)	alone table using UCB-defined search criteria. Opportunistic infections are identified in two steps using the attached spreadsheet for MedDRA v24.0:  OI_MedDRA24_0.xlsx Step 1: Refer to column B of the spreadsheet which identifies the Preferred Terms (PTs) to be classified as opportunistic infections using either a single 'x' or a double 'xx'. • TEAEs which code to a PT flagged with a single 'x' need to also be serious in order to be considered an opportunistic infection. • All TEAEs which code to a PT flagged with a double 'xx' are considered to be an opportunistic infection, regardless of seriousness. All serious TEAEs in the study database which code to a PT flagged with a single 'x' and all TEAEs in the study database which code to a PT flagged with a double 'xx' will be summarized as an opportunistic infection in the stand-alone table. [CQ97NAM= 'Opportunistic Infection - Automatic'] Step 2: Refer to column C of the spreadsheet which identifies the PTs that need to be evaluated on a case-by-case basis by the study physician and safety physician in order to determine whether it is a true opportunistic infection or not. The process for physician review is as follows: 1. Study programming team creates a spreadsheet which lists all of the subjects with a TEAE present in the database which codes to a PT identified as case-by-case. [CQ98NAM= Opportunistic Infection - Manual Review Candidate]	

		Information from the AE dataset to be included in the spreadsheet: Subject ID, AE verbatim term, System Organ Class (SOC), High Level Term (HLT), Lower Level Term (LLT), PT, AE start date, AE end date, seriousness, severity, relationship to study medication, action taken. Additionally, a column will be included where the study physician/safety physician can document their decision on the case. 2. Study physician/safety physician (SPs) reviews the cases in the spreadsheet separately and reconciles final decision, and indicates in the additional column which AEs are confirmed to be opportunistic infections via a single 'x'. 3. Study programming team incorporates these decisions into the AE dataset by merging the SPs decisions for individual subjects / PTs and flagging both the automatic and the confirmed opportunistic infections as such in the dataset. [CQ99NAM= 'Opportunistic Infection – Adjudicated'] The SPs reviews the context of all of a subject's data (AEs and possibly other) and concludes individually. Indicators of relevant cases may be e.g. repetitive occurrences, conjunction of other events or findings considered relevant. All subjects with a case-by-case PT reported that has been confirmed by the SPs to be an OI will be summarized as such in the stand-alone table, along with all of the events identified in Step 1 of this process. [CQ99NAM= 'Opportunistic Infection – Adjudicated'] The timing and frequency of Step 2 should be outlined and agreed to by the study team at the beginning of the study. It is suggested that this process be executed multiple times	

		throughout the course of the study, more frequently in the weeks leading up to database lock, and one final time immediately prior to database lock. Following the initial physician review of case-by-case events, subsequent reviews will be based on the cumulative set of case-by-case events present in the database at each time point of spreadsheet creation. Physician decisions from previous runs should be retained in each subsequent run. The final run of the spreadsheet, with all SP decisions on the full set of case-by-case events, will be archived at the conclusion of the study analysis prepared for agency submission.	
9	Reductions in albumin and plasma proteins	TEAEs with PT='Blood albumin decreased' or PT='Protein albumin ratio' or LLT='Plasma protein abnormal' or LLT='Proteins serum plasma low'	CSR/ SSD/ IB
10	Effects on the kidney	TEAEs in SMQ='Acute renal failure'	CSR/ SSD/ IB
11	Drug related hepatic disorders	TEAEs in SMQ='Drug related hepatic disorders - comprehensive search'	CSR/ SSD/ IB
12	Effect on lipids	TEAEs with PT= 'Blood cholesterol increased' or PT= 'Low density lipoprotein increased' or PT= 'Blood triglycerides increased' or PT= 'Hypercholesterolaemia' or PT= 'Hypertriglyceridaemia' or PT= 'Hyperlipidaemia' or PT= 'Dyslipidaemia' or PT= 'Lipids increased'	CSR/ SSD/IB
ITP specific output			
13	Thromboembolic events	Embolic and thrombotic events (SMQ)	CSR/ SSD/ IB
14	Worsening thrombocytopenia *	Haematopoietic thrombocytopenia (SMQ)	
15	Haemorrhagic events *	Haemorrhages (SMQ)	

* Data will be summarized by period and listed after adjudication of those events have been properly investigated

13.2 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 unless otherwise noted. If both high and low criteria are shown for a parameter, the criteria should be summarized separately in tabular or graphical data summaries.

13.2.1 Hematology

PARAMETER	UNIT (conventional)	UNIT (standard)	MARKED ABNORMALITY CRITERIA
Hemoglobin	g/dL	g/L	<8.0 g/dL; <80 g/L
WBC (Leukocytes)[1]	10^9/L	10^9/L	Low: <2.0 x 10^9/L
			High: >30 x 10^9/L
Lymphocytes Absolute	10^9/L	10^9/L	Low: <0.5 x 10^9/L
			High: >20 x 10^9/L
Neutrophils Absolute	10^9/L	10^9/L	<1.0 x 10^9/L
Platelets[2]	10^9/L	10^9/L	<50.0 x 10^9/L

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

[2]For blinded ITP protocols, Platelets will not be assessed for TEMA because this parameter will be blinded and is expected to be abnormally low due to the participant population and entry criteria.

13.2.2 Chemistry

PARAMETER	UNIT (conventional)	UNIT (standard)	MARKED ABNORMALITY CRITERIA
AST (SGOT)	U/L	U/L	>5.0 x ULN
ALT (SGPT)	U/L	U/L	>5.0 x ULN
ALP (Alkaline Phosphatase)	U/L	U/L	>5.0 x ULN
GGT (Gamma Glutamyl Transferase)[1]	U/L	U/L	>5.0 x ULN
Bilirubin (Total)	mg/dL	umol/L	>3.0 x ULN if Baseline value is normal; >3.0 x Baseline value if Baseline is abnormal
Albumin	g/dL	g/L	<2 g/dL; <20 g/L
Creatinine	mg/dL	umol/L	>3.0 x ULN
Estimate glomerular filtrate rate (eGFR)[2]	mL/min/1.73 m	mL/min/1.73 m	eGFR <29 mL/min/1.73 m
C reactive protein (CRP)[3]	mg/L	mg/L	>10mg/L
Corrected Calcium[4]	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[5]	(g/L)	(g/L)	≤1 g/L
Potassium	mmol/L	mmol/L	Low: <2.5 mmol/L
			High: >6.0 mmol/L
Sodium	mmol/L	mmol/L	Low: <125 mmol/L
			High: >155 mmol/L
Glucose[6]	mg/dL	mmol/L	Low: <40 mg/dL; <2.2 mmol/L
			High: > 250 mg/dL; >13.9 mmol/L
Total Cholesterol[1]	mg/dL	mmol/L	>400 mg/dL; >10.34 mmol/L
Triglycerides[1]	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 CTCAE, Version 5.0 unless otherwise noted.

[1]GGT, Total Cholesterol and Triglycerides were to be collected under Protocol Amendment 3 but were not collected under Protocol Amendment 2. Since no participants were enrolled under Protocol Amendment 3, these laboratory assessments will not summarized or listed.

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

[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/. A moderate elevation of CRP level per referred reference is used for the marked abnormality criteria for RLZ to ensure a change suggestive of inflammatory process is captured.

[4]Corrected Calcium = 0.02 * (40 – albumin (g/L)) + calcium (mmol/L)

[5]Immunoglobulin G criterion based on immunodeficiency literature and noted in RLZ study protocols.

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

13.3 Vital sign assessments - abnormal

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

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

13.4 Electrocardiogram (ECG) – Abnormal

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

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

Abbreviations: BL= Baseline, bpm = beats per minute; ms = milliseconds; QTc(F) = Fridericia corrected QT interval;
Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline

13.5 ITP-PAQ Scoring

13.5.1 ITP-PAQ Scales

Please see below for the items associated for each scale and the number of points in the Likert Scale that will be used per scale where higher numbers mean better health status.

Question	Scale	Response Categories
1	Physical Health: symptoms	0-4
2		
3		
4		
5		
6		
7	Physical Health: fatigue	0-4
8		
9		
10		
11	Physical Health: bother	0-4
12		0-6
13		0-6
14	Physical Health: activity	0-4
15		0-4
16	Emotional Health: psychological	0-4
17		0-4
18		0-4
19		0-4
20		0-4
21	Emotional Health: fear	0-4
22		0-4
23		0-4
24		0-4
25		0-4
26	Overall QoL	0-6
27		0-6
28		0-3
29		0-3
30		0-3
31	Social Activity	0-4
32		0-4
33		0-4
34		0-4
35	Women's reproductive health	0-4
36		0-4
37		0-4
38		0-4
39		0-4
40		0-4
41	Work	0-5
42		0-5
43		0-5
44		0-5

The ITP-PAQ domain scores will be obtained by transforming the raw sum of the item responses to a 0-100 scale. This can be obtained using the following formula:

$$\text{ITP-PAQ score} = \frac{\text{Sum of item scores within the scale}}{\text{raw sum range}} * 100$$

ITP-PAQ domain	Raw sum range
Symptoms	24
Fatigue	16
Bother	16
Activity	8
Psychological health	20
Fear	20
Work	20
Social activity	16
Women's reproductive health	24
Overall Quality of Life	21

Missing data:

A domain score is not calculated if there is more than half of the items of this domain are missing.

If 50% or more of the items are available, missing items are imputed using the mean of non-missing items. For domains that include items with a different number of categories, the imputed response for missing items has to be transformed on the range of the response scale of the missing item.

13.6 ITP bleeding score

The ITP-BAT tool version 1.0 consists of the following domains:

- Skin (S)
- Visible mucosae (M)
- Organs (O)

The domain for skin comprises the following bleeding types:

- Petechiae
- Ecchymoses
- Subcutaneous hematomas
- Bleeding from minor wounds

The domain for visible mucosae comprises the following bleeding types:

- Epistaxis
- Oral cavity- gum bleeding
- Oral cavity – hemorrhagic bullae or blisters
- Oral cavity – bleeding from bites to lips and tongue or after deciduous teeth loss
- Subconjunctival hemorrhage (not due to conjunctival disease)

The domain for organs comprises the following bleeding types:

- Gastrointestinal bleeding not explained by visible mucosal bleeding or lesion
- Lung bleeding
- Hematuria
- Menorrhagia
- Intramuscular hematomas
- Hemarthrosis
- Ocular bleeding
- Intracranial bleeding
- Other internal bleeding

The grading for each bleeding type within each domain is presented in Table 13-1. Each bleeding type is graded based on the worst manifestation that occurred during the most recent observation period (since the previous visit). The grade for each domain is then taken as the worst (most severe) grade across all bleeding types within that domain.

Missing data will not be imputed. In the case that data for one or more bleeding types are missing within a given domain, the grade for that domain will be evaluated based on the

available data. In the case that no data are available within a given domain, the score for that domain will not be evaluated at the specific visit.

Table 13-1: ITP-BAT scoring

Type of bleeding	**GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]**				
	0	**1**	**2**	**3**	**4**
SKIN					
Petechiae (does not include steroid–induced or senile purpura)	☐ No	☐ Less than or equal to 10 in a patient's palm-sized area[3] in the most affected body area[4] ☐ Any number if reported by the patient	☐ More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas[4], one above and one below the belt (in the most affected body areas)[4]	☐ More than 50, if scattered both above and below the belt	
Ecchymoses	☐ None or up to 2 in the same body area[4], but smaller than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/constriction[5]	☐ 3 or more in the same body area[4], but all smaller than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/constriction[5] ☐ At least 2 in two	☐ From 1 to 5 larger than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/constriction[5] with or without smaller ones	☐ More than 5 larger than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/constriction[5]	

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
		different body areas[4], smaller than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/constriction[5] ☐ Any number and size if reported by the patient			
Subcutaneous hematomas	☐ No	☐ 1 smaller than a patient's palm-sized area ☐ Any number and size if reported by the patient	☐ 2 smaller than a patient's palm-sized area, spontaneous ☐ 2 smaller than a patient's palm-sized area, disproportionate to trauma[5]	☐ More than 2 smaller or at least 1 larger than a patient's palm-sized area, spontaneous ☐ More than 2 smaller or at least 1 larger than a patient's palm-sized area, disproportionate to trauma[5]	

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
Bleeding from minor wounds[6]	☐ No	☐ Lasting <=5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Requiring protracted medical observation at the time of this visit ☐ Medical report describing patient's evaluation by a physician	
MUCOSAL					
Epistaxis[7]	☐ No	☐ Lasting <=5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Packing or cauterization or in-hospital evaluation at the time of this visit ☐ Medical report describing packing or cauterization or in-hospital evaluation	☐ RBC transfusion or Hb drop >2g/dL
Oral cavity – gum bleeding[7]	☐ No	☐ Lasting <=5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Requiring protracted medical observation at the time of this visit	

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
				☐ Medical report describing patient's evaluation by a physician	
Oral cavity – hemorrhagic bullae or blisters	☐ No	☐ Less than 3 ☐ Any number if reported by the patient	☐ From 3 to 10 but no difficulty with mastication	☐ More than 10 or more than 5 if difficulty with mastication	
Oral cavity - bleeding from bites to lips & tongue or after deciduous teeth loss	☐ No	☐ Lasting <=5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Interventions to ensure hemostasis or in-hospital evaluation at the time of this visit ☐ Medical report describing interventions to ensure hemostasis or in-hospital evaluation	
Subconjunctival hemorrhage (not due to conjunctival disease)	☐ No	☐ Petechiae/ hemorrhage partially involving one eye ☐ Any episode if	☐ Petechiae/ hemorrhage partially involving both eyes, or diffuse hemorrhage in one eye	☐ Diffuse hemorrhage in both eyes	

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
		reported by the patient			
ORGAN (and internal mucosae)					
Gastrointestinal bleeding not explained by visible mucosal bleeding or lesion: Hematemesis, Melena, Hematochezia, Rectorrhagia	☐ No	☐ Any episode if reported by the patient	☐ Present at the visit ☐ Described in a medical report	☐ Requiring endoscopy[8] or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ Medical report prescribing endoscopy[8] or other therapeutic procedures or in-hospital evaluation	☐ RBC transfusion or Hb drop >2g/dL
Lung bleeding Hemoptysis Tracheobronchial bleeding	☐ No	☐ Any episode if reported by the patient	☐ Present at this visit ☐ Described in a medical report	☐ Requiring bronchoscopy[8] or other therapeutic procedures or in-hospital evaluation	☐ RBC transfusion or Hb drop >2g/dL

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
				at the time of this visit ☐ An equivalent episode if described in a medical report	
Hematuria	☐ No	☐ Any episode if reported by the patient ☐ Microscopic (lab analysis exhibited)	☐ Macroscopic (lab analysis exhibited) ☐ Described in a medical report	☐ Macroscopic and requiring cystoscopy[8] or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop >2g/dL
Menorrhagia (compared to pre-ITP or to a phase of disease with normal platelet count)[9]	☐ No	☐ Doubling nr. of pads or tampons in last cycle compared to pre-ITP or to a phase of disease with normal platelet count ☐ Score >100 using	☐ Changing pads more frequently than every 2 hrs. or clot and flooding ☐ Requiring combined treatment with antifibrinolytics and hormonal	☐ Acute menorrhagia requiring hospital admission or endometrial ablation (either at this visit or described in	☐ RBC transfusion or Hb drop >2g/dL

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
		PBAC in the last cycle, if normal score in pre-ITP cycles or in a phase of disease with normal platelet count	therapy or gynecological investigation (either at this visit or described in a medical report)	a medical report)	
Intramuscular hematomas (only if diagnosed by a physician with an objective method)	☐ No	☐ Post trauma, diagnosed at this visit, if judged disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ Spontaneous, diagnosed at this visit ☐ An equivalent episode if described in a medical report	☐ Spontaneous or post trauma (if judged disproportionate to trauma) diagnosed at this visit and requiring hospital admission or surgical intervention ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop >2g/dL
Hemarthrosis (only if diagnosed by a physician with an objective method)	☐ No	☐ Post trauma, diagnosed at this visit, function conserved or minimally impaired, if judged	☐ Spontaneous, diagnosed at this visit, function conserved or minimally impaired	☐ Spontaneous or post trauma (if judged disproportionate to trauma), diagnosed at	☐ Spontaneous or post trauma (if judged disproportionate to trauma) diagnosed

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
		disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ An equivalent episode if described in a medical report	this visit and requiring immobilization or joint aspiration ☐ An equivalent episode if described in a medical report	at this visit and requiring surgical intervention ☐ An equivalent episode if described in a medical report
Ocular bleeding (only if diagnosed by a physician with an objective method)	☐ No		☐ Any post trauma vitreous or retinal hemorrhage involving one or both eyes with or without impaired/blurred vision present at this visit if judged disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ Spontaneous vitreous or retinal hemorrhage involving one or both eyes with impaired/blurred vision present at this visit ☐ An equivalent episode if described in a medical report	☐ Spontaneous vitreous or retinal hemorrhage with loss of vision in one or both eyes present at this visit ☐ An equivalent episode if described in a medical report
Intracranial bleeding[10]: intracerebral, intraventricular, subarachnoidal, subdural, extradural	☐ No		☐ Any post trauma event requiring hospitalization	☐ Any spontaneous event requiring hospitalization in presence of an underlying	☐ Any spontaneous event requiring hospitalization without an underlying

Type of bleeding	**GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]**				
	0	**1**	**2**	**3**	**4**
(only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)				intracranial lesion	intracranial lesion
Other internal bleeding: hemoperitoneum hemopericardium hemothorax retroperitoneal bleeding hepatic and splenic peliosis with organ rupture retroorbital bleeding metrorrhagia etc. **(only if diagnosed with an objective method at the visit or described in a medical report**	☐ No			☐ Any event requiring hospitalization <48 hrs.	☐ Any event requiring hospitalization >48 hrs. or RBC transfusion or Hb drop >2g/dL

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	1	2	3	4
provided by the patient)					

Grading is based on physical examination at the time of the visit by the physician or expert nurse or on patient's history supplemented by available medical reports. Bleeding manifestations reported by the patient but not visible at the time of data collection are graded 1. Grade 5 is assigned to fatal bleeding.
To receive a grade >1, all non-overt skin and non-overt mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vesicles/bullae subconjunctival bleeding) should be visible at the time of visit for grading by the physician or expert nurse taking the history.
For bleeding from minor wounds and overt-mucosal bleeding (epistaxis, gum, bleeding from bites to lips & tongue or after deciduous teeth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should be also taken into account for grading.
Requirement for ITP-specific treatments and anti-fibrinolytics (apart from menorrhagia) was not considered for grading, due to their subjective nature and their adoption not only to control actual bleeding but also to reduce the "risk" of impendent or future bleeding.

[1] In case of patients examined for the first time, all types of bleeding occurring at the visit and in the 15 days preceding the visit should be considered.
[2] Each type of bleeding should be graded based on the worst bleeding manifestation that occurred during each observation period or in the 15 days preceding the first visit.
[3] Patient's own palm size is commonly considered to be proportional to body surface area. Palm = the inner surface of the hand stretching between the distal crease of the wrist and the bases of the fingers (fingers surface excluded).
[4] Body areas include: face, neck, right and left upper limbs (considered separately), right and left lower limbs (considered separately), trunk, abdomen, and recumbent areas (for the ambulatory patient means the area below the knees).
[5] Bleedings considered proportionate to trauma/constriction on a clinical ground should not be reported for skin domain.
[6] Minor wound means superficial skin cuts (eg, by shaving razor, knife, or scissors).
[7] Epistaxis and gum bleeding are also reported in some normal subjects. Thus, a critical judgment is required in grading these manifestations; they should be reported only if judged more severe when compared with pre-ITP bleeding, if any.
[8] Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.
[9] In girls at menarche, grade 1 cannot be assigned, lacking comparison with previous cycles.
[10] Intracranial bleeding should always be reported, irrespective of its grade. For example, if a woman had S2 (subcutaneous hematoma) M2 (epistaxis) O3 (menorrhagia) and an intracranial bleeding grade 2 (post trauma, requiring hospitalization), the SMOG index is S2M2O3 (intracranial 2). If the same patient also had intracranial bleeding grade 3, the SMOG index is S2M2O3 (intracranial 3).

13.7 Classification of the SF-36v2 questionnaire

Items	Scales
3a. Vigorous activities 3b. Moderate activities 3c. Lifting or carrying groceries 3d. Climbing several flights 3e. Climbing one flight 3f. Bending, kneeling 3g. Walking more than a mile 3h. Walking several hundred yards 3i. Walking one hundred yards 3j. Bathing, dressing	Physical Functioning
4a. Cut down time 4b. Accomplished less 4c. Limited in the kind of work 4d. Had difficulty performing the work	Role-Physical
7. Pain magnitude 8. Pain interfere	Bodily Pain
1 Global health condition rating 11a. Sick easier 11b. As healthy 11c. Health to get worse 11d. Health excellent	General Health
9a. Full of life 9e. Energy 9g. Worn out 9i. Tired	Vitality
6. Social extent 10. Social time	Social Functioning
5a. Cut down time 5b. Accomplished less 5c. Not careful	Role-Emotional
9b. Nervous 9c. Down in dumps 9d. Peaceful 9f. Blue/sad 9h. Happy	Mental Health

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

14.1 AMENDMENT 3

Rationale for the amendment

The primary reason for this SAP amendment is to incorporate the changes from Protocol Amendment 3 and the reduced scope of analyses following sponsor's decision to terminate the study early.

Modifications and changes

Section # and Name	Description of Change	Brief Rationale
2.1.3	Removed objective "To evaluate the effects of rozanolixizumab on exploratory biomarkers"	Updated to align with Protocol Amendment 3
2.1.3	Added objective "To assess the effect of rozanolixizumab on response to vaccination in study participants who received COVID-19 vaccine"	
2.2.1.2	Removed "Including all intermediate timepoints" from ITP-PAQ endpoint	
2.2.1.4.1	Changed text of IgG, IgA, IgE and IgM endpoints	
2.2.1.4.1	Removed ITP-specific autoantibodies endpoint	
2.2.1.4.2	Removed several exploratory endpoints	
2.2.1.4.2	Added COVID-19 vaccination endpoint	
2.2.2.1	Removed α-globulin, and β-globulin endpoints	
2.2.2.1	Removed Cytokines endpoint	
2.3	Starting dose of [redacted]	
2.3	Dosing is QW instead of Q2W	
2.3	Study size reduced to 60 from a maximum of 90 participants	
2.3	Various other changes to study design that do not have a direct impact on analysis	
2.4	Changed derivation of sample size and power calculation table	To reflect the requirement to randomize a fixed number of participants on weekly sc infusions and removal of option to

Section # and Name	Description of Change	Brief Rationale
		increase sample size based on an interim analysis
3.2.4	Definition of dosing regimen groups (weekly and biweekly)	Need to define subsets of protocol-defined analysis sets which will be used for analysis
3.5.4	Change complete infusion to sufficient infusion	Requested by FDA
3.5.4	The FAS will no longer appear in any analysis	Owing to the sponsor's decision to terminate this study the set is no longer required.
3.5.5	The PD-PPS will no longer appear in any analysis	Owing to the sponsor's decision to terminate this study the set is no longer required.
3.8	Updated to MedDRA version 24 dictionary	New version available
3.8	Updated to WHODD, Mar 2021 version	New version available
3.9	Text added to describe analysis omitted because of early termination of study.	Sponsor decision to terminate study early.
4.2.1	Text referring to sensitivity analysis and MI MAR analysis removed.	Analysis no longer required.
4.2.2	Changed intercurrent event strategy for COVID-19 to composite strategy and platelet data set to 0	Requested by FDA
4.5.2 and throughout	Remove all references to interim analysis and to Stage 1 and Stage 2 analysis	Interim analysis removed in Protocol Amendment 3
4.7	Analysis described in this section removed.	Analysis is no longer required.
4.8	Analysis removed	Analysis is no longer required.
6.5.1	Modification to assignment of medications to treatment period	Be consistent with the definition of treatment period
8.1.2	Sensitivity and supplemental analysis has been removed.	Owing to the sponsor's decision to terminate this study the analysis is no longer required.
8.1.3	Analysis has been removed.	Owing to the sponsor's decision to terminate this

Section # and Name	Description of Change	Brief Rationale
8.1.4	Analysis has been removed.	study the analysis is no longer required.
8.1.5	Analysis has been removed.	
8.2	All formal statistical analysis has been removed	
8.3	Subsections 8.3.1 – 8.3.5 and 8.3.8 – 8.3.9 have been removed. Statistical analysis has been removed from section 8.3.6.	
8.42	Text modified to reflect that item responses will be listed only, no derived scores will be calculated, and no change from baseline will be computed.	
8.4.4	Text added to reflect that item responses will be listed only, no derived scores will be calculated, and no change from baseline will be computed	
9.2	Updated the analysis for antidrug antibodies	Owing to the sponsor's decision to terminate this study the majority of the analysis is no longer required.
9.3.1 – 9.3.4	Changed text of IgG, IgA, IgE and IgM endpoints	Updated to align with Protocol Amendment 3
9.3.5	Removed ITP specific autoantibodies endpoint	
9.4	Removed several exploratory endpoints	
10.1	Clarified definition for time at risk	Account for participants who roll over to TP0004
10.2	Clarified definitions of severity and intensity for adverse events	Clarify how severe adverse events will be summarized
10.2.2	Add AESIs and TEAEs leading to study discontinuation to overview	Categories in overview should match categories in adverse event tables
10.2.2	Removed some adverse event tables	No longer needed
10.2.2	Added AEs of focus: hemorrhagic events, worsening thrombocytopenia and effect on lipids	These were added to the AE of Focus document 3.0, or they were removed from the document but were still considered relevant for ITP

Section # and Name	Description of Change	Brief Rationale
10.5.1	Added "All values must be met at the same sample taken from the same visit"	Clarified how PDILI is defined
10.5.1	Added the components of the Hy's law definition presented separately in a stepwise fashion to the table	Provide more information about the components of PDILI
10.6	Removed α-globulin, and β-globulin endpoints	Updated to align with Protocol Amendment 3
10.7	Removed change from baseline for Complement endpoint	Owing to the sponsor's decision to terminate this study the analysis is no longer required.
10.8	Removed Cytokines endpoint	Updated to align with Protocol Amendment 3
13.2.2	Removed several labs from MA table	Labs not collected or calculated in TP0003
Throughout	Minor editorial and formatting changes have been made.	Minor, therefore have not been summarized.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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