Statistical Analysis Plan

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Phase I Study Evaluating Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of SOL-116 (a Humanized Monoclonal Anti-BSSL Antibody) in Healthy Subjects and Patients with Rheumatoid Arthritis
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
ADaM	Analysis data model
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	Body mass index
BSSL	Bile salt-stimulated lipase
CCP	Cyclic citrullinated peptide
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CS	Clinical significance
DAS28	Disease activity score 28
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End-of-study
ESR	Erythrocyte sedimentation rate
FIH	First-in-human
FSH	Follicle-stimulating hormone
FU	Follow-up
GGT	Gamma-glutamyltransferase
GIT	Gastro-intestinal tract
HDL	High-density lipoprotein
hsCRP	High sensitive C-reactive protein
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent ethics committee
IFN_{γ}	Interferon gamma
LDH	Lactate dehydrogenase

LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical history
MCP	Monocyte chemoattractant protein
MTX	Methotrexate
N	Number of subjects/patients
NCS	Non-clinical significance
PCV	Packed cell volume
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKAP	Pharmacokinetic analysis plan
PR	PR interval of the ECG
PT	Preferred Term
QRS	QRS interval of the ECG
QTcF	Corrected QT interval using Fridericia's formula
RA	Rheumatoid arthritis
RBC	Red blood cell
RDW-CV	Red blood cell distribution width
RR	RR interval of the ECG
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistics analysis system
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SC	Subcutaneous(ly)
SD	Standard deviation
SDTM	Study data tabulation model
SI	International system
SOC	System organ class
SOE	Schedule of events
SRC	Safety review committee
TEAE	Treatment-emergent adverse event

TESAE	Treatment-emergent serious adverse event
TNF_{α}	Tumor necrosis factor alpha
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
VS	Vital signs
WBC	White blood cell
WHO	World Health Organization

3 INTRODUCTION

3.1 Preface

This statistical analysis plan (SAP) is based on protocol LPM-116-001 Amendment 6, dated 05 August 2024. The SAP provides details of data handling procedures and statistical analysis methods for safety, tolerability and pharmacodynamic variables. It also outlines the statistical programming specifications for tables and listings, and other analyses details not provided in the study protocol.

The pharmacokinetic analysis plan (PKAP) is not part of this SAP. It will be described in a separate document.

The unblinding process and Database Lock (DBL) will be performed after each part are completed.

4 DOCUMENTS USED

Clinical Study Protocol (CSP)
A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Phase I Study Evaluating Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of SOL-116 (a Humanized Monoclonal Anti-BSSL Antibody) in Healthy Subjects and Patients with Rheumatoid Arthritis, LPM-116-001, Amendment 6, and Date of Release: 05-Aug-2024, C1 – COVID-19 CSP Addendum, Version 9, Date of Release: 08-Apr-2022.

Source/CRF
- Part 1
  - eCRF OpenClinica, Date of Release: 18-Sep-2023
  - eCRF ClinSpark, Date of Release: 12-Dec-2022
- Part 2
  - eCRF OpenClinica, Date of Release: 12-Feb-2024
- Part 3
  - eCRF OpenClinica, Date of Release: 05-Apr-2024
  - eCRF ClinSpark, Date of Release: 20-Sep-2022

4.1 Study Objectives

For single dosing (Parts 1 and 2):
Primary objective:
- To evaluate the safety and tolerability of single ascending doses of SOL-116 in healthy subjects and rheumatoid arthritis (RA) patients.

Secondary objective:
- To determine single dose pharmacokinetic (PK) characteristics of SOL-116 in healthy subjects and RA patients.
- To assess the immunogenicity of SOL-116 after single SC doses in healthy subjects and RA patients.

Exploratory objective:

- To evaluate the effect of single ascending doses of SOL-116 on bile salt-stimulated lipase (BSSL) concentration in the blood of healthy subjects and RA patients.
- To evaluate the pharmacodynamic (PD) effect of single ascending doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects and RA patients.

For multiple dosing (Part 3):

Primary objective:

- To evaluate the safety and tolerability of multiple dosing of SOL-116 in healthy subjects.

Secondary objective:

- To determine multiple dose PK characteristics of SOL-116 in healthy subjects.
- To assess the immunogenicity of SOL-116 after multiple SC doses in healthy subjects.

Exploratory objective:

- To evaluate the effect of multiple doses of SOL-116 on BSSL concentration in the blood of healthy subjects.
- To evaluate the PD effect of multiple doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects.

4.2 Data Sources

All analyses will be carried out using data from the eCRF (OpenClinica, ClinSpark) and external data including external laboratory data and the protocol deviation list (if applicable). Datasets will be extracted from OpenClinica, ClinSpark and converted to Study Data Tabulation Model (SDTM) datasets and Analysis Data Model (ADaM) datasets.

5 OVERALL STUDY DESIGN AND PLAN

5.1 Study Design

This is a randomized, double-blind, placebo-controlled Phase I, first-in-human (FIH) study in three parts: healthy subjects and adult RA patients (Parts 1 and 2) and multiple SC doses in healthy subjects (Part 3).

The study will be monitored by a safety review committee (SRC). The intent of the SRC is to ensure that treatment does not pose undue risk to subjects/patients. Safety, tolerability and available PK data will be assessed by the SRC after each cohort before ascending to the next dose level.

Part 1

Eligibility will be assessed during a screening period of up to 28 days. For the treatment period, subjects/patients will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects/patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Subjects/patients will be released from the clinic on Day 2 (Part 1) , after all required study

procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, in both parts the clinic stay may be extended up to Day 7 if medically indicated and/or based on emerging data. In total, patients will return to the clinic for up to 8 ambulant visits up to Day 63. Subjects/patients will return to the clinic on Day 90 for an end-of-study (EOS)/ follow-up visit.

Part 2
Eligibility will be assessed during a screening period of up to 42 days. For the treatment period, patients will check into the clinic one day prior to dosing (Day -1). On Day 1, all patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Patients will be released from the clinic on Day 2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, the clinic stay may be extended up to Day 7, if medically indicated and/or based on emerging data. In total, patients will return to the clinic for up to 8 ambulant visits up to Day 63. Patients will return to the clinic on Day 90 for an EOS/follow-up visit.

Part 3
Eligibility will be assessed during a screening period of up to 28 days. For the first dose, subjects will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects will receive SOL-116 or placebo. Subjects will be released from the clinic on Day 2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7. Subjects will return to the clinic for 15 ambulant visits up to Day 154. Subjects will return to the clinic on Day 169 for an EOS/follow-up visit. After the second and third dose, a phone contact will be made (3 to 7 days after the dose) with the subject to ensure no new adverse events or if new medication has been added.

Based on SRC recommendations, the visit schedule may be adjusted.

5.2 Study Drug Administration

The SOL-116 will be administered as abdominal subcutaneous(ly) (SC) injection(s). The injection volume will be no more than 2.0 mL per injection. The number of SC injections given to administer the single dose in Cohort 2 to Cohort 7 may be increased to up to 4 injections. For more information see the CSP.

Subjects/patients will not be allowed to eat or drink (except water) from 10 hours prior to the administration of study drug or placebo.

All study drugs will be dispensed by the Investigator or a person supervised by the Investigator. The time of administration of SOL-116 or placebo will be recorded in the eCRF.

In Part 3, the same applies but 4 dose administrations (with maximum 4 injections per occasion) will be administered with 28 days' interval (in MD1).

In Part 2, there should be at least 24 hours between administration of SOL-116 and the preceding MTX dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose.

5.3 Study Details

The subject population will include healthy adult subjects (Cohort 1-6) and patients (Cohort 7) who satisfy all entry criteria.

Part 1
Up to 5 single doses are planned to be tested in 5 cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohort 1 to Cohort 5). One additional cohort (Cohort 6) of 8 healthy subjects (6 active, 2 placebo) may be added based on emerging data, i.e. in total 40 or 48 subjects will be randomized and dosed.

Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.

After each cohort completes dosing, a dose escalation SRC meeting will take place. Escalation to the next higher dose level may occur only after evaluation of the safety/tolerability and available PK data up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14) and after approval by the independent ethics committee (IEC). This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.

Part 2
In a cohort of up to 8 RA patients (6 active, 2 placebo) will be randomized and dosed (Cohort 7), one of the single doses tested in healthy subjects will be tested.

The cohort with RA patients (Cohort 7) will be run after the completion of all cohorts with healthy subjects. The dose level of Cohort 7 will be determined based on the safety and PK results of all preceding cohorts and will not exceed that of the already given dose levels in healthy subjects. There should be at least 24 hours between administration of SOL-116 and the preceding methotrexate (MTX) dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose.

Sentinel dosing will be employed. Thus, initially 1 patient will receive SOL-116 and 1 patient will receive placebo. The remaining 6 subjects of the cohort can be dosed at least 48 hours after dosing, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 patients of the cohort.

Part 3
Up to two multiple dosing cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohorts MD1 and MD2) are planned, i.e. in total up to 16 subjects will be randomized and dosed.

Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.

After each cohort completes dosing, a dose escalation SRC meeting will take place. Escalation to the next MD dose cohort may occur only after evaluation of the safety/tolerability and available PK data up to and including 28 days post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.

5.4 Sample Size

As this is a first in human study, no formal sample size calculation has been performed. The proposed sample size is considered sufficient to provide adequate information for the study objectives.

5.5 Study Flow Chart/Schedule of Events (SOE)

The study will consist of two parts.

In Part 1, there are a Screening period (Day -28 to Day -2), a treatment period (Day -1 to Day 63±3), and a follow-up evaluation (Day 90±3 days).

In Part 2, there are a Screening period (Day -28 to Day -2), a treatment period (Day -1 to Day 63±3), and a follow-up evaluation (Day 90±3 days).

In Part 3, there are a Screening period (Day -28 to Day -2), a treatment period (Day -1 to Day 154±3), and a follow-up evaluation (Day 169±5 days).

The complete schedules of prescheduled visits and all procedures for Part 1, Part 2, and Part 3 are presented in Table 5-1, Table 5-2, and Table 5-3 respectively in the CSP.

6 DESCRIPTION OF INCLUDED SUBJECTS

6.1 Analysis Populations

6.1.1 All-treated set

This analysis set includes all randomized subjects/patients who received study drug (at least one dose).

6.1.2 Safety set

This analysis set includes subjects/patients from the All-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.

6.1.3 Immunogenicity set

This analysis set includes all subjects/patients who received the study treatment and had at least 1 post-dose immunogenicity sample collected.

6.1.4 Per-protocol set

This analysis set comprises all subjects/patients included in the All-treated set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations. The Per-protocol set will be employed in the analysis of PK and exploratory variables.

6.1.5 PD (exploratory) set

This analysis set comprises all subjects/patients included in the All-treated set who did not violate the protocol in a way that might significantly affect the ability to analyze exploratory endpoints (i.e. RA patients who received more than 2 intra-articular injections in large joints and/or 6 intra-articular injections in small joints during the study are excluded).

6.2 Status of the Subjects

The status of the subjects will be presented using a status dataset, Subject-Level Analysis Dataset (ADSL), that will be created and used throughout the tables and listings. This status dataset will contain information on the eligible, randomized, received study drug, completed, and reason for non-completion subjects. In addition, it contains the information for subjects in the all-treated, safety, immunogenicity, per-protocol, and the PD (exploratory) set.

6.3 Protocol Deviations

The Protocol Deviation list is a list that presents the deviations by subject, description of actual deviation and category (major or minor). The Protocol Deviation list will serve as input for the selection of subjects for inclusion in the per-protocol set. The Protocol Deviation list is created by

the Data Manager but may involve collaboration with the Biostatistician and/or the SAS programmer and is preferably based upon a predefined set of protocol deviations that is as inclusive as possible. The Protocol Deviation list will be discussed and agreed with the Sponsor at a mutual Protocol Deviation review meeting prior to DBL.

The deviation list will be finalized before Database Lock (DBL).

6.4 Creation and Documentation of Analysis Population

The Biostatistician will create an analysis population list indicating which subjects will be included in each analysis set as mentioned in Section 6.1 of the SAP.

This information will be presented in a Listing which is intended to be included in the Appendix of the Clinical Study Report.

7 REPORT SPECIFICATIONS AND STATISTICAL ANALYSES

7.1 General Considerations

For safety and tolerability analyses, the descriptive statistics presented will be frequency counts (n) and percentages for qualitative variables. Quantitative variables will be summarized using the number of available observations (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) values.

For decimal display, appropriate rounding will be performed for all summary table: mean and median will be presented with one more decimal than the original data; SD will be presented with two more decimals than the original data; minimum and maximum values will be presented with the same precision as the original data. Percentages will be presented with 2 decimals and no decimals will be presented for integer value (For example, zero will be presented as 0 %).

Extra measurements (such as additional visits or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings only.

For the calculation of baseline corrected values, baseline is defined the last value measured prior to (the first) study drug intake (vital signs, ECG, laboratory parameters, bile salt-stimulated lipase , C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and S-calprotectin and high sensitive CRP (hsCRP) (only RA patients)), unless otherwise specified. If no value prior to dosing is collected, the baseline value will be treated as missing for analysis.

For any results reported as above upper limit of quantification (>ULOQ), the numeric value for calculating summary statistics used to replace this label will be the ULOQ value, plus one unit of the smallest digit of the ULOQ number. For example, if the ULOQ is 2.3 units then the smallest digit is 0.3 and one unit greater at that decimal point would be 0.4. A ULOQ designation would then be replaced numerically as 2.3 + 0.1 or 2.4 units. Similarly, if the ULOQ was 20.3, then ">ULOQ" would be replaced by 20.4. In addition, for any results reported as below lower limit of quantification (<LLOQ), the numeric value used for this label will be the half of LLOQ value. For

example, if the LLOQ is 0.5 units then the final value for statistical summary will be the half of 0.5 which is a value 0.25 units. In case an >ULOQ or <LLOQ value will be replaced as described here (for the purpose of summarizing the data), this will be indicated in a footnote beneath the table.

All placebo subjects from the different cohorts at each part will be combined into a single group for summary purposes. Data will be summarized by treatment groups (dose levels and placebo). No statistical inference will be performed.

Note: some minor modifications may be necessary to the planned design of tables and listings to accommodate data collected during the actual study conduct. This is not considered a deviation from the preplanned statistical analysis.

7.2 Incomplete and Missing Data

Subjects who drop-out might be replaced but only upon mutual agreement between the Investigator and the Sponsor unless withdrawal is due to adverse event (AE). The replacing subject will receive the same treatment as was assigned to the subject whom he/she replaces.

No imputation will be performed on missing data. All analyses will be performed on data available at the time point considered. In summary tables, the number of subjects with missing data will be presented unless otherwise specified. In calculation of percentages, subjects with missing data will not be considered in numerator or denominator unless otherwise specified.

For the safety evaluation, subjects with missing data are included until their last assessment in both listings and tables.

In listings, dates will be presented as exported from the database, also in case of partial dates.

7.3 Demographic and Baseline Characteristics

Descriptive tabulations of the screening data for demographics will be made. Demographic data of continuous variables (age, height, weight, and body mass index (BMI)) as well as qualitative demographic characteristics (sex, ethnicity and race) will be presented appropriate descriptive statistics. Individual subject listings of demographic data will be provided.

Previous and concomitant medications will be coded according to the latest version (version 2022 or higher) of the world health organization (WHO) drug code and the anatomic therapeutic chemical (ATC) class code. Concomitant medications will be summarized by tabulating the number and percentages of subjects treated.

Based on the status dataset (see Section 6.2), a summary of all screened/ randomized, treated and completed subjects by treatment groups will be given (“subject disposition”) for all-treated set.

Other baseline subject characteristics including medical history (MH), physical examination, previous medication, inclusion/exclusion checklist, alcohol breath test, urine drug screen, urine cotinine screen, serology, anti-CCP antibody, and QuantiFERON® test will only be listed.

MH data will in addition be coded with the latest version of the medical dictionary for regulatory activities (MedDRA) coding system used during the clinical conduct of the study: this is version 25.1 or higher. The SAS programmer or Data Manager of the study will add the coding (using the MedDRA system and SAS) to the MH descriptions extracted from the database.

Distributions of these parameters will be compared between the treatment groups only descriptively. No statistical inference will be performed.

7.4 Study Subjects and Conduct

The status of the subjects will be given in a summary table by dose level:
- the number of subjects screened
- the number of subjects randomized
- the number of subjects receive study drug
- the number of subjects which completed the study
- the number of subjects for the non-completion reason
- the number of subjects in the all-treated set
- the number of subjects in the safety set
- the number of subjects in the immunogenicity set
- the number of subjects in the per-protocol set
- the number of subjects in the PD (exploratory) set

Subject eligibility and the criteria not met will be listed in the Subject Eligibility Not Met listing. Subject disposition, completion and the reasons for discontinuation will be listed in the Subject Disposition (Complete Status) listing. The reasons for exclusion from all-treated set, safety set, immunogenicity set, per-protocol set, and PD (exploratory) set will be listed in the Subject Excluded from the Analysis.

7.5 Immunogenicity Analyses

7.5.1 Immunogenicity Parameters

The immunogenicity parameters to be presented are:
- Development of anti-drug antibodies (ADA). If confirmed ADA positive, the following may be determined:
  - Estimation of ADA titers
  - Neutralizing capacity
  - Isotype
  - Epitope map

The immunogenicity parameters will be summarized by using descriptive statistics of absolute values for each time point. Where applicable, change from baseline will also be calculated and summarized.

The immunogenicity set will be used for analyses.

7.6 Exploratory Analyses

7.6.1 Exploratory Parameters

The exploratory parameters to be presented are:

- BSSL concentration
- Inflammatory biomarkers (except BSSL): CRP, ESR for all subjects/patients, and S-calprotectin and hsCRP (only RA patients)

The exploratory parameters will be summarized by using descriptive statistics of absolute values for each time point. Where applicable, change from baseline will also be calculated and summarized.

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

The PD (Exploratory) set will be used for analyses. Also, the Per-protocol (PP) set and the "all-treated set" will be used (see CSP section 10.2).

7.7 Safety Tolerability Evaluations

7.7.1 General Considerations

Safety evaluations will be conducted at screening, at clinic check-in, periodically throughout study conduct, and at follow-up evaluation. See Table 5-1, Table 5-2, and Table 5-3 in the CSP for the details of evaluation time points. All safety and tolerability assessments, including but not limited to adverse events, clinical laboratory assessments including hematology, serum biochemistry, coagulation and urinalysis, vital signs, 12-lead ECG and 3-lead ECG.

7.7.2 Safety and Tolerability Variables

The following are defined as safety/tolerability variables:

- Injection site reactions
- Physical examination
- Adverse events
- Clinical laboratory assessments including hematology, serum biochemistry, and urinalysis
- Vital Signs
- 12-lead ECG
- 3-lead ECG (telemetry)
- Immune reactions
- Concomitant medications/therapy

The safety set will be used for analyses.

7.7.3 Analysis of Safety and Tolerability Endpoints

7.7.3.1 Injection Site Reactions

Injection site reactions consisting of dryness, redness, swelling, pain/tenderness and itching assessed by the Investigator will be summarized by tabulating the number and percentages for each time point. For evaluations: severity (none, mild, moderate, severe) and clinical significance (Abnormal NCS and Abnormal CS), the count and percentage will be provided.

7.7.3.2 Physical Examination

Results of physical examinations consisting of general appearance, skin/subcutaneous tissue, ears / eyes / nose / throat, head / neck, lungs / chest, cardiovascular system, gastro-intestinal tract (GIT), musculoskeletal (extremities), neurological, and lymphnodes conducted throughout the study will be presented in listings.

7.7.3.3 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A treatment-emergent AE (TEAE) is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug. A drug-related TEAE is defined as any TEAE that is assessed by the Investigator as possibly, probably, or definitely related to study drug.

Adverse event data will in addition be coded with the latest version of the MedDRA coding system used during the clinical conduct of the study: this is version 25.1 or higher. The SAS programmer or Data Manager of the study will add the coding (using the MedDRA system and SAS) to the AE descriptions extracted from the database.

The TEAEs are tabulated by system organ class (SOC) and preferred terms (PT) within each SOC according to the MedDRA terminology list. They will be tabulated broken down by treatment groups. TEAEs will be summarized in descending order according to incidence of SOC and PT, using the number and percentage of subjects experiencing a TEAE, as well as the number of events.

The TEAEs will also be tabulated by intensity and by relationship to study drug. If the same TEAE recorded separately in more than two rows due to worsen severity, the severity of the AE to the tables will be the highest one. Summary tables will be accompanied by individual subject listings broken down by treatment groups. The same tabulations and listings will be presented for treatment-emergent serious adverse events (TESAEs).

A SAE is defined by the International Council for Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Results in death.

- Is life-threatening. Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires subject's hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

The following calculations and derivations will be used, making the most conservative judgment.

For study day of AE relative to study drug:

- Study day = AE start date minus date of (prior) dose administration + 1 by treatment groups if the AE occurred post dosing.
- Study day = 'Prior' if the AE occurred prior to dosing.
- If start date is unknown, study day will be missing.

For duration of AE:

- Duration = stop date and time of the event minus start date and time of the event.
- If start or stop time unknown, then the duration will be calculated based on stop date and start date only, and +1 day is added.
- If start or stop date is unknown, duration will be missing.
- Will be display as "XXDXXHXXM".

A general summary of all TEAEs and will be provided. This summary will present the numbers and percentages of subjects according to the following categories:

- Subject with Any TEAE
- Subject with Any TESAE
- Subject with Any Drug-Related TEAE
- Intensity
- Action Taken
- Relationship to Study drug
- Outcome
- Serious AE
- Serious criteria

Other summary tables for AEs will be tabulated:

- Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events – MedDRA
- Treatment-Emergent Adverse Events by Intensity – MedDRA
- Treatment-Emergent Adverse Events by Relationship – MedDRA
- Treatment-Emergent Adverse Events – MedDRA (Preferred Term over XX %)
- Treatment-Emergent Serious Adverse Events - MedDRA
- Treatment-Emergent Serious Adverse Events by Intensity - MedDRA
- Treatment-Emergent Serious Adverse Events by Relationship – MedDRA
- Listing of Subjects with Treatment-Emergent Serious Adverse Events

- Listing of Subjects with Treatment-Emergent AEs Leading to Death
- Listing of Subjects with Treatment-Emergent AEs Leading to Premature Discontinuation of Study Drug

A general summary of all TEAEs will be provided according to the following categories (empty categories will also be included) on Table 14.3.1.1.

7.7.3.4 Safety Clinical Laboratory Evaluations

Laboratory parameters to be determined per protocol are:

Hematology	Chemistry	Urinalysis	Others
Hemoglobin	Creatinine and eGFR	Nitrates	FSH[b]
Hematocrit (packed cell volume [PCV])	Fasting glucose[d]	pH	Bata-HCG[b]
RBC count	Sodium	Glucose	
Platelet count	Potassium	Albumin or micro albumin	
WBC count	ALT	Erythrocytes	
Neutrophils	AST	Leukocytes	
Eosinophils	GGT	Ketones	
Monocytes	Bilirubin (total, direct and indirect)	Microscopy[a]	
Basophils	Alkaline phosphatase	Specific gravity	
Lymphocytes	Albumin	Creatinine	
Mean corpuscular volume	Cholesterol (total) – lipid status[d]	Protein	
Mean corpuscular hemoglobin[f]	LDL – lipid status[d]		
Mean corpuscular hemoglobin concentration[f]	HDL – lipid status[d]		
Erytoblasts[f]	Triglycerides – lipid status[d]		
Red blood cell distribution width (RDW-CV)[f]	LDH – lipid status[d]		
ESR	α-tocopherol[e] Rheumatoid factor[c] Chloride CRP hsCRP (Part 2 only) Calcium (corrected) Inorganic phosphate Uric acid Blood urea nitrogen Pancreatic lipase[g]		

[a] If there is an abnormality in urine in accordance with the clinical laboratory standard procedures.
[b] Required of postmenopausal females only during Screening.
[c] Only at Screening.
[d] Only at Screening, pre-dose on Day 1, Day 14 and Day 35 (Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS).
[e] Only pre-dose on Day 1, Day 14 and Day 35 (Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS).
[f] Only applicable for Part 2
[g] Not on Day 92 of Part 3

Listings will be created of the laboratory data according to protocol and only present the original values, units and reference ranges as received from the laboratory.

All qualitative laboratory data will be supplied per lab manual, which is checked on the use of International System (SI) units by clinic and (if necessary) converted to SI units for the descriptive statistics.

Listings of all clinical laboratory data for each subject will be provided and values outside the normal range are flagged. For continuous data, abnormal values will be flagged with 'L' (low) for values below the lower limit of the laboratory's normal range, or 'H' (high) for values above the upper limit of the laboratory's normal range. Qualitative results outside of the laboratory's normal range will be flagged as 'A' (Abnormal). For evaluations (Normal, Abnormal NCS and Abnormal CS), the count and percentage will be provided.

Laboratory safety data will be summarized according to protocol scheme time point. Where applicable, change from baseline will also be calculated and summarized. Baseline is defined as the last value measured on Day -1 (or pre-dose on Day 1) The evaluations from baseline over time will be summarized as a shift table.

7.7.3.5 Vital Signs

Vital signs (systolic BP, diastolic BP, pulse rate, SpO_2, and temperature) collected according to protocol will be summarized using descriptive statistics for each time point. Where applicable, change from baseline will be calculated. For evaluations (Normal, Abnormal NCS and Abnormal CS), the count and percentage will be provided.

7.7.3.6 12-lead ECG

Twelve-lead electrocardiogram parameters (heart rate, PR, QRS - duration, QT, QTcB, QTcF, QTcB average, and QTcF average) collected according to protocol will be summarized using descriptive statistics for each time point. Where applicable, change from baseline will be calculated. The count and percentage of evaluations (Normal, Abnormal NCS and Abnormal CS) will be summarized according to protocol scheme time as well.

7.7.3.7 3-lead ECG (Telemetry)

Three-lead electrocardiogram collected evaluation according to protocol will be summarized using descriptive statistics on Day 1. For evaluations (Normal, Abnormal NCS and Abnormal CS), the count and percentage will be provided.

7.7.3.8 RA Previous and Concomitant Medication

RA previous medication and concomitant medications will be coded according to the latest version (version 2022 or higher) of the WHO drug code and the ATC class code. And will be summarized in descending order according to the ATC level 2, ATC level 4, and generic name using the number and percentage of subjects taking, as well as the number of events.

8 CHANGES FROM PROTOCOL AND OTHER REMARKS

There were no significant changes to the analyses planned in the study protocol.

9 SOFTWARE

9.1 Coding Systems

Adverse Events, Medical History, and Concomitant Medication will be coded as described in the Data Management documentation.

9.2 Statistical Software

The statistical analysis and reporting will be done using SAS for Windows™ version 9.4 or higher. SAS output will be saved and imported into PDF.

9.3 Reporting

All output will be generated as SAS tables and listings. All tables and listings will be created such that they fit landscape pages. All tables and listings will be created using SAS with an PDF output, and font Courier New size 9 will be used.

A list of tables and listings is presented (per report section) in Section 10.

The QPS template tables and listings will be used, and a separate templates document will be supplied together with the SAP. Adaptations to template layout are possible depending on the design of the study, the length of variables and the number of variables. It should be noted that all data as collected will be presented in listings and/or tabulations. The examples in the templates document may not cover all possible collected data, or examples may be present of data not collected for this specific study.

All tables and listings created will need to adhere to the following margins to fit the appendix layout if the CSR:

Landscape: Top - 1.14 inch
Bottom - 0.79 inch
Left - 1 inch
Right - 1 inch

10 TABLES, LISTINGS AND FIGURES

10.1 List of Tables and Figures – core text

All tables mentioned here will be presented in the report and will be supplied to the Medical Writer as separate .RTF or .DOCX files.

- Summary table of demographic data, baseline parameters, and concomitant medications for all-treated set: mean, median, standard deviation, minimum, maximum, and number of

available observations for continuous variable. Counts and percentages for qualitative characteristics.

- Adverse event summary containing the number and percentage of subjects experiencing any TEAE or TESAE. Table will contain information concerning the intensity and relationship and discontinuation due to an AE. Table will be presented by treatment groups.

- Adverse event summary containing the number and percentage of subjects experiencing TEAEs. AEs are tabulated by SOC and PT and summarized by treatment groups. AEs will be summarized in descending order according to incidence of SOC and PT.

- If applicable, the same tabulations will be presented for TESAEs.

- If applicable, summary listing of TESAEs containing description of event, MedDRA preferred term, subject number, intensity, action taken, relationship, and outcome.

10.2 List of Tables – end of text

All tables mentioned here will be presented according to ICH guidelines in appendix 14 of the report. A complete document (batch load) will be created in Word for the Medical Writer, in the order and with section number and title as stated.

Mock table is provided as a separate document to this SAP.

14.1 Demographic Data Summary figures and tables
14.2 Efficacy Data Summary figures and Tables
14.3 Safety Data Summary figures and tables
- 14.3.1 Displays of Adverse Events
- 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events
- 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
- 14.3.4 Abnormal Laboratory Value Listing (each subject)

Section	Title	Notes
14.1.1	Summary of Subject Disposition	Summary of all eligible, randomized, receiving study drug, completed subjects, the number of subjects in the all-treated set, immunogenicity set, per-protocol set, and safety set by treatment groups.
14.1.2	Summary of Demographics, Baseline Parameters, and Concomitant Medications	Descriptive statistics for demographic data, baseline parameters and CM for all-treated set by treatment groups.
14.2.1	Summary of Bile Salt-Stimulated Lipase (BSSL) in Blood	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.

14.2.2	Summary of Serum C-reactive Protein (CRP)	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.
14.2.3	Summary of Erythrocyte Sedimentation Rate (ESR)	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.
14.2.4	Summary of Immunogenicity	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.
14.2.5	Summary of S-Calprotectin	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.
14.2.6	Summary of hsCRP	Descriptive statistics for absolute values and change from baseline by time point, per treatment groups.
14.3.1.1	Treatment-Emergent Adverse Events	Adverse event summary containing the number and percentage of subjects experiencing any TEAE or TESAE. Table will contain information on the intensity, action taken, relationship to study drug, outcome, and serious of AE. Table will be presented by treatment groups.
14.3.1.2	Treatment-Emergent Adverse Events - MedDRA	Adverse event summary containing the number and percentage of subjects experiencing TEAEs. TEAEs are tabulated by SOC and PT and summarized by treatment groups. The summary will be presented in descending according to SOC and PT.
14.3.1.3	Treatment-Emergent Adverse Events by Intensity - MedDRA	The same tabulation as 14.3.1.2 will be created for TEAEs by intensity.
14.3.1.4	Treatment-Emergent Adverse Events by Relationship - MedDRA	The same tabulation as 14.3.1.2 will be created for TEAEs by relationship to study drug.
14.3.1.5	Treatment-Emergent Adverse Events - MedDRA (Preferred Term over XX %)	Adverse event summary containing the number and percentage of subjects experiencing TEAEs. TEAEs are tabulated by PT and summarized by treatment groups.
14.3.1.6	Treatment-Emergent Serious Adverse Events - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs.
14.3.1.7	Treatment-Emergent Serious Adverse Events by Intensity - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs by intensity.

14.3.1.8	Treatment-Emergent Serious Adverse Events by Relationship - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs by relationship to study drug.
14.3.2.1	Listing of Subjects with Treatment-Emergent Serious Adverse Events	Listing for all TESAE.
14.3.2.2	Listing of Subjects with Treatment-Emergent AEs Leading to Death	Listing for AEs leading to death.
14.3.2.3	Listing of Subjects with Treatment-Emergent AEs Leading to Premature Discontinuation of Study Drug	Listing for AEs leading to premature discontinuation.
14.3.4	Abnormal Laboratory Values for All Subjects	A subject listing of all data outside the (investigators) reference range, containing the variables test, age, sex, date/time, unit, value, reference range, and whether there were clinical implications (NCS/CS).
14.3.5.1-14.3.5.3	Laboratory Values over Time - Hematology/ Serum Biochemistry/ Urinalysis	Descriptive statistics for values and change from baseline by time point, per treatment groups.
14.3.5.4-14.3.5.6	Individual Subject Changes (Shift Table) - Hematology/ Serum Biochemistry/ Urinalysis	Shift table for LB data.
14.3.6	Summary of Vital Sign	Descriptive statistics for values and change from baseline by time point, per treatment groups.
14.3.7-14.3.8	Summary of 12-Lead ECG/ 3-Lead ECG (Telemetry)	Descriptive statistics for values and change from baseline by time point, per treatment groups.
14.3.9	Summary of Injection Site Reaction	Descriptive statistics by time point, per treatment groups.
14.3.10	Summary of RA Previous and Concomitant Medication by ATC Level	Summary containing the number and percentage of subjects taking RA previous and concomitant medication by ATC Level.

Full details are provided in SAP Mock Table.

10.3 List of Subject Data Listings

All listings mentioned here will be presented according to ICH guidelines in Appendix 16.2 of the report. A complete document (“batch load”) will be created in Word for the Medical Writer, in the order and with section number and title as stated.

Mock listing is provided as a separate document to this SAP.

16.2 Subject data listings
- 16.2.1 Discontinued subjects
- 16.2.2 Protocol deviations

16.2.3 Subjects excluded from the efficacy analysis
16.2.4 Demographic data
16.2.5 Compliance and/or drug concentration data
16.2.6 Individual efficacy response data
16.2.7 Adverse event listings
16.2.8 Listing of individual laboratory measurements by subject
16.4 Individual Subject Data Listing

Individual listings will be prepared of all the data collected in the database. No combining of data other than mentioned in this paragraph will be performed. Listings will be presented per dose level or placebo. The key variables in all listings will be subject number, cohort, and dose level or treatment. If applicable, visit number, day and time point will be listed additionally. For laboratory data, age and sex will be added to the listing, if deemed relevant. For AE data, duration and time to start (study day) will be added.

Additionally, a listing containing study dates and times will be presented, as well as containing PK sampling time deviations.

For inclusion/exclusion criteria, the text from the core protocol will be used (not the text from the synopsis or the source/eCRF) for listing purposes.

Section	Title	Notes
16.2.1.1	Subject Disposition (Complete Status)	
16.2.1.2	Subject Eligibility Not Met	
16.2.1.3	Randomization	
16.2.2	Protocol Deviations List	
16.2.3	Subject Excluded from the Analysis	Reason for exclusion of all-treated, safety, immunogenicity, per-protocol, and PD (exploratory) set.
16.2.4.1	Individual Subject Demographics	
16.2.4.2	Medical History	Including MedDRA coding
16.2.4.3	Prior Medication	Including WHO-ATC coding
16.2.4.4	Concomitant Medications	Including WHO-ATC coding
16.2.4.5-16.2.4.9	Clinical Laboratory Tests - Alcohol Breath Test/ Urine Drug Screen/ Urine Cotinine Test/ Serology/ Anti-CCP Antibody	
16.2.4.9-16.2.4.13	Individual Subject Covid-19 Test/ Height, Weight, BMI/ QuantiFERON® Test/ 3-Lead ECG (Telemetry)	
16.2.4.14-16.2.4.16	Individual RA Patient Medical History/ Medical History (Previous Treatment)/ Chest X-Ray/ DAS28 and VAS	
16.2.5.1	Study Drug Administration	
16.2.5.2	Individual Subject Pharmacokinetic Blood Sampling Time	Including scheduled and actual times

16.2.5.3	Individual Subject Immunogenicity Sampling Time	
16.2.6.1-16.2.6.3	Individual Subject Bile Salt-Stimulated Lipase (BSSL) Blood Sampling/ Cytokine and Chemokine Blood Sampling/ Future Exploratory Analysis Sampling Time	
16.2.6.4-16.2.6.6	Individual RA Patient S-calprotectin/ hsCRP/ Flow Cytometry and Whole Blood Stimulation Sampling	
16.2.7	Individual Subjects Adverse Events	Including MedDRA coding
16.2.8.1-16.2.8.6	Clinical Laboratory Tests – Hematology/ Serum Biochemistry/ Urinalysis/ Microscopic Exam/ Coagulation/ Urine Pregnancy Test	
16.4.1-16.4.5	Individual Subject Vital Signs/ Physical Examination/ 12-Lead Electrocardiogram (ECG)/ Injection Site Reaction	

Full details are provided in SAP Mock Listing.