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Study Title: Randomized, Double-blind, Placebo-controlled, 28-Day Daily-dose Crossover Study of the Safety and Tolerability of SB-121 (Lactobacillus reuteri with Sephadex® and Maltose) in Subjects, ages 15 to 45 years, diagnosed with Autistic Disorder

Protocol Reference Number: SBI-SB121-20-01

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Statistical Analysis Plan

Randomized, Double-blind, Placebo-controlled, 28-Day Daily-dose Crossover Study of the Safety and Tolerability of SB-121 (Lactobacillus reuteri with Sephadex® and Maltose) in Subjects, ages 15 to 45 years, diagnosed with Autistic Disorder

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[redacted]

Sponsor: Scioto Biosciences Inc.

Author:
[redacted] Principal Biostatistician

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company / Organization
[redacted], Director of Biostatistics	Peer Review Statistician	Draft 0.1	[redacted] Drug Development
Sanjeev Ahuja, MD	Sponsor CMO	Draft 3.0	Scioto Biosciences

Glossary of Abbreviations

Abbreviation	Term
AD	Autistic Disorder
AE	Adverse Event
AESI	AE of Special Interest
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
DB	Double-Blind
DBP	Diastolic BP
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
IP	Investigational Product
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
PT	Preferred Term
SAE	Serious AE
SAP	Statistical Analysis Plan
SBP	Systolic BP
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent AEs
TFLs	Tables, Figures and Listings
WHO DD	World Health Organization Drug Dictionary

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	15Oct2021	4.0
eCRF	10Dec2021	5.0

2. Protocol Details

2.1. Overall Study Design

This is a phase 1, single-center, randomized, double-blind, placebo-controlled, cross-over study to evaluate the safety and tolerability of 28-days of once daily oral administration of SB-121 (a preparation of L. reuteri with Sephadex® and maltose), to subjects with autistic disorder (AD).

Up to 16 eligible subjects will be randomized 1:1 to receive treatment with either SB-121 or placebo for 28 days. After a washout period of approximately 14 days, the subjects will be crossed over to the alternate treatment for approximately 28 days.

Subjects will undergo screening within approximately 14 days before the first administration of the investigational product (IP). All subjects (or parent/authorized designee) will be required to provide written informed consent before any study-specific procedures are performed. Subjects will also be asked to provide consent to allow storage of biological samples for future analysis that will not involve genetic tests. Subjects' eligibility for the study will be determined at Screening by assessment of inclusion and exclusion criteria. Eligible subjects will be provided with a stool sampling kit to collect a pretreatment stool sample within 48 hours before receiving the IP.

Subjects will return to the study site (clinic) on Day 1. Following confirmation of eligibility criteria, they will be randomized to receive SB-121 or placebo. Following baseline tests, all subjects will be given their first dose of either SB-121 or placebo at the clinic.

Subjects will undergo study-specific procedures on Day 1 in accordance with the schedule of events and will be discharged after all Day 1 evaluations have been completed. They will then take the IP at home once a day for the remaining approximately 27-days. They will then return to the clinic on Day 28.

Following the approximately 14 day washout period, all subjects will cross-over to the other treatment (SB-121 or placebo) for approximately 28-days and the study procedures will be repeated.

Follow-up clinic visits will be conducted on Day 28 of Treatment Period 1, Day 1 of Treatment Period 2, and Day 28 of Treatment Period 2.

2.2. Study Objectives

2.2.1. Primary Objective(s)

To evaluate the safety and tolerability of multiple doses of SB-121 in subjects with AD

2.2.1.1. Estimands for the Primary Objective(s)

Not applicable

2.2.2. Secondary Objective(s)

- To monitor the elimination of Sephadex® from the GI tract in subjects with AD
- To assess the impact of multiple doses of SB-121 on circulating oxytocin levels in subjects with AD
- To assess the impact of multiple doses of SB-121 on tests of AD
- To evaluate biomarkers of microbiota function, immune modulation, and inflammation following multiple doses of SB-121 in subjects with AD

2.2.2.1. Estimands for the Secondary Objective(s)

Not applicable

2.3. Sample Size and Power

The sample size was not determined based on statistical assumptions. Evaluation of up to 8 subjects per treatment group (16 subjects total) was considered sufficient to allow evaluation of the study's objectives.

2.4. Primary Efficacy Variable(s)

The main objective of this study is to evaluate safety and tolerability of SB-121. There are no primary efficacy variables to assess.

2.5. Secondary Efficacy Variable(s)

Secondary efficacy variables include circulating oxytocin levels, tests of AD, and biomarkers of microbiota function, immune modulation, and inflammation.

2.6. Exploratory Efficacy Variable(s)

Not applicable

2.7. Safety Variable(s)

Safety variables include: Incidence and severity of treatment-emergent AEs (TEAEs), serious AEs (SAEs), AESIs, and AEs leading to discontinuation from the study; incidence of presence of Sephadex® microspheres in the stool: incidence of symptomatic bacteremia with positive *L. reuteri* identification. Additionally, clinical laboratory values that are abnormal and considered clinically significant, vital signs, and abnormal physical examination results will be evaluated.

3. Estimand(s)

3.1. Estimands for the primary / secondary objective(s)

Not applicable

4. Analysis Populations

In accordance with ICH E3 and E9[1], the following analysis sets will be used for the analyses.

4.1. All Screened Population

The All Screened population will consist of all subjects screened. It will be used for summary and listing of screen failures.

4.2. Intent-to-Treat Population

The Intent-to-Treat population (ITT) will consist of all randomized subjects who signed the informed consent form. ITT subjects will be analyzed according to their randomized treatment.

The ITT will be used for summaries and analysis of disposition, demographics and baseline characteristics, and prior and concomitant medications.

4.3. Safety Population

The Safety population will consist of all subjects in the ITT population who received at least one dose of IP. Safety analyses will be analyzed according to their treatment received.

The Safety population will be used for all safety analyses.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

First dose date in Treatment Period 1 will be considered relative day 1, and the day before the first dose in Treatment Period 1 will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known:

For days on or after the first dose in Treatment Period 1:

Date of Assessment – Period 1 First Dose Date + 1.

For days before the first dose in Treatment Period 1:

Date of Assessment – Period 1 First Dose Date.

5.1.2. Screening / Baseline Period

For all subjects, the screening period will be defined as the period from informed consent to the first dose of treatment in Treatment Period 1.

Baseline values for analyses of Treatment Period 1 will be the last observation prior to dosing in Period 1. Baseline values for analyses of Treatment Period 2 will be the last observation after the Treatment Period 1 washout and prior to dosing in Treatment Period 2. An additional analysis will be done for change of certain parameters, as discussed in Section 6.1, to the end of Treatment Period 1 and to the end of Treatment Period 2, respectively, utilizing as Baseline values the last observation prior to dosing in Treatment Period 1. This will be done for each treatment group.

5.1.3. Treatment Period

There will be 2 treatment periods. The Treatment Period 1 will be defined as the period from the date/time of the first dose of treatment (Visit 1/Day 1) and up to and including the date of Visit 2/Day 28. Following Treatment Period 1 will be a washout period occurring for approximately 14 days. The Treatment Period 2 will be defined as the period from the date/time of first dose of cross-over treatment (Visit 3/Day 42) and up to and including the date of Visit 4/Day 70. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Period 1 Day 1 and Period 2 Day 1 assessments are to be performed prior to the first dose of treatment in the study period, the data collected at Day 1 will be assigned to the baseline period of the respective period. However, adverse events with missing time starting on Day 1 and medications starting on Day 1 of each period, will be assigned to the respective treatment period.

5.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule per the protocol and eCRF. No visit windows will be applied for summary and analysis.

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

Not applicable

5.2.2. Handling of Missing Safety Data

Drop-outs will not be replaced in this study.

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the study up until 14 days after study treatment, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this imputation will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of: the earliest possible start date, and the date of first dose of treatment.
- The latest possible start date.
- The latest possible stop date.

For a missing / incomplete stop date the later date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month at 00:00hrs, if month and year are available but the day is missing.
- The date of the first day of the year at 00:00hrs, if year is available but day and month are missing.
- 00:00hrs on the day of informed consent, if the date is completely missing.

The latest possible date / time is defined as:

- The date itself if available.
- The date of the last day of the month at 23:59hrs, if month and year are available but the day is missing.
- The date of the last day of the year at 23:59hrs, if year is available but day and month are missing.
- 23:59hrs on the date of last known date on the study for the subject plus one year, if the date is completely missing.

6. Statistical Methods

6.1. General Principles

For the purposes of this SAP, all data processing, summarization and analyses will be performed using [redacted] Drug Development's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package. When summarizing data by treatment group, results will be combined across the study periods. For example, the data from subjects who received SB-121 in Treatment Period 1 will be combined with the data from subjects who received SB-121 in Treatment Period 2. An additional analysis will be done for change of certain parameters to end of Treatment Period 1 and end of Treatment Period 2, respectively, utilizing as Baseline values the last observation prior to dosing in Treatment Period 1. This will be done for each treatment group. These parameters may include fecal calprotectin and lactoferrin, serum hs-CRP and tumor necrosis factor-α, and plasma oxytocin and vasopressin levels.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those subjects with data.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

For the TFLs, the laboratory results will be summarized or presented in International System of Units (SI) units.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

6.2. Subject Disposition and Data Sets Analyzed

Subject disposition will be summarized by treatment sequence for the ITT population. The following information will be reported:

- Number and percentage of screened subjects and reasons for screen failure.
- Number and percentage of subjects for the following categories:
    - Randomized,

  - Treated in Period 1,
  - Not Treated in Period 1,
  - Completed Treatment in Period 1,
  - Discontinued Treatment in Period 1,
  - Reasons for Treatment discontinuation in Period 1,
  - Treated in Period 2,
  - Not Treated in Period 2,
  - Completed Treatment in Period 2,
  - Discontinued Treatment in Period 2,
  - Reasons for Treatment discontinuation in Period 2,
  - Completed the study,
  - Discontinued the Study,
  - Reasons for study discontinuation.
- Number and percentage of subjects included in each study population

A subject will be regarded as having completed the study if Disposition – End of Study eCRF response to 'Did the subject complete the study?' is Yes. A subject will be considered as having discontinued the study if they have an eCRF response to 'Did the subject complete the study?' of No. Otherwise, the subject will be considered as ongoing in the study.

A listing of all subjects with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the ITT population.

A listing of all screen failed subjects with their reasons for screen failure will be presented for all subjects. A separate listing of subjects who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for all subjects.

A listing of all randomized subjects with their randomization details, including first dose date and actual treatment received will be presented for the ITT population.

A listing of all subjects excluded from at least one analysis population will be presented for the All Screened population.

6.3. Protocol Deviations

All major protocol deviations will be summarized for the ITT population by treatment group as described below:

- The number of unique subjects with at least one major protocol deviation as well as the number of subjects in each major protocol deviation category will be presented by descriptive summary statistics.

A listing of all subjects with one or more protocol deviations will be presented for the ITT population.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the ITT population by treatment sequence and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (kg/m^2) at baseline

Total counts and percentages of subjects will be presented for the categorical variables of:

- Sex
- Race
- Ethnicity

Demographic characteristics will be listed for the ITT population.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the ITT by treatment sequence and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

Total counts and percentages of subjects will be presented for the categorical variables of:

- ADOS-2 Score at Screening
- DSM-5 checklist at Screening
- Pregnancy test results at Screening
- Drug of abuse at Screening per the urine drug screen

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the ITT population.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the subject may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 24.0] and will be presented by System Organ Class (SOC) and Preferred Term (PT). Medical history will be sorted alphabetically by SOC and descending frequency of PT.

Medical history records will be summarized for the ITT population by treatment sequence and overall.

Medical history records will be listed by-subject and within-subject by medical history start date for the ITT population.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, B3 Sep 2021, Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those that started prior to the start of dosing in Treatment Period 1.
- Concomitant medications are those with a start date on or after the start of dosing in Treatment Period 1, or those with a start date before the start of dosing in Treatment Period 1 and either a stop date after the start of the Treatment Period 1 or are ongoing during the study.
- If a medication starts prior to dosing in Treatment Period 1 and continues after dosing in Treatment Period 1 has started, it will be considered both prior and concomitant.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior medications will be summarized for the ITT population by treatment sequence and overall, and concomitant medications will be summarized separately for the ITT population by treatment group as follows:

- The number and percentage of subjects with at least one prior/concomitant medication will be presented.
- The number and percentage of subjects with at least one prior/concomitant medication within each Anatomical Group (ATC Level 1) and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the ITT population. In the listings, the relative start and stop day of prior medication use will be calculated relative to the first dose date of Treatment Period 1. In the listings, the relative start and stop day of concomitant medication use will be calculated relative to the first dose date of treatment in the period when the medication started and will be presented for those subjects who received at least one dose of treatment. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Treatment Compliance

Treatment compliance is defined as the number of doses that were actually taken relative to the number of doses that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance, assessed by dose count for each Treatment Period, will be calculated as follows:

$$\textit{Compliance (\%)} = \frac{\textit{(Number of kits dispensed - Number of kits returned)}}{\textit{Number of days on treatment} \times \textit{Number of kits prescribed per day}} \times 100\%$$

Number of days on treatment will be calculated as follows:

(last dose date of treatment in a Treatment Period- first dose date of treatment in a Treatment Period) +1

The calculated percentage compliance will be categorized as:

- < 80% compliance
- ≥ 80% compliance

Compliance will be summarized for the ITT population by treatment group as follows:

- Percent compliance will be presented by summary statistics.
- Number and percentage of subjects within each of the compliance categories will be presented. Any subjects with missing data will be presented as part of a "Missing" category.

Treatment compliance will be listed together with exposure for the ITT population. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy

6.6.1. Primary Efficacy Analysis

There is no primary efficacy analysis. The primary objective of the study is to evaluate safety and tolerability of SB-121. All safety assessments are presented in the applicable safety sections.

6.6.2. Secondary Analysis

[redacted]. These measures are: Clinical Global Impressions Severity and Improvement Subscales, Vineland Adaptive Behavior Scales (3rd edition), Aberrant Behavior Checklist, Woodcock Johnson Test (3rd Edition), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), Test of Attentional Performance for Children (KiTap), Neurophysiology Measures including EEG resting state, auditory habituation, and chirp modulated sweep auditory evoked response, and Eye Tracking and Pupillometry measures.

The number and percentage of subjects with incidence of presence of Sephadex® microspheres in the stool and incidence of symptomatic bacteremia with positive L. reuteri identification will be summarized by treatment group by visit and listed based on the ITT population.

The stool and blood samples will be used for the evaluations of potential biomarkers of inflammation (fecal calprotectin and lactoferrin and blood hs-CRP and tumor necrosis factor-α). In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The following will be summarized by treatment group for the ITT population:

- Observed values and percentage change from baseline at each assessed visit, including comparison of baseline to end of Treatment Period 1 and baseline to end of Treatment Period 2, for each biomarker parameter using summary statistics for continuous variables;

A listing of all biomarkers data including derived change from baseline will be provided for the Safety population.

Plasma oxytocin and vasopressin levels will also be analyzed. In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The following will be summarized by treatment group for the ITT population:

- Observed values and percentage change from baseline at each assessed visit, including comparison of baseline to end of Treatment Period 1 and baseline to end of Treatment Period 2, for each parameter using summary statistics for continuous variables;

A listing of all plasma oxytocin and vasopressin data including derived change from baseline will be provided for the ITT population.

6.7. Safety

6.7.1. Extent of Exposure

Duration of exposure will be defined in days for each Treatment Period as:

Exposure (days) = [date of last dose in a Treatment Period– date of first dose in a Treatment Period] + 1 – off-treatment days

Duration of exposure will be summarized for the Safety population by treatment group using descriptive statistics.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the Safety population.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 24.0] and classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the start of Treatment Period 1.
- TEAEs are either events with start date after the start of the Treatment Period 1 (during or after the first dose of IP), or events with start date prior to the start of the Treatment Period whose severity worsens on or after the start of the Treatment Period (during or after the first dose of IP). A TEAE occurring on or after the first dose of treatment in Treatment Period 1 up until the first dose of treatment in Treatment Period 2 will be assigned to the treatment group received in Treatment Period 1. A TEAE occurring on or after the first dose of treatment in Treatment Period 2 up until the end of study will be assigned to the treatment group received in Treatment Period 2.

- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious = "Yes".
- The relationship between a TEAE and SB-121 is assessed as definitely, probably, possibly, unlikely, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as definitely, probably, or possibly related to treatment or with unknown / missing relationship to treatment.
- Assessment of AE severity / intensity will be based on the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[2], version 5.0). If an NCI-CTCAE scale is not available for a given AE, the following definitions will be used:

• Grade 1 (mild)	• asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
• Grade 2 (moderate)	• minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living
• Grade 3 (severe)	• medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
• Grade 4 (life-threatening)	• Life-threatening consequences; urgent intervention indicated
• Grade 5	• Death related to AE

In addition to the aforementioned AE types, TEAEs of special interest will be identified as collected in the eCRF.

Adverse events will be summarized by descriptive summary statistics for categorical variables for the Safety population by treatment group as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one TEAE type.
    - Any TEAE
        - TEAEs of Special Interest
        - Leading to discontinuation of study treatment
        - Leading to death
        - Grade 1 severity (mild)
        - Grade 2 severity (moderate)
        - Grade 3 severity (severe)
        - Grade 4 severity (life-threatening)

        - Grade 5 severity (death)
    - Any study treatment related TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
    - Any serious TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
    - Any serious study treatment related TEAE
        - Leading to discontinuation of study treatment
        - Leading to death

- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
    - TEAEs of Special Interest
    - TEAEs Leading to Interruption of Study Treatment
    - TEAEs Leading to Discontinuation of Study Treatment
    - TEAEs Leading to Death
    - TEAEs by Maximum Severity
    - TEAEs that are Related to Study Treatment
    - Serious TEAEs
    - Serious TEAEs that are Related to Study Treatment

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included in the counts of the 'Number of Subjects with at least one TEAE', 'System Organ Class' and 'Preferred Term' rows of the summary but they will not be included in the counts by severity.

Summaries by SOCs and PTs will be sorted by SOCs and PTs within SOC by descending order of total incidence in the active treatment group. Where preferred terms tie PTs will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment in the Treatment Period when the AE started and will be presented for those subjects who received at least one dose of treatment. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of AEs Leading to Interruption of Study Treatment
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs of Special Interest

6.7.3. Laboratory Evaluations

Data for the following hematology, biochemistry, and urinalysis analytes recorded in the eCRF are to be measured at the scheduled visits.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, white blood cell count including differential (to also include absolute neutrophil, lymphocyte and eosinophil counts)
Serum Chemistry:	albumin, total and direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, highly sensitive C-reactive protein
Urinalysis (dipstick):	pH, specific gravity, blood, glucose, protein, ketones

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived for quantitative data as follows:

Absolute change (unit) = (post-baseline value – baseline value)

All laboratory data will be reported in SI units. Categorization of abnormal laboratory results along with clinical significance will be collected in a spreadsheet outside of the EDC database and utilized for the below outlined analysis. The same data (abnormal values) collected within the EDC will not be used in any statistical analysis. All normal results will continue to be collected and presented from the EDC. All quantitative laboratory test values at each assessed visit will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries which present worst value with respect to the reference range at the subject level, low and high are each chosen in preference to normal values. For parameters with values that are both low and high, subjects will be counted within each category for worst value summary tables.

Laboratory data will be summarized by descriptive summary statistics for continuous and categorical variables for the Safety population by treatment group as follows:

- Observed values and change from baseline for each Treatment Period at each assessed visit for each standard continuous laboratory parameter;
- Number and percentage of subjects with categorized shift (low, normal, and high) values relative to the reference range at baseline compared to each post-baseline at each visit for each Treatment Period
- Number and percentage of subjects with worst categorized (low, normal, and high) values relative to the reference range;

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety population. Within each listing, laboratory values outside the normal ranges flagged as either high or low will be provided for applicable laboratory assessments. Listings of pregnancy results will also be provided for the Safety population.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (bpm);
- body temperature (°C).

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The following will be summarized by treatment group for the Safety population:

- Observed values and percentage change from baseline at each assessed visit for each standard vital sign parameter using summary statistics for continuous variables;

A listing of all vital signs data including derived percentage change from baseline will be provided for the Safety population.

6.7.5. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, not clinically significant / abnormal, clinically significant
- Heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTcB interval (msec).

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

The ECG findings will be summarized by treatment group for the Safety population as follows:

- Observed values and percentage change from baseline at each assessed visit for each ECG parameter using summary statistics for continuous variables;
- The ECG overall assessment as reported by the investigator will be summarized at each assessed visit by providing number and percentage of subjects within each assessment category;

A listing of all ECG data will be provided for the Safety population.

6.7.6. Physical Examination

For each physical examination body system, the number and percentage of subjects with abnormalities at baseline and at each assessed visit will be summarized by treatment group for the Safety population.

Physical examination findings (normal / abnormal) and details of abnormalities will be listed for each subject at each assessed visit for the Safety population.

6.7.7. Interim Analysis and Data Monitoring

No interim analysis and data monitoring is planned for this study.

6.8. Pharmacokinetic Assessments

No PK assessments are planned for this study.

7. Changes in the Conduct of the Study or Planned Analysis

There were no changes in the conduct of the study at the time of preparing this SAP. There were no changes in the analysis planned in the protocol of the study at the time of preparing this SAP.

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Draft, 09Nov2021	Not applicable; the first version
Version 2.0, Draft, 15Dec2021	Updated text based on Client comments in Draft 1.0
Version 3.0, Draft, 12Jan2022	Updated text based on Client comments in Draft 2.0
Version 1.0, Final, 20Jan2022	Final version with all agreed client comments from drafts

8. References

[1]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[2]*Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Available at* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50