# STATISTICAL REPORTING AND ANALYSIS PLAN

## A RANDOMIZED, OPEN LABEL, SINGLE CENTER, SINGLE DOSE, TWO PERIOD, TWO SEQUENCE, CROSSOVER BIOEQUIVALENCE STUDY OF PARACETAMOL IN A NEW PEDIATRIC PARACETAMOL ORAL SUSPENSION COMPARED TO A MARKETED PARACETAMOL ORAL SUSPENSION (PANADOL BABY & INFANT) IN HEALTHY ADULT SUBJECTS

**Protocol Number:** 215262

**Phase:** 1

## Document History

| Document | Version Date | Summary of Changes (New analysis or Change in planned analysis) |
|---|---|---|
| Original Analysis Plan | 21-Oct-2021 | Not applicable (N/A) |

Amendments incorporate all revisions to date.

## Table of contents

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 215262.

# 1 Summary of Key Protocol Information

## 1.1 Study Design

This is a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects.

Subjects will be screened for eligibility within 15 days prior to dosing. Subjects will receive each of the two study treatments in fasted state during a 6-day (5-overnight stay) residential period at the study site. Subjects will receiveeach treatment in a randomized order with a washout period of at least 72 hours between doses. During each treatment period, subjects will provide a pre-dose blood sample 1 hour before dosing and 20 post-dose blood samples at 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours, for bioanalytical analyses of paracetamol.

**Figure 1-1 Study design**

| Screening | Period 1 | Washout[a] | Period 2 | End of study visit |
|---|---|---|---|---|
| Day -15 to -2 | Day -1 to 2 | Day 1[b]-3 | Day 4-5 | Day 5 |

a: Washout period of at least 72 hours between the doses

b: Begins post administration of first dose

## 1.2 Study Objectives

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Primary Endpoint** |
| • To demonstrate the bioequivalence of paracetamol in a new paracetamol oral suspension versus the marketed paracetamol oral suspension (Panadol B&I) | • $AUC_{0\text{-}tlast}$ (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule)<br>• $t_{max}$ (The time of the maximum observed post-dose concentration)<br>• $C_{max}$ (The maximum observed post- dose concentration) |

| Objectives | Endpoints |
|---|---|
| **Secondary Objectives** | **Secondary Endpoints** |
| • Assess the pharmacokinetic (PK) profile of the new and the marketed paracetamol oral suspension | • $AUC_{0\text{-}inf}$ (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0\text{-}inf} = AUC_{0\text{-}tlast} + C_{last}/\lambda_z$ where $C_{last}$ is the last measurable concentration and $\lambda_z$ is the terminal elimination rate constant)<br>• $\%AUC_{ex}$ (Percentage of AUC0-inf obtained by extrapolation, calculated as $(1 - [AUC_{0\text{-}tlast} / AUC_{0\text{-}inf}]) \times 100$)<br>• $\lambda_z$ (The terminal elimination rate constant computed as the slope of the regression line of ln (concentration) vs time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time) |
| Safety | |
| • Assess the safety profile of both products | • AEs, vital signs and clinical safety laboratory test results |

## 1.3 Treatments

Single oral dose of Test Product (new paracetamol oral suspension) or Reference Product (Panadol B & I) will be administered to all subjects in each study period.

| | Test Product | Reference Product |
|---|---|---|
| Product | New paracetamol oral suspension (24 mg/ml paracetamol) | Panadol B&I (24 mg/ml paracetamol) |
| Dose | 42 mL (1g paracetamol) | 42 mL (1g paracetamol) |
| Route of administration | Oral | Oral |
| Marketing Authorization Holder & Source market | GSKCH, Finland | GSKCH, Czech Republic (CZ) |

## 1.4 Sample Size Calculation

Approximately 110 subjects will be screened to randomize approximately 37 healthy adult subjects to ensure at least 31 evaluable subjects complete the entire study, assuming a 15% dropout and non-evaluable rate. CCI [redacted]

CCI [redacted]

# 2 Planned Analyses

## 2.1 Interim Analysis

No interim analysis is planned.

## 2.2 Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have either completed or discontinued the study as defined in the protocol
2. All required database cleaning activities including any external data reconciliation have been completed and database has been locked.
3. The randomization codes have been distributed.

# 3 Considerations for data analyses and Data Handling Conventions

## 3.1 Baseline Definition

For safety analyses:

- Subject level baseline is defined as the latest assessment with a non-missing value before the first dosing.

For PK analyses:

- Subject level baseline is defined as the latest assessment with a non-missing value before dosing in each period.

Unless otherwise stated, if baseline data is missing no imputation will be performed and will be set to missing.

## 3.2 Subgroups/Stratifications

Not applicable.

## 3.3 Pooling by center

This will be a single center study.

## 3.4 Timepoints and Visit Windows

Refer to Section 4.4.1.3 for handling of PK samples that are outside the of protocol-specified collection window.

# 4 Data Analysis

Derivation of the PK parameters for paracetamol in plasma will be the responsibility of the clinical pharmacokineticist at PPD . The PK and safety summaries, figures, and data listings, as well as the statistical analysis of the PK variables, will be the responsibility of the study biostatistician at PPD . Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, L.P. Princeton, New Jersey). The statistical analysis software used will be SAS® version 9.4 (in a WINDOWS environment using SAS Enterprise Guide).

Prior to database closure, a Blind Data Review Meeting (BDRM) will be conducted in which various aspects of the trial will be discussed and agreed. PPD Biostatistics will generate listing outputs with no treatment information for inclusion/exclusion, protocol deviations, adverse events, drug compliance, medical history, and concomitant medications to support the BDRM.

One aspect that will be considered prior to or during BDRM is the assessment of the number of subjects who have discontinued or been discontinued from the study due to pandemic related events (e.g. COVID-19) and the potential need of a sensitivity analysis. Any major changes to planned analyses will need an amendment to the Reporting and Analysis Plan (RAP).

Except as described below, all listings will be produced for all randomized subjects.

## 4.1 Populations for Analysis

Tables described in this section will be produced for all randomized subjects. Subject disposition will include all screened subjects (CCI ). All screen failure subject data will be listed.

### 4.1.1 Subject Disposition and Eligibility for Analysis Populations

Subject disposition for all screened subjects will be summarized as the number of subjects screened, number of subjects passed screening, number of subjects failed screening with reason, number of subjects randomized, number and percentage of subjects who received any study medication, completed the study, and who discontinued with the reason for discontinuation by sequence and overall (CCI [redacted]). Subject disposition including the subject status (completed, Yes/No), critical demographic data (age, sex, race), date of completion/discontinuation and the specific reason for discontinuation, will be listed in Listing 16.2.1.1.

### 4.1.2 Protocol Deviations

Protocol deviations will be collected and stored in PPD Clinical Trial Management System (CTMS). All deviations collected in CTMS will be provided by the PPD clinical study manager as a Microsoft Excel file and read into SDTM to generate the data listing.

The protocol deviation management plan (PDMP) lists the potential protocol deviations and associated severity by category for the study. Prior to database lock, all protocol deviations will be classified as critical, major or minor.

Important (critical and major) protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed. The number and percentage of subjects with any critical or major protocol deviation will be presented (CCI [redacted]). Critical and major protocol deviations will be listed in Listing 16.2.2.1. Minor protocol deviations will be listed similarly (CCI [redacted]).

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to closure of the database to ensure all deviations are captured and categorised appropriately.

Changes to the procedures or events which may impact the quality of the PK data will also be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. They may potentially affect as little as a single concentration record or an entire profile (concentration-time profile and/or primary PK parameters). Examples affecting a single concentration record include, but may not be limited to, a single sample missed or collected outside the protocol-specified window at non-critical times. These protocol deviations may not impact the quality of the PK data. Examples affecting an entire profile include, but may not be limited to, vomiting following oral dosing occurring within 103 minutes post-dose, concomitant administration of medications with the potential to impact PK, and/or inaccurate dosing on the day of PK sampling. A subject may not have $C_{max}$ or $t_{max}$ correctly evaluated if 2 or more samples are missed around the median $t_{max}$. A subject may not have $AUC_{0\text{-tlast}}$ correctly evaluated if 1 or more samples are missed in the descending

phase of the curve following the last quantifiable concentration. If protocol deviations or events impacting entire profiles occur in any treatment period, subjects will be excluded from the PK analysis population and PK data collected during both treatment periods will be excluded from statistical analyses.

Subjects with baseline paracetamol concentration >5% of the individual $C_{max}$ for either period will be excluded from the PK population. If >10% of subjects are excluded from the PK population due to baseline paracetamol concentration >5% of the individual $C_{max}$, a sensitivity analysis will be conducted including all subjects, even those with the affected data.

### 4.1.3 Analysis Populations

Three analysis populations are defined.

| Population | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| All Subjects | • Comprise of all subjects who signed the informed consent to participate in the study. | • Disposition<br>• Study Population |
| Safety | • Comprise of all randomized subjects who receive at least one study medication.<br>• This population will be based on the treatment the subject actually received. | • Demography<br>• Safety |
| Pharmacokinetic | • Subjects in the 'Safety' population who complete the two periods and who have no major protocol deviations concerning PK. | • PK |

**NOTES :**

- Please refer to Attachment 1: List of Data Displays which details the population to be used for each display being generated.

The numbers of subjects included in each of the analysis populations, and the number excluded from each population broken down by the reason for exclusion will be presented (CCI [redacted]). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1, with the reason for exclusion. Any data excluded from PK population will be listed in Listing 16.2.3.2.

## 4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the Safety population.

### 4.2.1 Demographic Characteristics

Categorical demographic variables include sex, race, ethnicity and method of contraception. These variables will be summarized by the number and percentage of subjects with each relevant characteristic by treatment sequence and for all subjects overall. Body Mass Index (BMI) will be calculated as weight (kg)/[height (m)]$^2$. Age, weight, height and BMI will be summarized by the mean, standard deviation (SD), median, minimum and maximum values in each treatment sequence and overall. All demographic information will be tabulated in Table 14.1.4.1 for safety population, Table 14.1.4.2 for pharmacokinetic population and listed in Listing 16.2.4.1 for all subjects screened.

### 4.2.2 Other Baseline Characteristics

Informed consent details will be listed in Listing 16.2.4.2. Study eligibility will be listed in Listing 16.2.4.3. Results from virology and pregnancy test (in females) will be presented in Listing 16.2.4.5 and Listing 16.2.4.6, respectively. Listing of drug and alcohol screen (urine illicit drug screen, urine cotinine, alcohol screen) will be provided in Listings 16.2.4.7 – 16.2.4.9.

### 4.2.3 Medical History

Medical diagnoses/surgeries within the past 1 year will be listed in Listing 16.2.4.4, with start date and end date or ongoing at the start of study medication. Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

## 4.3 Treatments (Study Products, Other Concomitant Therapies, Compliance)

Exposure to study products and other medications will be summarized on the Safety Population.

### 4.3.1 Study Product Compliance and Exposure

Study product exposure to the treatment will be summarized as follows by treatment (Table 14.2.1.1):

- number (%) of subjects exposed to each treatment
- number (%) of subjects fully compliant to dosing requirements (without any deviation)
- number (%) of subjects with deviations from dosing requirements:
    - partial exposure
        - number (%) of subjects vomiting within 103 minutes post-dose
        - number (%) of subjects with baseline > 5% of the $C_{max}$ post-dose

Study product administration will be listed in Listing 16.2.5.1. Study products will be administered under the supervision of investigator site personnel and hence compliance is not calculated.

### 4.3.2 Prior and Concomitant Medication

Prior and concomitant medications will be coded using GSK WHO Drug Dictionary (Version 3.0).

All prior and concomitant medications will be listed. Medication/treatments taken within 30 days prior to signing the informed consent form and stopped before first dose of study product administration will be documented as a prior medication/treatment. Medications/treatments taken after first dose of study product will be documented as concomitant medication/treatments. Prior medications and concomitant medications will be listed by subject, with preferred term, indication, dose, dose form, frequency, route, start date and end date (CCI [redacted]). Concomitant medications (ongoing at Day 1 or started on or after Day 1) will be listed similarly (CCI [redacted]). Concomitant medications will be summarized (CCI [redacted]) for the safety population.

## 4.4 Analysis of Pharmacokinetics

### 4.4.1 Primary Pharmacokinetic Endpoint

#### 4.4.1.1 Primary Pharmacokinetic Endpoint Definition

Pharmacokinetic blood samples will be taken at pre-dose (1 hour before dosing), and 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, and 180 minutes and 4, 5, 6, 8, 10, 12, 14, and 16 hours post-dose in Period 1 and Period 2.

Plasma concentrations of paracetamol will be determined using a specific and highly sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) methodology in a laboratory with Good Lab Practices (GLP) certification. The targeted lower limit of quantitation (LLOQ) for paracetamol is 0.25 µg/mL.

The primary objective will be evaluated based on the following comparison:

The new paracetamol oral suspension (Test) versus the marketed paracetamol oral suspension Panadol B&I (Reference), in terms of $AUC_{0\text{-tlast}}$, $C_{max}$, and $t_{max}$.

The primary statistical analyses will be done using the PK population. The safety population will be used for the individual plasma concentration listing and figures. The PK population will be used for mean concentration-time figures.

#### 4.4.1.2 Calculation of Primary Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma paracetamol concentration-time data using Phoenix® WinNonlin® Version 8.3. Actual sample times will be used in the calculations of PK parameters. The calculation of the actual time for paracetamol will be in respect to the start of dose administration time of oral suspension on Day 1 (Period 1) or Day 4 (Period 2). All primary PK parameters included in the protocol are listed in Table 4-1 below and are defined as appropriate for study design.

Table 4-1: Noncompartmental Primary PK Parameters to be Calculated

| Parameter | Label to be Used in the Text, Tables, and Figures | Definition | Method of Determination |
|---|---|---|---|
| $AUC_{0\text{-}tlast}$ | AUC(0-tlast) | Area under the plasma concentration versus time curve from time zero to the last measurable sampling time point, $t_{last}$ | Calculated using the Linear Trapezoidal with Linear Interpolation Method |
| $C_{max}$ | Cmax | The maximum observed plasma paracetamol post-dose concentration | Taken directly from bioanalytical data |
| $t_{max}$ | tmax | The time of the maximum observed plasma paracetamol post-dose concentration | Taken directly from bioanalytical data |

Pharmacokinetic parameters will not be calculated for profiles with less than 3 consecutive post-dose time points with quantifiable concentrations. Profiles with insufficient data to calculate PK parameters will be included in the concentration listings only and excluded from the statistical analysis (summary and inferential statistics).

#### 4.4.1.3 Statistical Hypothesis, Model, and Method of Analysis

Pharmacokinetic Population will be used for testing the statistical hypothesis. The PK parameters that will be used in the primary analyses are $AUC_{0\text{-}tlast}$, $C_{max}$, and $t_{max}$.

The null and alternate hypotheses to be tested in the primary analyses are:

$AUC_{0\text{-}tlast}$ and $C_{max}$

**$H_0$**: The (geometric) mean $AUC_{0\text{-}tlast}$ (likewise $C_{max}$) of a new paracetamol oral suspension (Test) is less than 80.0% or greater than 125.0% of that of Panadol B&I (Reference).

**$H_1$**: The (geometric) mean $AUC_{0\text{-}tlast}$ (likewise $C_{max}$) of a new paracetamol oral suspension (Test) is between 80.0% and 125.0% of that of Panadol B&I (Reference).

$t_{max}$

**$H_0$**: There is no difference between a new paracetamol oral suspension (Test) and Panadol B&I (Reference).

**$H_1$**: There is a difference between a new paracetamol oral suspension (Test) and Panadol B&I (Reference).

An Analysis of Variance (ANOVA) model will be fit to the log-transformed PK parameters ($AUC_{0\text{-}tlast}$ and $C_{max}$), as the dependent variable, and treatment, period, sequence, and subject nested within sequence as fixed effects (CCI [redacted]). For each pairwise comparison, only the data from the two, corresponding treatments will be included in the model. The presence of a statistically significant sequence effect will be noted, and its implications will be discussed. Least squares estimate of treatment effects will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its 90% CI will be exponentiated to obtain the ratio of the geometric least square means between the test and reference and its CI. Bioequivalence will be determined if the 90% CI for the treatment geometric least square mean ratio lies completely within the range 0.80 to 1.25.

$t_{max}$ will be analyzed nonparametrically using Wilcoxon signed-rank test ([redacted] CCI [redacted]). Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on the PK population.

Individual plasma concentrations of paracetamol will be listed (CCI [redacted]) for the safety population and summarized descriptively by treatment at each time point for the PK population (number of observations [n], arithmetic mean, SD, CV%, median, minimum, and maximum) (CCI [redacted]). Samples that are outside the protocol-specified collection window (+/-2 minutes during first 6 hours after drug administration, +/-15 minutes for all remaining sampling intervals) will not be included in the descriptive statistics. Mean plasma concentration versus nominal time profiles by treatment will be graphed for the PK population (CCI [redacted]). Individual plasma concentration versus actual time profiles by treatment will be graphed for the safety population (CCI [redacted]).

All concentration-time profiles (except $t_{max}$) will be shown on both linear and semi-logarithmic scales.

All PK parameters will be summarized for each treatment by descriptive statistics. For $t_{max}$: n, median, minimum, and maximum. For $AUC_{0\text{-}tlast}$ and $C_{max}$: n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum) for the PK population (CCI ). Comparative plots of individual paracetamol plasma $C_{max}$ and $AUC_{0\text{-}tlast}$ values versus treatment will be provided (CCI ). A listing containing individual PK parameter values will be provided (CCI ).

Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters, with the exception of $t_{max}$, which will be presented to 2 decimal places. The level of precision for each concentration and PK parameter statistic will be presented as follows:

- Minimum/maximum in same precision as bioanalytical data or parameter output,
- Geometric mean/arithmetic mean/median in 1 more level of precision than minimum/maximum,
- SD in 1 more level of precision than geometric mean/arithmetic mean/median,
- n will be presented as an integer, and
- Geometric CV%/CV% will be presented to the nearest tenth.

### 4.4.2 Handling of Missing Values/Censoring/Discontinuations

Subjects who deviate from the protocol, as well as individual PK samples with protocol deviations impacting PK, will be identified and excluded from the PK analyses as agreed by the biostatistician, pharmacokineticist, and medical director or designee. For the primary analysis of PK parameters, subjects with baseline concentrations greater than 5% $C_{max}$ will be excluded from the PK population.

For concentration listings:

- Below lower limit of quantitation (BLOQ) values will be listed as "Not detectable" (ND)

For the computation of descriptive statistics and mean concentration-time plots::

- BLOQ values will be treated as zero.

For PK parameter calculations and individual concentration-time plots:

- BLOQ values preceding quantifiable samples in the initial portion of the profile will be assigned a value of zero,

- BLOQ values that occur between quantifiable data points, especially prior to $C_{max}$, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the BLOQ is warranted,
- Following $C_{max}$, BLOQ values embedded between 2 quantifiable data points will be treated as missing,
- BLOQ values at the end of the collection interval (after the last quantifiable concentration) will be set to missing. If consecutive BLOQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be excluded from the PK parameter calculation by setting them to missing, unless otherwise warranted by the concentration-time profile.

Missing concentration or parameter values will not be imputed.

## 4.5 Analysis of Secondary Objectives

### 4.5.1 Pharmacokinetics (Secondary)

#### 4.5.1.1 Secondary Pharmacokinetic Endpoint Definition

The secondary statistical analyses will be done using the PK population.

#### 4.5.1.2 Calculation of Secondary Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma paracetamol concentration-time data using Phoenix® WinNonlin® Version 8.3. Actual sample times will be used in the calculations of PK parameters. The calculation of the actual time for paracetamol will be in respect to the start of dose administration time of oral suspension on Day 1 (Period 1) or Day 4 (Period 2). All secondary PK parameters included in the protocol are listed in Table 4-2 below and are defined as appropriate for study design.

Table 4-2: Noncompartmental Secondary PK Parameters to be Calculated

| Parameter | Label to be Used in the Text, Tables, and Figures | Definition | Method of Determination |
|---|---|---|---|
| $AUC_{0\text{-inf}}$ | AUC(0-inf) | Area under the plasma concentration versus time curve calculated from time zero to infinity | $AUC_{0\text{-inf}} = AUC_{0\text{-tlast}} + (C_{last}/\lambda_z)$ where $C_{last}$ is the last measurable concentration and $\lambda_z$ is the |

| | | | |
|---|---|---|---|
| | | | terminal elimination rate constant |
| $\%AUC_{ex}$ | %AUCex | Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation | $\%AUC_{ex} = (1 - [AUC_{0\text{-}tlast}/AUC_{0\text{-}inf}])*100$ |
| $\lambda_z$ | λz | The terminal elimination rate constant | Computed as the slope of the regression line of ln(concentration) vs time. The regression should generally involve at least 3 consecutive measurable concentrations (including the last quantifiable concentration) that decrease monotonically over time. |
| $t_{1/2}$ | t1/2 | Apparent elimination half-life | $t_{1/2} = \ln(2)/\lambda_z$ |

The $\lambda_z$ will be determined using linear regression composed of at least 3 data points. The $\lambda_z$ will not be assigned if 1) the terminal elimination phase is not apparent or 2) if $t_{max}$ is 1 of the 3 last data points. In cases where the $\lambda_z$ is not assigned, the values of $\lambda_z$, $AUC_{0\text{-}inf}$, and $\%AUC_{ex}$ are not calculable and will not be reported. The $\lambda_z$ will be considered unreliable 1) if the adjusted regression coefficient value is less than 0.80 or 2) if $\%AUC_{ex}$ is greater than 20%. In cases where the $\lambda_z$ is considered unreliable, the values of $\lambda_z$, $AUC_{0\text{-}inf}$, $\%AUC_{ex}$, and $t_{1/2}$ will be included in the listing only and excluded from the summary statistics

Additional PK parameters may be calculated or statistical analyses performed, as appropriate.

#### 4.5.1.3 Statistical Hypothesis, Model, and Method of Analysis

$AUC_{0\text{-}inf}$ will be analyzed and presented using the same ANOVA model method as for $AUC_{0\text{-}tlast}$ and $C_{max}$ ([redacted]) but will not be a part of BE determination.

All secondary PK parameters will be summarized for each treatment by descriptive statistics (n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum) for the PK population. A listing containing individual PK parameter values will be provided.

Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters. The level of precision for each PK parameter statistic will be presented as follows:

- Minimum/maximum in same precision as bioanalytical data or parameter output,
- Geometric mean/arithmetic mean/median in 1 more level of precision than minimum/maximum,
- SD in 1 more level of precision than geometric mean/arithmetic mean/median,
- n will be presented as an integer, and
- Geometric CV%/CV% will be presented to the nearest tenth.

## 4.6 Analysis of Safety

For the reporting of descriptive statistics of the safety variables (e.g. vital signs), the mean, median, standard deviation, and confidence intervals will be presented to one digit more precision than the source data. The minimum and maximum will be presented to the same precision as the source data.

### 4.6.1 Adverse Events and Serious Adverse Events

Treatment Emergent adverse events (TEAEs) are AEs that are emergent or that worsen after the first study product (test of reference) administration. All TEAEs will be summarized by primary system organ class and preferred term.

Treatment emergent adverse events will be summarized with an overview (CCI [redacted]) and then by the number and percentage of subjects having any TEAE, a TEAE in each System Organ Class, and each individual TEAE (preferred term) (CCI [redacted]). Treatment-emergent AEs suspected of a relationship to study medication will be presented in a similar manner (CCI [redacted]). All TEAEs will also be tabulated by severity (CCI [redacted]) and by relatedness and severity (CCI [redacted]).

Additionally, all TEAEs will be listed CCI [redacted]

Each AE will be attributed to the treatment taken most recently before the onset of the AE.

Adverse events due to COVID-19 will be listed and tabulated separately (CCI [redacted] and CCI [redacted]).

Adverse events with fatal outcome will be listed by treatment. (CCI [redacted]). Non-fatal serious adverse events and adverse events causing study treatment discontinuation will be listed (CCI [redacted]).

### 4.6.2 Laboratory Tests

Listing of all laboratory test results (biochemistry, hematology, coagulation, urinalysis) will be provided in PPD –PPD . with abnormal values flagged for the safety population. Results from COVID-19 test will be provided in PPD and PPD .

### 4.6.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiration and body temperature) will be summarized for the safety population with descriptive statistics (mean, SD, median, minimum and maximum) for the observed and change from baseline values by time point CCI ). Vital signs at each assessment, including body weight, will also be listed (CCI ).

### 4.6.4 Findings on Physical Examination

Findings from physical examination will be listed (CCI ). Any abnormal findings judged to be clinically significant which occurred after signing the informed consent form will be recorded as an AE. Any physical examination findings documented as AEs will be included in the summary of AEs.

### 4.6.5 Other Safety Variables

Data for ECG (CCI ) will be listed only.

## 5 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 3 Version 4.0 (Dated: 05/AUG/2021).

## Attachment 1: List of Data Displays

## Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

| Signer Full Name | Meaning of Signature | Date and Time |
|---|---|---|
| PPD | Document Approval (I certify that I have the education, training and experience to perform this task) | PPD |
| PPD | Document Approval (I certify that I have the education, training and experience to perform this task) | PPD |
| PPD | Document Approval (I certify that I have the education, training and experience to perform this task) | PPD |
| PPD | Document Approval (I certify that I have the education, training and experience to perform this task) | PPD |
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