NCT #: NCT05395104

# Statistical Analysis Plan

A Phase 1, open-label, 1-sequence crossover, drug-drug interaction study to assess the effect of repeated doses of cefiderocol on the pharmacokinetics of midazolam in healthy adult participants

Protocol Number: 2136R2118

Protocol Version: Version 2.0 (Amendment 1) 08-MAR-2022

SAP Version *2.0*

SAP Issue Date: *29-SEP-2022*

SAP Authors: [redacted]

Previous SAP Versions

1.0

## SAP Amendments Before Database Lock

| Version | Issue Date | Section | Revision / Addition | Rationale |
|---|---|---|---|---|
| 1.0 | *29-JUL-2022* | | Original Document | |
| 2.0 | *29-SEP-2022* | 6.22 | Replacing the word "drug" with the text "intervention (cefiderocol and midazolam)" | To improve clarity |
| | | 6.23 | Replacing the word "midazolam" with "cefiderocol" | To improve clarity |
| | | 6.7 | Replacing the word "drug" with the word "intervention" | To improve clarity |
| | | 6.91 | 1. Replacing the word "drug" with the word "intervention"<br>2. Addition of cefiderocol and/or midazolam to several descriptions of treatment-related TEAEs to improve clarity | To improve clarity |
| 2.0 | *29-SEP-2022* | TFL shells | Various changes made | To reflect changes made to the SAP, to improve clarity in presentation, and to make some minor text changes |

## Table of Contents

# 1 INTRODUCTION

This document details the planned statistical analyses for the Shionogi Inc., protocol "2136R2118" study titled "A Phase 1, open-label, 1-sequence crossover, drug-drug interaction study to assess the effect of repeated doses of cefiderocol on the pharmacokinetics of midazolam in healthy adult participants."

The proposed analyses are based on the contents of Version 2.0 (Amendment 1) of the protocol (dated 08-MAR-2022).

This will be a Phase 1, open-label, 1-sequence crossover study in healthy adult participants. The study will consist of a Screening Period (Days −28 to −3), including a Screening Visit; a Treatment Period (with confinement in the clinical research unit [CRU] from Days −2 to 16, single oral administration of midazolam 5 mg in the morning on Days −1 and 15, and intravenous infusion of cefiderocol 2 g every 8 hours [q8h] from Day 1 through Day 15 or 16 (depending on the start time of the first of the 3 administrations of cefiderocol, the final administration may occur in the early hours of Day 16), and discharge from the CRU on Day 16); and a Follow-up Period, including a Follow-up (Day 23 ± 2) or Early Termination Visit.

A total of 2 doses of midazolam and 45 doses of cefiderocol will be administered to each participant during the study.

Midazolam will be administered orally alone in the fasted state in the morning on Day −1. The intravenous infusion of cefiderocol q8h will be started in the morning on Day 1 and continue for 15 days. Midazolam and cefiderocol will be co-administered in the fasted state in the morning on Day 15 and then 2 additional doses of cefiderocol will be administered 8 and 16 hours after the coadministration of midazolam and cefiderocol.

# 2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the effect of repeated doses of cefiderocol on the pharmacokinetics (PK) of midazolam, a CYP3A substrate, in healthy adult participants.

Secondary Objectives:

- To evaluate the PK of cefiderocol after coadministration with midazolam

- To evaluate the safety and tolerability of cefiderocol after coadministration with midazolam.

# 3 ENDPOINTS

## 3.1 Primary Endpoint

- Midazolam: $C_{max}$, $T_{max}$, AUC, $t_{1/2,z}$, $\lambda_z$, CL/F, $V_z$/F, and MRT

## 3.2 Secondary Endpoints

- Cefiderocol: $C_{max}$, $T_{max}$, AUC, and CL
- Physical examination findings, vital sign measurements, 12-lead electrocardiogram (ECG) results, clinical laboratory test values, and treatment-emergent adverse events (TEAEs)

# 4 SAMPLE SIZE

It is planned that 14 participants will be enrolled to receive study intervention (cefiderocol and midazolam). No formal calculations were performed to determine sample size for this study.

# 5 RANDOMIZATION

This study is not randomized and will be open-label in nature. All participants will be administered each treatment according to the fixed-sequence scheme.

# 6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

## 6.1 Analysis Populations

Participants excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

### 6.1.1 Enrolled Analysis Population

Enrolled means a participant has agreed to participate in the clinical study following completion of the Informed Consent Form (ICF), the participant has completed all screening assessments, and the participant has met all eligibility requirements.

A screened participant is one who has completed the ICF and all screening assessments (the participant may subsequently withdraw consent and/or may not meet all eligibility criteria).

### 6.1.2 Safety Analysis Population

All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.

### 6.1.3 Pharmacokinetics Analysis Population

The PK concentration population will include all study participants who receive at least 1 dose of cefiderocol or midazolam and have at least 1 evaluable concentration of cefiderocol or midazolam. This population will be used for the concentration listing.

The PK parameter population will include all study participants with at least 1 PK parameter estimated appropriately. This population will be used for PK parameter listing and summary. This population will also be used for plotting of the concentration-time data, the concentration summary and statistical analysis.

## 6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

### 6.2.1 Race

Where more than 1 race category has been selected for a participant, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

### 6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study intervention (cefiderocol and midazolam).

### 6.2.3 Discontinuation Assessments

Discontinuation assessments will be tabulated with End of Study (EOS).

### 6.2.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of cefiderocol.

- date of event – date of first dose of a study drug + 1, for events on or after first dose
- date of event – date of first dose of a study drug, for events before first dose

### 6.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an adverse event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

If AE start/end time is missing the onset/resolution hour will be calculated as: ([date of AE start/end - date of dose +1]*24).

All dates presented in the individual participant listings will be as recorded on the Electronic Case Report Form (eCRF).

### 6.2.6 Exposure to Study Drug

All dosing information for each participant will be listed. Exposure to cefiderocol will be summarized.

Exposure to cefiderocol will be calculated as the stop date of last dosing minus the start date of first dosing + 1.

### 6.2.7 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

### 6.2.8 Unscheduled Visits

Only scheduled post-baseline assessments will be tabulated. Post-baseline repeat/unscheduled assessments will not be summarized, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

### 6.2.9 Pharmacokinetic Analysis

#### *6.2.9.1 Plasma Concentrations*

Blood samples will be collected for PK analysis at:

Midazolam:

- Day -1: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 16 hours after midazolam administration
- Day 1: 24 hours after midazolam administration
- Day 15: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 16 hours after the coadministration
- Day 16: 24 hours after the coadministration

Cefiderocol:

- Days 3, 6, 9, and 12: predose (0 hours) cefiderocol in the morning
- Day 15: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 16 hours after the coadministration
- Day 16: 24 hours after the coadministration

Plasma concentrations of midazolam and cefiderocol will be listed and summarized by treatment (midazolam alone, midazolam + cefiderocol, cefiderocol alone) and nominal sampling time with the number of nonmissing observations (N), arithmetic mean (mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/mean × 100), geometric mean and coefficient of variation for geometric mean (geometric CV%), and median, minimum, and maximum values at each sampling time. The geometric CV% will be calculated according to a

formula geometric CV% = [exp ($sd^2$)-1]$^{1/2}$ × 100, where sd is the standard deviation for natural log (ln)-transformed data. Predose concentrations of cefiderocol will also be summarized by study day (Days 3, 6, 9, and 12).

Mean and individual concentration-time profiles will be created using linear and semi-logarithmic scales. Mean concentration-time profiles will be created using nominal time and individual concentration-time profiles will be created using actual time.

The following concentration-time profiles will be created:

1.) Mean (SD) Midazolam Concentration-Time Profile (Midazolam Alone [Day -1] and Midazolam + Cefiderocol [Day 15] plotted together)
2.) Mean (SD) Predose Cefiderocol Concentration-Time Profiles on Days 3 through 12
3.) Mean (SD) Cefiderocol Concentration-Time Profile on Day 15
4.) All Subject Midazolam Concentration Time-Profiles (Spaghetti plots; all subjects plotted together per treatment [Midazolam Alone, Midazolam + Cefiderocol])
5.) All Subject Predose Cefiderocol Concentration-Time Profiles (Spaghetti plots; all subjects plotted together across Days 3, 6, 9, and 12)
6.) All Subject Cefiderocol Concentration-Time Profiles (Spaghetti plots; all subjects plotted together on Day 15)
7.) Individual Subject Midazolam Concentration Time-Profiles (Midazolam Alone [Day -1] and Midazolam + Cefiderocol [Day 15] plotted together for each subject).

Plasma concentrations that are below the lower limit of quantitation (BLQ) will be treated as zero (0) for calculations of mean, SD, CV%, median, minimum, and maximum values and treated as missing for calculation of geometric mean and geometric CV% mean values. Plasma concentrations at 24 hours after the administration on Days 1 and 16 will be included for the plots on Days -1 and 15, respectively.

#### *6.2.9.2 Pharmacokietic Parameters*

Concentration-time data for midazolam and cefiderocol will be analyzed using noncompartmental methods in Phoenix WinNonlin® (Version 8.1 or higher, Certara, L.P.)[2] in conjunction with the internet-accessible implementation of the Pharsight® Knowledgebase Server™ (PKSO, or comparable product release, Version 4.0.4, Certara, L.P.)[3]. PKSO provides

protected and structured storage, audit trails, and version control for study data, analyses, and related files, supporting 21 CFR Part 11 compliance.

In the PK analysis, BLQ concentrations will be treated as zero from time-zero up to the time at which the first quantifiable concentration is observed; embedded and/or terminal BLQ concentrations will be treated as missing.

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the PK scientist. Any such exclusion will be clearly represented in the study report along with justification for exclusion.

The estimated PK parameters for midazolam will be computed for each subject using the actual sample collection times recorded during the study. Plasma concentrations at 24 hours after the administration on Days 1 and 16 will be included for the parameter estimation on Days -1 and 15, respectively.

| | |
|---|---|
| $C_{max}$ (ng/mL) | Maximum plasma concentration on Days -1 and 15 |
| $T_{max}$ (h) | Time of the maximum plasma concentration on Days -1 and 15 |
| $AUC_{0\text{-last}}$ (ng*h/mL) | Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing on Days -1 and 15<br>(Linear Up/Log Down Trapezoidal Method) |
| $AUC_{0\text{-inf}}$ (ng*h/mL) | Area under the concentration-time curve extrapolated from time zero to infinity, calculated as $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + [C_{last}/\lambda_z]$, where $C_{last}$ is the last measured concentration and $\lambda_z$ is the plasma terminal elimination rate constant on Days -1 and 15 |
| $AUC_{extr}$ (%) | The percentage of $AUC_{0\text{-inf}}$ based on extrapolation, calculated as:<br>$AUC_{extr}$ (%) = 100 × ($AUC_{0\text{-inf}}$ − $AUC_{0\text{-last}}$)/$AUC_{0\text{-inf}}$<br>(See additional criteria below) |
| $\lambda_z$ (1/h) | Terminal elimination rate constant, where $\lambda_z$ is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase on Days -1 and 15<br>(See additional criteria below) |
| $t_{1/2,z}$ (h) | Terminal elimination half-life, where $t_{1/2,z} = (\ln 2)/\lambda_z$ on Days -1 and 15 |

| | |
|---|---|
| CL/F (L/h) | Apparent total clearance, where CL/F = Dose/$AUC_{0\text{-}inf}$ on Days -1 and 15 |
| $V_z$/F (L) | Apparent volume of distribution in the terminal elimination phase, where $V_z$/F = Dose/$AUC_{0\text{-}inf}$/$\lambda_z$ on Days -1 and 15 |
| MRT (h) | Mean residence time, where MRT = $AUMC_{0\text{-}inf}$/$AUC_{0\text{-}inf}$ and $AUMC_{0\text{-}inf}$ is the area under the first moment curve extrapolated to infinity on Days -1 and 15 |

The estimated PK parameters for cefiderocol will be computed for each subject using the actual sample collection times recorded during the study.

| | |
|---|---|
| $C_{max}$ (µg/mL) | Maximum plasma concentration on Day 15 |
| $T_{max}$ (h) | Time of the maximum plasma concentration on Day 15 |
| $AUC_{0\text{-}\tau}$ (µg*h/mL) | Area under the plasma concentration-time curve over the dosing interval τ (8 hours) on Day 15, calculated by Linear Up/Log Down Trapezoidal Method<br>(see additional criteria below) |
| CL (L/h) | Total clearance, where CL = Dose/$AUC_{0\text{-}\tau}$ on Day 15 |

Lambda-z ($\lambda_z$) and $AUC_{0\text{-}inf}$ Reporting Criteria

The following criteria will be used to report $\lambda_z$:

- At least 3 quantifiable concentrations will be used in the regression.
- $C_{max}$ or data prior to $C_{max}$ will not be included in the regression.
- The adjusted regression coefficient ($R^2$ adj) should be ≥ 0.800.

If these acceptance criteria are not met, then that study participant's $\lambda_z$, $AUC_{0\text{-}inf}$, $t_{1/2,z}$, MRT, CL/F, and $V_z$/F derived from $\lambda_z$ will be flagged in the data listing and excluded from the descriptive and statistical analysis. If $\lambda_z$ cannot be determined, then $AUC_{0\text{-}inf}$, $t_{1/2,z}$, MRT, CL/F, and $V_z$/F will not be estimated.

If lambda-z acceptance criteria are met and $AUC_{0\text{-}inf}$ is estimable, the following criteria are used to report $AUC_{0\text{-}inf}$:

- The percentage of $AUC_{0\text{-}inf}$ based on extrapolation should be ≤20.0%.

If the $AUC_{extr}$ is greater than 20%, then $AUC_{0\text{-}inf}$, MRT, CL/F, and $V_z/F$ derived from $AUC_{0\text{-}inf}$ will be flagged in the data listing and excluded from the descriptive statistics and statistical analysis.

$AUC_{0\text{-}\tau}$ Calculations

The $AUC_{0\text{-}\tau}$ at steady state will be calculated with observed plasma concentrations from time 0 to $\tau$ (actual time) on Day 15 without extrapolation or interpolation. The actual time for the predose (0 hours) on Day 15 will be replaced with 0. If observed plasma concentration at $\tau$ on Day 15 is BLQ, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-}last}$) will be used as $AUC_{0\text{-}\tau}$.

The estimated PK parameters except for $T_{max}$ will be summarized by treatment with N, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum values. The $T_{max}$ will be summarized by analyte and treatment with N, mean, SD, CV%, median, minimum, and maximum values. If the n for estimable PK parameters is < 3, the data will not be summarized for that parameter.

### 6.2.10 Conventions

All data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.4 or higher[1].

Pharmacokinetics data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.1 or higher)[2] or SAS (Version 9.4 or higher)[1]. PK concentration data will be summarized by treatment at each nominal sample time. PK parameter data will be summarized by treatment.

For summaries presented by treatment group and overall, treatment group labels will be displayed as follows:

| Midazolam alone (5 mg) | Cefiderocol alone (2 g) | Midazolam + Cefiderocol (5 mg + 2 g) | Overall |
|---|---|---|---|

For summaries presented by overall, the label will be displayed as follows:

Overall

Listings will be sorted in the following order participant, parameter, and visit unless otherwise stated.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

### 6.2.11 Decimal Places

Means, medians and percentiles will be displayed to 1 additional decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with 1 decimal place.

For PK data, individual concentrations will be reported to 3 significant figures. PK parameters will be reported with precision specified as the following:

3 significant figures for $C_{max}$, $t_{1/2,z}$, CL/F, $V_z$/F, MRT, and CL;

2 decimal places for $T_{max}$;

4 significant figures for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $AUC_{0\text{-}\tau}$;

1 decimal place for $AUC_{extr}$;

4 decimal places for $\lambda_z$.

For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, and geometric mean will be reported to the same precision as for individual data; CV% and geometric CV% will be reported to 1 decimal place. P-values will be reported to 4 decimal places. Percent ratios of the geometric least squares means and associated 90% confidence intervals (CIs) will be reported to 4 decimal places.

## 6.3 Participant Disposition

Participant disposition will be summarized as follows:

- The number of screen failures by reasons will be summarized for all screened participants.
- The number of participants who are in each analysis population will be summarized overall for the enrolled analysis population.

- The number of discontinuation and the reasons for discontinuation will be tabulated overall for the enrolled analysis population.

## 6.4 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

## 6.5 Demographics and Baseline

The participant demographics and baseline characteristics (age, sex, fertility status, ethnicity, race, height, weight and BMI) will be summarized for the Safety Analysis Population and the PK parameter population in a descriptive manner, but no formal statistical testing will be performed.

## 6.6 Medical History

Medical history will be summarized and listed for the Safety Analysis Population. Conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA 25.0) primary system organ class and preferred term.

## 6.7 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Analysis Population. Prior medications are defined as all medications starting and stopping before the date of first dose of study intervention. Concomitant medications are defined as medications taken on or after the date of first dose of study intervention. Any medication starting before first dose of the study intervention and continuing after first dose of the study intervention will be considered as both prior and concomitant medication.

## 6.8 Statistical Analysis of Pharmacokinetic Data

When data are available, the effect of cefiderocol on the PK of midazolam will be assessed. An analysis of variance (ANOVA) will be performed using SAS Proc Mixed for ln-transformed $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of midazolam. In case of unbalanced data, the Kenward-Roger method will be used to compute the denominator degrees of freedom for the tests of a fixed effect in the analysis. The point estimates and their 90% CIs will be generated for the differences between midazolam co-administered with cefiderocol and midazolam alone for ln-transformed

$C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. The point estimates and their 90% CIs will be back-transformed to obtain the corresponding geometric least squares mean ratios and 90% CIs as the following ratio:

(midazolam co-administered with cefiderocol [Day 15]) / (midazolam alone [Day 1])

The following linear mixed effects model will be used:

ln (Parameter) = Treatment + Subject + Random error

Where Treatment is a fixed effect of treatment, Subject is a random effect of study participant, and Random error is a random residual error.

SAS code for the analysis will be of the form:

```
proc mixed data = pk_data;
  class subjid day ;
  model ln_parameter = day/ ddfm = kr;
  random subjid;
  lsmeans day / pdiff cl alpha=0.1;
  estimate "Day 15 vs Day 1" day -1  1;
run;
```

Where subjid is participant number and day is confinement period.

The drug interaction will be assessed by whether the 90% CIs for $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of midazolam are completely contained within the range of 0.8000 to 1.2500.

The comparison of $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ together with $T_{max}$, $\lambda_z$, $t_{1/2,z}$, CL/F, $V_z$/F, and MRT between midazolam alone and midazolam co-administered with cefiderocol will be graphically represented via pair plots between treatments of individual and mean (SD) data for each parameter.

The effect of cefiderocol on the PK of midazolam will be concluded based on the point estimates and 90% CIs of the ANOVA model and visual inspection of the corresponding plots.

## 6.9 Safety Analyses

The safety analyses will be presented for the Safety Analysis Population.

### 6.9.1 Adverse Events

A TEAE is defined as:

- Any AE that emerges on or after initiation of study intervention (having been absent pre-treatment).

A treatment-related TEAE is defined as an TEAE as being related to the study intervention.

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented by treatment group, midazolam alone (Day -1 to pre-dose on Day 1), cefiderocol alone [Days 1 (post-dose) through Day 15 (pre-dose of midazolam)], and midazolam + cefiderocol [Day 15 post-dose of midazolam through End of Follow-up] and overall:

- Overall incidence and the number of TEAEs, each of cefiderocol and midazolam treatment-related TEAE, serious adverse events (SAEs), serious treatment-related TEAE, TEAEs leading to withdrawal with each of cefiderocol-related and midazolam-related, TEAE leading to death
- The number (percentage) of study participants who had TEAE and the associated number of events by system organ class and preferred term
- The number (percentage) of study participants who had each of cefiderocol and midazolam treatment-related TEAEs and the associated number of events by system organ class and preferred term
- The number (percentage) of study participants who had TEAE by system organ class, preferred term and maximum severity, incidence
- The number (percentage) of study participants who had each of cefiderocol and midazolam treatment related TEAE by system organ class, preferred term and maximum severity, incidence
- The number (percentage) of study participants who had TEAE by system organ class, preferred term and relationship, incidence
- Listing of TEAEs leading to withdrawal with each of cefiderocol-related and midazolam-related by system organ class and preferred term, incidence
- Listing of SAEs (presented in the Table section of the appendices)
- Listing of deaths (presented in the Table section of the appendices)

All AEs will be listed.

### 6.9.2 Laboratory Data

All clinical laboratory data will be listed. For clinical laboratory tests (hematology, blood chemistry, urinalysis, coagulation, lipid profile tests, and liver chemistry), summary statistics for each parameter and for the change from baseline (latest observation prior to first administration) to each time point will be calculated.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

### 6.9.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiratory rate (breaths/min)
- Temperature (degrees Celsius)

All vital sign data will be listed. A listing of clinically significant vital signs will be provided.

### 6.9.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each visit:

- Heart Rate (bpm)
- PR Interval (ms)
- QRS Duration (ms)
- QT Interval (ms)
- QTc Interval (ms)

Shift tables in relation to the overall interpretation i.e. Normal, Abnormal Not Clinically Significant (NCS), and Abnormal Clinically Significant (CS), from baseline to each follow-up visit will be presented.

All ECG data, including details of any abnormalities, will be listed.

### 6.9.5 Physical Examination

The body systems within the physical examination data will be summarized overall (Normal, Abnormal NCS, Abnormal CS) by visit. Changes from baseline will also be tabulated. All data, including details of clinically significant findings will be listed.

## 7 INTERIM ANALYSIS

No interim analyses are planned.

## 8 DATA SAFETY MONITORING BOARD ANALYSIS

No Data Safety Monitoring Board (DSMB) analyses are planned.

## 9 CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes were made to planned protocol analysis.

# 10 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.)
3. Pharsight® Knowledgebase ServerTM (PKSO; Version 4.0.4 or comparable product release, Certara, L.P.)