Statistical Analysis Plan for Interventional Studies (Early Phase)

A Phase 1, Open-Label, Randomized, 4-Period, 4-Way Crossover, Comparative Bioavailability Study of Zavegepant (BHV-3500) Oral Formulations Under Fasting Conditions

Sponsor Study Number: BHV3500-113
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CONFIDENTIAL

SIGNATURES

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
ANOVA	analysis of variance
ALP	alkaline phosphatase
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{extrap\%}$	percentage of AUC_{inf} due to extrapolation from the time of the last observed concentration to infinity
AUC_{last}	area under the concentration-time curve from time zero until the last observed concentration
BLQ	below the lower limit of quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximal observed concentration
CPK	creatine phosphokinase
CTCAE	Common Technical Criteria for Adverse Events
CV	coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDM	dodecylmaltoside
ECG	electrocardiogram
eDISH	evaluation of drug induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GGT	gamma-glutamyl transferase
IR	immediate release
INR	international normalized ratio
K_{el}	terminal elimination rate constant
$K_{el\ Lower}$	the timepoint where ln-linear K_{el} calculation begins
$K_{el\ Upper}$	the actual sampling time of the last measurable concentration used to estimate the K_{el}
LFT	liver function test
LLN	lower limit of normal
Ln	natural logarithm
max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum

N/A	not applicable
PK	pharmacokinetic(s)
PT	preferred term or prothrombin time
RBC	red blood cells
Rsq	R-squared
SAP	statistical analysis plan
SD	standard deviation
SGC	soft gel capsule
SOC	system organ class
S-STS	Sheehan suicidality tracking scale
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
T_{max}	time when the maximal concentration is observed
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBC	white blood cells
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document outlines the pre-specified plan for the summarization and analysis of clinical data collected in Sponsor Study BHV3500-113 and is intended to give a detailed description of the summaries and the analyses that will be generated for the present study by Syneos Health or a designee. Analyses specified in this plan are based on the Biohaven Pharmaceuticals Holding Company Limited Study Protocol No. BHV3500-113, version 2.0 (Amendment 01) dated August 16, 2022 (Syneos Health Project No. 222025). Safety, tolerability, and pharmacokinetic (PK) analyses will be described.

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented. No revision to this document is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document. If additional analyses are required to supplement the planned analyses described in this document, the changes and justification for the changes will be outlined in the associated clinical study report. No change will be made without prior approval of the Sponsor.

When applicable, all methodologies and related processes will be conducted according to Syneos Health's standard operating procedures, as appropriate. Shells for all statistical tables, listings, and figures (TLFs) referred to in this document will be displayed in a separate document.

2 STUDY OBJECTIVES

The objective of this study is to compare the rate and extent of absorption of zavegepant 100 mg oral non-enteric coated soft gel capsule (SGC) (Test 1), zavegepant 100 mg immediate release (IR) oral tablet + dodecylmaltoside (DDM) dosage form (Test 2), zavegepant 1 x 200 mg IR oral tablet + DDM dosage form or zavegepant 2 x 100 mg IR tablets + DDM dosage form (Test 3), and zavegepant (BHV-3500) 4 x 25 mg enteric coated oral SGC (Reference), under fasting conditions.

3 STUDY DESIGN

3.1 General Design

This is a Phase 1, single center, open-label, single dose, 4-period, crossover study designed to compare the PK of zavegepant from the Test and Reference products. The study may be dosed in more than 1 Group.

The 4 sequences will be: ACBD, CDAB, BADC, and DBCA. In each period, participants will receive one of the following: Treatment A, B, C, or D on Day 1, followed by 24 hours of PK and safety assessments. On Day 2 participants will be discharged from the unit and instructed to return after at least a 7 day washout time has passed for subsequent periods of treatment.

3.2 Study Procedures

The overall schedule of procedures and assessments is provided in the protocol.

3.3 Treatment Administration

Randomization schedules will be generated through SAS® for Windows software, prior to study execution. Participants enrolled in this study will be assigned to ACBD, CDAB, BADC, or DBCA sequences using a blocked randomization.

On Day 1 of each period, participants will receive a single oral dose of one of the following oral treatments, under fasting conditions, according to the assigned sequence on the randomization schedule.

Treatment	Description
A (Test 1)	1 x 100 mg zavegepant non-enteric coated SGC (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.
B (Test 2)	1 x 100 mg zavegepant IR tablet + DDM dosage form (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.
C (Test 3)	1 x 200 mg zavegepant IR tablet (total dose of 200 mg) + DDM dosage form. The dose for Treatment C may instead be administered as 2 x 100 mg IR tablets + DDM dosage form for a total zavegepant dose of 200 mg (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.
D (Reference)	4 x 25 mg zavegepant enteric coated SGC (total dose of 100 mg) (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.

3.4 Sample Size

Approximately fifty- two (52) healthy, non-smoking, male and female participants, aged 18 to 55 years, will be enrolled in this study.

CCI [redacted] Thus, assuming a CV of 40%, and under the scenario of test versus reference ratio of geometric means of 1.0, the width of the 90% confidence interval (CI) for the ratio of geometric means is expected to approximately be 0.25 with fifty- two (52) participants. The expected width of the 90% CI for the ratio of geometric means will slightly decrease/increase from 0.25 as the ratio of geometrics means decrease/increase from 1.0.

3.5 Participant Withdrawal and Replacement

Over the course of the study, the Sponsor and the Investigator or designee may withdraw any participant from the study for one of the reasons described below; participant withdrawal will be done in accordance with the clinical site's SOP:

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation;
- Positive pregnancy test, drug screen, cotinine test, or alcohol breath test;
- Vomiting within 4 hours post-dose;
- Positive COVID-19 test.

Participants excluded from dosing in one period as per criteria listed above, may be invited to participate in subsequent periods of the study if deemed appropriate by the Investigator and appropriate from a statistical standpoint (i.e., would permit adequate statistical comparison). However, participants with positive pregnancy test, COVID-19 test, drug screen, cotinine test, or alcohol breath test will be definitively withdrawn from the study.

Participants experiencing emesis following study drug administration may be withdrawn. An evaluation will be done on a case-by-case basis in order to decide if withdrawal is appropriate.

Participants who withdraw, or are withdrawn, prior to dosing may be replaced. Participants who withdraw, or are withdrawn, from the study after dosing will not be replaced.

4 CHANGES FROM THE PROTOCOL

There are no changes in planned analyses compared to the protocol.

5 PHARMACOKINETIC AND SAFETY PARAMETERS

For PK analyses, AUC_{last}, AUC_{inf}, and C_{max} calculated using zavegepant concentration data will be the primary endpoints. $AUC_{extrap\%}$, T_{max}, $T_{½}$, K_{el}, V_z/F and CL/F for zavegepant will be secondary endpoints; reference section 11.3.

Safety and tolerability parameters are secondary endpoints; reference section 10.

6 ANALYSIS POPULATIONS

All participants' inclusion status into each analysis population will be determined after database lock for the final analysis.

6.1 Screened Population

The screened population will include all participant who sign the informed consent form.

6.2 Randomized Population

The randomized population will include all participants who are randomized.

6.3 Safety Population

The safety population is defined as all participants who receive at least one dose of any study drug. In each period, participants will be analyzed according to treatment received.

6.4 Pharmacokinetic Population

The PK population will include all participants from the safety population who receive at least one dose of zavegepant, and for whom the PK profile can be adequately characterized. The PK population will be used for calculation of PK parameters.

6.5 Pharmacokinetic Statistical Population

The PK statistical population will include all participants from the PK population who complete at least one period of treatment for at least one PK parameter and who have not experienced any protocol deviations or other circumstances to exclude the participant from the PK statistical analysis.

A participant with pre-dose concentrations may be excluded from descriptive statistics and ANOVA if the pre-dose concentration is greater than 5% of the C_{max} value for that participant. A participant may be excluded from the descriptive statistics and ANOVA if the participant has experienced emesis within 2 times median T_{max} for a given treatment. For the period where this would apply as appropriate, data (concentrations and PK parameters) from these participants will be presented in data listings but excluded from the statistical analyses.

7 INTERIM ANALYSIS

No formal interim analysis is planned. However, a preliminary descriptive PK analysis may be performed when the final PK concentration data will be available. For this analysis, the scheduled times could be used in the calculation of the PK parameters.

8 SCHEDULE OF ANALYSIS

The final statistical analysis will be performed once all participants completed the study, the bioanalysis of all samples are complete and the database is locked.

9 STUDY POPULATION AND EXPOSURE

Each participant's inclusion or exclusion from each analysis population will be presented in a data listing. The study drug administration details, including date and time of administrations, will also be listed by participant.

9.1 Participant Disposition

The number of participants who were screened, screened failures, who were enrolled, who were randomized, who were dosed, who completed the study, and who were discontinued from the study and reasons for discontinuation, will be summarized. This summary table will also include the number of participants in each analysis population. The data (frequency and the percentage of participants) will be presented by treatment group and/or overall as appropriate, and listed by participant.

9.2 Protocol Deviations

Participant data will be examined for evidence of protocol deviations. All protocol deviations will be categorized and listed by participant.

9.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics (including weight, height, and body mass index [BMI]) will be summarized overall, and they will be listed by participant.

Descriptive statistics (mean, standard deviation [SD], minimum [min], median, and maximum [max]) will be calculated for continuous variables, using the last results obtained prior to first study drug administration. Frequency counts and percentages will be tabulated for categorical variables.

9.4 Medical History

Medical history will be presented by participant in a data listing. The Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 will be used to classify all medical history findings by system organ class (SOC) and preferred term (PT).

9.5 Prior and Concomitant Medications

Prior medications are medications started before and ongoing at the time of ICF, or started at the time of ICF and in either case stopped prior to first study drug administration. Concomitant medications are medications started before and ongoing at the time of study drug administration, or started after first study drug administration. Both prior and concomitant medications will be listed by participant. The World Health Organization Drug Dictionary (WHO DD) Version B3, Mar 2022 will be used to define the anatomical therapeutic chemical (ATC) classification code (2nd level), and preferred name for each prior and concomitant medication. When 2nd level classification code is not available, 1st level classification will be used instead.

10 SAFETY ANALYSIS

Safety and tolerability analysis will be performed for all participants in the safety population. No inferential statistical analysis of safety data is planned.

Safety and tolerability to treatments will be evaluated through the assessment of adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory parameters. Safety and tolerability data will be reported using descriptive statistics (mean, median, SD, Min, Max, and sample size).

10.1 Physical Examination Findings

Participants will undergo a complete physical examination at screening, and a brief physical examination on Day -1 of each period and at study exit. Individual results will be presented in a data listing.

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, depending upon time of observation, as appropriate. Any physical examination findings documented as AEs will be included in AE summaries.

10.2 Adverse Events

AEs, which are collected from the time of enrollment, will be coded using the latest version of MedDRA (Version 25.0).

All AE summaries will be restricted to treatment-emergent adverse events (TEAEs) only. TEAEs will be defined as AEs that occur on or after the date and time of first study drug administration. Any AE that first occurs prior to first study drug administration but worsens in severity after the first study drug administration will also be considered a TEAE. Non-TEAEs are those that occur prior to the first administration of the study medication and resolved prior to dosing or that first occur prior to the first study drug administration, but do not worsen in severity after dosing. TEAEs will be attributed to the most recent study drug taken. A TEAE with a start date and time during the washout period (ending at the time of next study drug administration) will be attributed to the study drug taken during the previous treatment period (unless there was worsening following the next drug administration).

TEAEs will be summarized by treatment for the safety population. The number and percentage of participants experiencing TEAEs and the number of TEAEs will be tabulated. Participants who experience the same AE (in terms of MedDRA PT) more than once will only be counted once for that event, however, the total number of events will also be counted per category. This also applies to sub-categories and SOCs displayed in the summaries.

In each table, TEAEs will be sorted by SOC and PT in descending order of overall frequency. The following summaries will be presented:

- Overall summary of TEAEs

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- TEAEs by SOC, PT, and maximum relationship to study drug
- Serious TEAEs by SOC and PT

All AEs will be presented in data listings. This will include a separate listing of TEAEs, Non-TEAEs and serious AEs. AEs leading to discontinuation will also be listed separately.

10.3 Laboratory Parameters

Clinical laboratory tests, including biochemistry, hematology, and urinalysis will be performed at screening and at Day -1 of each period, and at study exit.

Biochemistry will include albumin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), calcium, chloride, creatinine, creatine phosphokinase (CPK), estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) equation, gamma-glutamyl transferase (GGT), glucose, phosphorus, potassium, sodium, total, direct and indirect bilirubin, total protein, and urea (BUN). Considering that indirect bilirubin is calculated from total and direct bilirubin values, indirect bilirubin result would not be available in case of direct bilirubin below the limit of quantification. Hematology will include: haptoglobin, hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, reticulocyte, and white blood cell (WBC) count and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils). Haptoglobin and reticulocyte count will be performed only in case of decrease in hemoglobin levels below the lower limit of normal (LLN) on Day -1 of each period and at study exit. Urinalysis will include bilirubin, blood (occult), color and appearance, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination (in the event of abnormal findings).

Coagulation tests (activated partial thromboplastin time [aPTT), international normalized ratio [INR] and prothrombin time [PT]) will be performed only in case of abnormal LFTs (i.e., ALP, AST, or ALT is >3x upper limit of normal [ULN]) on Day -1 of each period and at study exit. The results will be listed if applicable.

Other laboratory assessments include serology tests, drug, cotinine, and alcohol screens, COVID-19 tests, and hormone screens (for female participants). Serology tests and follicle-stimulating hormone (FSH) levels will be measured at screening only. Drug, cotinine, and alcohol screens will be performed at screening and at Day -1 of each period. A COVID-19 test will be performed on Day -1 of each period. Pregnancy tests will be administered to females of childbearing potential at screening, Day -1 of each period, and at study exit. Results of urine drug screens, serology tests, pregnancy tests, alcohol breath tests, and urine cotinine tests will be listed.

Individual clinical laboratory results, change from baseline and reference ranges will be presented in data listings. Baseline will be defined as the last results (scheduled or unscheduled)

obtained prior to the first drug administration. Abnormal results will be flagged, as appropriate, in these listings. Clinically significant laboratory abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in the latest version of Common Technical Criteria for Adverse Events (CTCAE), if available, otherwise, according to the latest version of Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.

Additionally, a listing presenting abnormal LFTs (values greater than 3 times the upper limit of the normal [ULN] range for ALT, ALP or AST and values greater than 2 times ULN for total bilirubin) will be provided. An evaluation of drug-induced serious hepatotoxicity (eDISH) will be provided graphically. For this eDISH plot, the data will consist of the maximum values of ALT and total bilirubin that are observed at any time during or after dosing with zavegepant.

10.4 Vital Signs

Blood pressure, heart rate, respiratory rate, and oral temperature will be measured at screening, Day -1 of each period and at study exit. Blood pressure and pulse rate will be measured at pre-dose, and at 2 hours post-dose in each period.

Individual results and reference ranges will be presented in a data listing. For each vital sign measurement, observed values and changes from baseline for quantitative test results will be summarized by treatment or overall, as appropriate, for each timepoint using descriptive statistics. Baseline will be defined for each vital sign measurement as the last results (scheduled or unscheduled) obtained prior to study drug administration in each period. Unscheduled results will not be used in the summary tables except for baseline if applicable.

10.5 12-lead Electrocardiograms

Standard 12-lead ECGs will be recorded at screening, on Day -1 of each period, and at study exit.

Individual results and change from baseline will be presented in a data listing. Baseline will be defined for each ECG parameter as the last results (scheduled or unscheduled) obtained prior to first study drug administration. Abnormal results will be flagged, as applicable.

10.6 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS will be administered at screening and at study exit. Individual total scores with change from baseline will be presented in a data listing.

11 PHARMACOKINETIC ANALYSES

11.1 Below the Lower Limit of Quantification and the No Reportable Concentration

Plasma concentrations will be listed and summarized, by nominal sampling time, and treatment. Concentrations below the quantification limit (BLQ) will be set to zero for calculation of PK parameters and in summary tables. Samples with invalid concentration (due to bioanalytical issue) will be replaced by "0.00" when it occurs prior to dosing. Otherwise they will be set to missing for tabulation, graphical representation, and calculation purposes if it occurs after dosing. BLQ will be displayed in listings. For geometric mean calculations for PK parameters involving zero values, zero values will be substituted with 0.0001.

For individual plots, the BLQ values will be set to zero. For mean plots, BLQ will be set to zero.

11.2 Difference between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded using electronic data capture. For all sampling times, the actual sampling times will be calculated as the difference between the actual clock time of sample collection and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. Scheduled nominal sampling times will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs in the PK section of the report. Actual sampling times also will be used for final PK parameter derivation. If actual sampling time is missing, then nominal time will be used. A listing of the actual times for PK sampling will be provided for PK samples.

11.3 PK Parameters

Blood samples will be collected for zavegepant PK analysis at pre-dose (within 1 hour prior to dosing), and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose in each period. Bioanalysis of all associated plasma samples should be completed prior to the initiation of the PK and statistical analyses. Analysis will be performed using a fully-validated analytical method by a qualified bioanalytical laboratory.

The following PK parameters will be calculated, based on the PK population, by standard non-compartmental methods using the plasma concentrations of zavegepant.

Parameter	Definition
AUC_{last}	area under the concentration-time curve from time zero until the last observed concentration
AUC_{inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{extrap\%}$	percentage of $AUC_{0\text{-}inf}$ due to extrapolation from the time of the last observed concentration to infinity, calculated as $[1 - (AUC_{last}/AUC_{inf})] \times 100$
C_{max}	maximal observed concentration
T_{max}	time when the maximal concentration is observed
$T_{1/2}$	terminal elimination half-life
K_{el}	terminal elimination rate constant
CL/F	apparent clearance
V_z/F	apparent volume of distribution

PK of Treatment C (AUCs and C_{max}) will be normalized to a dose of 100 mg.

Additional PK parameters may be calculated.

Note: AUC parameters will be calculated using linear up log down trapezoidal method, where the linear trapezoidal rule is used any time the concentration data is increasing, and the logarithmic trapezoidal rule is used any time that the concentration data is decreasing.

Note: K_{el} will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. The best fit method, in Phoenix WinNonlin, will be used to calculate the K_{el} from at least three concentration data points, excluding C_{max}. Rsq (R-squared) adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.9. If the K_{el} cannot be measured (e.g.: there are fewer than three non-zero concentrations in the terminal elimination phase or Rsq adjusted <0.9), the PK parameters derived from K_{el} (AUC_{inf}, $AUC_{extrap\%}$, $T_{½}$, CL/F, V_z/F) will be presented in listing with a flag and excluded from descriptive statistics and statistical analyses. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), as well as the Rsq adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported.

If the $AUC_{extrap\%}$ is more than 20%, the individual result should be flagged as well as all parameters depending on AUC_{inf}. All the derived parameters (i.e., AUC_{inf}, $AUC_{extrap\%}$, $T_{½}$, CL/F, V_z/F) will be flagged accordingly, and they will be removed from the analyses and the descriptive statistics.

Some PK parameters may not be calculated for all participants, at the discretion of the Syneos pharmacokineticist with Sponsor agreement if the concentration data is not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated will be provided in the report.

11.4 Statistical Analyses

Statistical analysis described in this section will be based on the PK statistical population.

11.4.1 PK Parameters in Plasma

Individual, mean and median plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, SD, CV%, geometric mean CV%, Min, Max, and median) of the plasma concentrations versus time will be presented as well for the PK parameters.

11.4.2 Treatment Comparisons

For zavegepant, using the MIXED procedure in SAS, an ANOVA will be performed on ln-transformed (dose-normalized to 100 mg) AUC_{last}, AUC_{inf}, and C_{max}. No adjustments will be made to alpha for multiple pairwise comparisons. As the study was dosed in more than one Group, the following terms will be included in the statistical model: Group, Sequence, Sequence by Group, Period within Group, Treatment, and Treatment by Group. A random effect of Participant within Sequence by Group will also be included. In case of a non-statistically significant Treatment by Group interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. The ratio of geometric means and 90% confidence intervals (A/D), (B/D), and (C/D) based on least-squares means from the ANOVA of the ln-transformed data will be calculated for AUC_{last}, AUC_{inf}, and C_{max}. The point estimates and confidence intervals will be exponentiated using base e in order to obtain a point and interval estimate for the ratio of geometric means. Other ratio of geometric means among treatments may be explored. Untransformed T_{max} will also be analyzed using the MIXED model with the difference of least-squares means from the ANOVA calculated for (A-D), (B-D), and (C-D). Other differences of least-square means between treatments may be explored. The K_{el}, and $T_{½}$ will be summarized descriptively.

The SAS code to fit the model will follow the format below (using the Mixed Procedure). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data = basepk;
  class Group Sequence Period Treatment Participant;
  model VAR = Group Sequence Sequence*Group Period(Group) Treatment
              Treatment*Group / ddfm = kenwardroger;
  random Participant(Sequence*Group);
  lsmeans Treatment;
  estimate 'A versus D' Treatment 1 0 0 -1 / cl alpha = 0.1;
  estimate 'B versus D' Treatment 0 1 0 -1 / cl alpha = 0.1;
  estimate 'C versus D' Treatment 0 0 1 -1 / cl alpha = 0.1;
  ods output estimates = estimates tests3 = tests covparms = covparms;
run;
```

Additional PK statistical analysis may be performed.

12 PERCENTAGES AND DECIMAL PLACES

Percentages:

Percentages based on count data should be displayed as follows in TLFs:

- 0 < percentage < 0.1 as "<0.1"
- 99.9 < percentage < 100 as ">99.9"
- 100 percentage as "100"
- 0 count without a percentage in frequency tables
- Rounded to 1 decimal place otherwise.

For response rates (proportions), measures of variability such as standard error (SE) and confidence interval (CI) should be displayed rounded to 1 decimal place.

Continuous Variables Non-PK Data:

Descriptive statistics for continuous variables in tables should be displayed as follows:

- Values and changes from baseline
  - Minimum and maximum: same precision as the data collected or rounded to a specified precision if derived
  - Mean and percentiles: rounded to 1 decimal place more than the data collected or derived
  - Measure of variability (e.g., standard deviation [SD], SE, CI): rounded to 2 decimal places more than the data collected or derived
- Percent change from baseline
  - Minimum and maximum: rounded to 0 decimal places (i.e., integers)
  - Mean and percentiles: rounded to 1 decimal place
  - Measure of variability: rounded to 2 decimal places.

Individual data in listings should be displayed to the same precision as the data collected or rounded to a specified precision if derived.

Derived variables should be calculated using all precision from collected components. For example, BMI should be derived as needed using all precision from collected height and weight. However, the specified precision for reporting BMI should be 1 decimal place.

Continuous Variables PK Data:

Concentration data for parameter calculations: The concentration data as reported by the respective bioanalytical groups should be used, without rounding, for all analyses.

Concentration data listings: By default, concentration values should be presented in listings exactly as reported by the respective bioanalytical groups. However, in cases when concentration data may be supplied electronically with unrealistic precision, rounded values may be presented. A default of 3 significant figures is suggested, and the rounding used should be described in the clinical study report.

Parameter data listings: The non-compartmental parameters should not be reported to any greater precision than that of the concentration data. A default of 3 significant figures is preferred.

Concentration and parameter summary data: The following guidance for reporting precision is intended to provide specifications for programming and defaults for documents based on those presentations. It is recognized that data from external sources may follow different standards. Refer to below for additional guidance on parameter summary statistics for study report and summary documents.

Parameter values (and if applicable, concentration values) should be rounded to the same precision used in data listings prior to any statistical analysis or descriptive summaries.

Descriptive summaries:

- Means, median[a], CIs - 1 more significant figure than the data
- SD - 1 more significant figure than means
- CV% - whole numbers
- Min, Max - same significant figures as the data

[a] Exception: for T_{max}, T_{lag}, and any other parameters which are direct time observations, median will have the same significant figures as the data (mean is generally not presented for these parameters).

Statistical summaries:

- Means, differences, CIs (non-transformed data) - 1 more significant figure than the data.

13 DATA HANDLING

For the final analyses, the PK, safety, and tolerability data will be received as SAS datasets. Screening failures and ineligible volunteer's data (participant disposition) will be received from the clinical site as source data.

14 MISSING DATA

There will be no imputation for missing data, unless otherwise specified. Missing data will be presented in participant listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated will be presented as "-".

Incomplete AE start and stop dates will be imputed as follows:

- If an AE is recorded with an onset date corresponding to a dosing day, but the time is missing, then the AE will be assigned to that day treatment (e.g., an AE with an onset date on Day 1 without time will be allocated to the treatment received on Day 1, and considered treatment-emergent).

- If an AE is recorded with an onset date that does not correspond to a dosing day, but the time is missing, then the AE will be assigned to the planned treatment that covers the AE onset day and considered treatment-emergent if onset date is after the date of first dosing.

- If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to the planned treatment will be done on a case-by-case basis considering available information (i.e., AE recording date, AE end date, AE comments, participant disposition).

For PK analysis, only observed concentration data will be used in the data analysis, except for concentration values BLQ as described in section 11.1. No attempt will be made to extrapolate or interpolate estimates for missing data.

15 SOFTWARE

All tables, figures, and listings and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software in accordance with Food and Drug Administration (FDA) guidelines.

Phoenix WinNonlin, version 8.3.4 (Certara USA, Inc., Princeton, NJ) will be used for all PK analyses. This software was validated by Syneos in compliance with US 21 CFR Part 11 regulation.

16 REFERENCE LIST