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# A Pivotal, Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Crossover, Bioequivalence Study of Sapropterin Dihydrochloride 100 mg/mL Oral Suspension (Product Code: RLF-OD032) and Kuvan® (sapropterin dihydrochloride) 100 mg Powder for Oral Solution in Healthy Participants under Fed Conditions

## STATISTICAL ANALYSIS PLAN

Version 1.0 (August 06, 2025)

Protocol N$^{O}$./Sponsor Study N$^{O}$: 2024-5705

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Pharma Medica Research Inc.
6100 Belgrave Road
Mississauga, Ontario, Canada
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For

APR Applied Pharma Research s.a.
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PHARMA MEDICA
RESEARCH INC.

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Date

Aug. 12, 2025

Zia Tayab
Vice President, Pharmacokinetics
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Date

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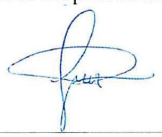
Sponsor Representative:



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## 2.0 Table of Contents

## 2.1 List of Tables

## 3.0 List of Abbreviations

**Table 1** List of Abbreviations Referred to in the Statistical Analysis Plan

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Co-Variance |
| $AUC_{inf}$ | The area under the analyte concentration versus time curve from time zero to infinity |
| $AUC_t$ | The area under the analyte concentration versus time curve from time zero to the time of the last measurable analyte concentration (t) |
| BE | Bioequivalence |
| BMI | Body mass index |
| CI | Confidence interval |
| $C_{max}$ | Maximum measured plasma analyte concentration over the sampling period |
| CV | Coefficient of Variation |
| ECG | Electrocardiogram |
| GMR | Geometric mean ratio |
| IMP | Investigational medicinal product |
| $K_{el}$ | Apparent first-order elimination rate constant |
| LQCT | Last Quantifiable Concentration Time |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| NTEAE | Non-Treatment Emergent Adverse Event |
| PK | Pharmacokinetic |
| PMRI | Pharma Medica Research Inc. |
| PR | Pulse Rate |
| PT | Preferred Term |
| $R^2$ | Coefficient of determination obtained from regression analysis |
| RR | Respiration Rate |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| $T_{half}$ | The apparent elimination half-life |
| TLIN | Start time for linear regression |
| $T_{max}$ | Time of the maximum measured analyte concentration over the sampling period |
| TRAE | Treatment-Related Adverse Event |

## 4.0 Introduction

The analyses outlined in this document are designed in support of the Protocol N$^{O}$./Sponsor Study N$^{O}$: 2024-5705, Version 1.0 (June 13, 2025). This Statistical Analysis Plan (SAP) has been developed prior to database lock and final analysis.

All final analyses will be conducted after the clinical trial data are entered into the database, any discrepancies in the data have been resolved, and the database is authorized (closed to changes). In addition, protocol deviations must be identified prior to the start of the data analyses. Any deviation from this SAP must be substantiated by a sound statistical rationale and described in the Clinical Study Report (CSR).

Pharmacokinetic (PK) parameter calculations may commence prior to database lock once the PK data is clean and not subject to change.

## 5.0 Study Objectives and Rationale

### 5.1 Study Objectives

The objectives of this study are described in Table 2.

**Table 2** Study Objectives

| **Primary Objective** |
|---|
| To evaluate the bioequivalence (BE) between:<br>• Sapropterin dihydrochloride 100 mg/mL oral suspension from APR Applied Pharma Research s.a., Switzerland and<br>• Kuvan® (sapropterin dihydrochloride) 100 mg powder for oral solution from BioMarin Pharmaceutical Inc., USA<br>following a 10 mg/kg single dose in healthy adult participants under fed conditions. |
| **Secondary Objective** |
| To evaluate the safety and tolerability of the study treatments. |

### 5.2 Study Rationale

APR Applied Pharma Research s.a. is developing an oral suspension of 100 mg/mL sapropterin dihydrochloride. This study will compare the bioavailability of the Test formulation to a Comparator Product (Kuvan® [sapropterin dihydrochloride] 100 mg powder for oral solution coming from the US market) under fed conditions.

Bioequivalence between the Test and Comparator Products will be determined by a statistical comparison of the $AUC_t$, $AUC_{inf}$, and $C_{max}$ parameters for sapropterin.[1,2]

## 6.0 Study Design

### 6.1 Design

This is an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, two-stage adaptive, BE study.

The washout between drug administrations in Periods 1 and 2 for each participant will be at least seven (7) days (±3 hours) in Stage 1, and in Stage 2 if it is required.

## 6.2 Study Flowchart

**Stage 1**

| Sequence | Period 1 | Washout (at least 7 days) | Period 2 |
|---|---|---|---|
| AB | Treatment A<br>Test Product | | Treatment B<br>Comparator Product |
| BA | Treatment B<br>Comparator Product | | Treatment A<br>Test Product |

**Interim Analysis:** PK and statistical analysis of Stage 1 data will be conducted after the completion of Stage 1.

**Stage 2**

If required, Stage 2 will be conducted after Sponsor has reviewed the data from Stage 1.

| Sequence | Period 1 | Washout (at least 7 days) | Period 2 |
|---|---|---|---|
| AB | Treatment A<br>Test Product | | Treatment B<br>Comparator Product |
| BA | Treatment B<br>Comparator Product | | Treatment A<br>Test Product |

## 6.3 Drug Products and Treatments

The drug products and treatments administered in this study are described in Table 3. In each period, participants will receive one (1) of the following two (2) treatments:

**Table 3** Drug Products and Treatments

| Treatment | A<br>(Test Product) | B<br>(Comparator Product) |
|---|---|---|
| **Drug Product** | Sapropterin dihydrochloride 100 mg/mL oral suspension | Kuvan® (sapropterin dihydrochloride) 100 mg powder for oral solution |
| **Dose** | one (1) × 10 mg/kg dose of 100 mg/mL | one (1) × 10 mg/kg dose of 100 mg |
| **Dosing Condition** | 30 minutes after the start of a high-fat, high-calorie breakfast | |
| **Dosed with** | | dissolved in 120±2 mL of water followed by two rinses of the dosing cup with 60±1 mL of water each time |

The dose for each participant will be calculated by multiplying the participant's weight measured at Period 1 check-in by 10 mg/kg and then rounding up to the next

100 mg dose. For example, the weight of a 70.5 kg participant would be multiplied by 10 mg/kg, resulting in 705 mg, and after rounding up, this participant would be assigned a dose of 800 mg.

## 6.4 Sample Size

Forty-two (42) participants will be randomized in Stage 1 of this study. To ensure 42 participants participate in Stage 1, extra standby volunteers will be enrolled. These extra volunteers may not be required to participate in the study. If, however, a participant chooses to withdraw from the study for any reason prior to drug administration in Period 1, a standby participant will be used as a replacement.

If Stage 2 is required, total sample size re-estimation will be conducted after Stage 1 assuming an α level of 0.0294 and a GMR of 0.95. Based on the results of Stage 1, additional participants, including extra standby volunteers, will be enrolled.

A maximum of 100 participants will be enrolled into this study. Volunteers who are dosed in Stage 1 cannot be dosed in Stage 2. Volunteers who are enrolled in Stage 1, but not dosed in Stage 1, may be considered for Stage 2 (they will have to sign the consent form for Stage 2).

## 6.5 Randomization

In Stage 1, and in Stage 2, if it is required, participants will be randomly assigned to one (1) treatment sequence outlined in Table 4 according to a predetermined computer-generated randomization scheme (procedure PLAN in SAS®).

**Table 4** Treatment Sequence

| Sequence | Treatment | |
|---|---|---|
| | Period 1 | Period 2 |
| AB | A | B |
| BA | B | A |

Participants will be assigned consecutive numbers in an ascending order. Each number will identify a participant and determine the sequence of drug product administration according to the randomization scheme.

## 6.6 Blinding

This is an open label study. Blinding is not applicable.

Samples that are shipped to the analytical laboratory will not contain treatment information on the sample label.

## 6.7 Pharmacokinetic Sample Collection

Blood samples will be collected for the assay of sapropterin as defined in Table 5. The time tolerance window for blood samples collected from -1 to 0.5 hours will be

±5 minutes, within 10 minutes prior to dosing for 0 hour, ±1 minute for samples collected from >0 to 10 hours, and ±3 minutes for samples collected after 10 hours. Sample collections done outside the pre-defined time windows will not be considered as protocol deviations. The actual post-dose sampling times will be used for the PK and statistical analyses.

**Table 5** Pharmacokinetic Sample Collection

| **Treatments A and B** | |
|---|---|
| **Analyte** | **Time Points** |
| Sapropterin | Pre-dose at (-1, -0.5, and 0-hour) and at 0.333, 0.667, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, and 24 hours after drug administration (22 sampling times) |

# 7.0 Rules and Definitions

## 7.1 General Rules

There are no general rules for this study.

## 7.2 Strata and Covariates

There are no pre-defined strata for this study. The actual total dose will be included in the analysis of co-variance (ANCOVA) statistical model as a covariate.

## 7.3 Multicentre Analysis

This is not a multicentre study.

## 7.4 Multiple Comparison/Multiplicity

If at least one power estimated from $AUC_t$, $AUC_{inf}$, and $C_{max}$ is less than 80% from the Stage 1 interim analysis, then multiplicity adjustment will be considered when evaluating BE (i.e., $\alpha$=0.0294) for Stage 1 or 2.

## 7.5 Examination of Subgroups

No examination of subgroups is planned for this study.

## 7.6 Pooling of Centres

No pooling of centres is applicable since this is a single centre study.

## 7.7 Interim Analysis and Data Monitoring

An analysis of the $AUC_t$, $AUC_{inf}$, and $C_{max}$**Error! Bookmark not defined.** parameters for baseline-corrected and uncorrected sapropterin will be performed after the 42 participants have completed Stage 1 (i.e., concentration data and clinical data become available). The interim analysis results will be used for evaluating the need and initiation of Stage 2. Details of the interim analysis are described in Section

10.2.1 *Stage 1: Interim Analysis, Criteria for Initiation of Stage 2 and Criteria for Evaluation*.

## 8.0 Dataset Definitions

### 8.1 Safety Dataset

The safety dataset will include participants who receive at least one (1) administration of any study treatment. Data from participants in this dataset will be used for the assessment of safety.

### 8.2 Pharmacokinetic Dataset

Data from the following participants will be included in the PK dataset:

- Participants from whom the estimation of $C_{max}$ and/or AUC parameters will be possible for both periods; and
- Participants who complied with all protocol requirements or encountered protocol deviations that do not impact the estimation of the PK parameters.

The PK dataset will be defined prior to the assay of samples for each stage. However, if a sufficient reason to exclude a participant's data is identified during the analysis (i.e. suspected non-compliance, insufficient quantifiable data, etc.) the participant's data may be excluded from the PK dataset at the discretion of the PK Scientist. Data from participants in this dataset will be used for the PK analysis. If deviations occur, they will be assessed for their impact on the PK dataset and will be included in the study report.

### 8.3 Statistical Dataset

The statistical dataset for each stage will include all data in the PK dataset modified by the following occurrences:

- Individual period data for the affected analyte will be excluded for a participant who exhibits lack of any measurable concentrations or only very low plasma concentrations of the analyte for the Test or Comparator Product in a given period. A participant is considered to have very low plasma concentrations if the AUC is less than 5% of the Test or Comparator Product geometric mean AUC calculated from the PK dataset for each stage (which should be calculated without inclusion of data from the outlying participant); and
- Individual period data will be excluded if a pre-dose concentration (0-hour) greater than 5% of the corresponding $C_{max}$ is observed for a participant in a given period.

If none of these exclusions are met, the statistical dataset for each stage will be identical to the PK dataset. Data from participants in this dataset will be used for the statistical analysis.

## 9.0 Pharmacokinetic Analysis

### 9.1 Baseline Correction

Sapropterin is an endogenous compound and therefore it is to be analyzed both with and without baseline correction. Pharmacokinetic parameters will be calculated based on uncorrected plasma concentrations and baseline-corrected plasma concentrations, as appropriate. Baseline corrected for sapropterin will be performed by calculating the mean plasma pre-dose levels for each participant within each period of the study using the measured concentrations at the -1, -0.5, and the 0-hour time points. The mean of these pre-dose values will be the baseline for that period for that participant. The baseline value will be subtracted from all subsequent measured concentrations (including 0-hour) for the same participant within the same period. Negative baseline adjusted levels will be set to zero before the PK analysis. No adjustment of the pre-dose or post dose concentrations will be performed for the baseline uncorrected data.

### 9.2 Pharmacokinetic Parameters

Pharmacokinetic analysis will be performed on available data from participants in the PK dataset. The actual post-dose sample collection times will be used in the PK analysis.

The following PK parameters/observations described in Table 6 will be estimated for baseline-corrected and uncorrected sapropterin using a non-compartmental approach in Phoenix™ WinNonlin®.

**Table 6** Pharmacokinetic Parameters/Observations Estimated for Baseline-corrected and Uncorrected Sapropterin

| | |
|---|---|
| $AUC_t$: | The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear trapezoidal method. |
| $AUC_{inf}$: | The area under the analyte concentration versus time curve from time zero to infinity. $AUC_{inf} = AUC_t + C_t/K_{el}$, where $C_t$ is the last measurable analyte concentration. |
| $C_{max}$: | Maximum measured analyte concentration over the sampling period. |
| $T_{max}$: | Time of the maximum measured analyte concentration over the sampling period. |
| $T_{lag}$: | Time of observation prior to the first observation with a measurable (non-zero) concentration |
| $K_{el}$: | The apparent first-order elimination rate constant. |
| $T_{half}$: | The apparent elimination half-life. |
| Cl/F: | Apparent clearance |

| | |
|---|---|
| $V_z/F$: | Apparent volume of distribution |
| $AUC_t/AUC_{inf}$: | The ratio of $AUC_t$ to $AUC_{inf}$. |
| Residual Area: | $(AUC_{inf} - AUC_t)/AUC_{inf}$. |
| TLIN: | Start time for linear regression. |
| LQCT: | Last quantifiable concentration time. |
| $R^2$: | Coefficient of determination obtained from regression analysis. |

$K_{el}$, $T_{half}$, and $AUC_{inf}$ parameters will not be estimated for concentration-time profiles where the terminal linear phase is not clearly defined.

The following rules apply for the selection of data points (ln[concentration]-time data pairs) used in the linear regression for the selection of $K_{el}$:

- The maximum number of data points that lead to the best fit should be used;
- At least 3 data points at the end of the concentration-time curve should be used; and
- Coefficient of correlation ($R^2$) should be equal or larger than 0.7000.

Individual and mean plasma concentration versus time curves will be plotted. Additional PK analyses may be conducted if deemed appropriate.

## 9.3 Actual/Scheduled PK Sampling Times

The pre-dose (0-hour) sample will be set to time zero regardless of the time of sample collection. For post-dose samples, the actual clock time of each sample collection will be recorded.

If the actual sampling time is not available, the scheduled sampling time will be used for the PK analysis.

## 9.4 Handling of Missing PK Data

Time points with missing concentration values will be excluded from the PK dataset prior to the PK analysis.

## 9.5 Concentrations Below LOQ

Concentrations below the lower limit of quantitation (BLQ) will be set to zero prior to the PK analysis with the exception of the values that are BLQ and occur between two quantifiable post-dose concentrations. These values will be assigned as missing.

# 10.0 Statistical Analyses

## 10.1 General Considerations

Descriptive statistics for baseline-corrected and uncorrected sapropterin plasma concentrations for each nominal time point will be provided for each treatment, including number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), CV%, median, minimum, and maximum.

Descriptive statistics for baseline-corrected and uncorrected sapropterin PK parameters will be provided for each treatment, including number of observations, arithmetic mean, SD, geometric mean (where applicable), CV%, median, minimum, and maximum.

## 10.2 Statistical Analysis of the Pharmacokinetic Data

Statistical analysis will be performed on quality assured data, with unbalanced sequences, if necessary, from participants in the statistical dataset at each stage.

Analysis of co-variance (ANCOVA) will be applied for baseline-corrected and uncorrected sapropterin on log-transformed $AUC_t$, $AUC_{inf}$, and $C_{max}$ parameters. The PROC GLM procedure from SAS® will be used to estimate the statistics. The ratio of geometric least square means for treatments and the corresponding confidence interval (CI) for the ratio of geometric least square means, based on least squares means from the ANCOVA of the log-transformed data, will be calculated for $AUC_t$, $AUC_{inf}$, and $C_{max}$.

Additional statistical analyses may be conducted if deemed appropriate. For example, an analysis with potency corrected data will be completed (to adjust the ratio and CI for the comparison between Test and Comparator Products). Potency correction will be done if the difference in assay is >5%. Potency correction will be accomplished by dividing the relevant PK parameters by the reported potency value for that specific treatment.[3]

### 10.2.1 Stage 1: Interim Analysis, Criteria for Initiation of Stage 2 and Criteria for Evaluation

An analysis on the $AUC_t$, $AUC_{inf}$, and $C_{max}$[1] parameters for baseline-corrected and uncorrected sapropterin will be performed after the 42 participants have completed Stage 1 (i.e., concentration data and clinical data become available).

Analysis of co-variance (ANCOVA) will be applied for baseline-corrected and uncorrected sapropterin on log-transformed $AUC_t$, $AUC_{inf}$, and $C_{max}$ parameters. The model will include treatment, period, sequence, subject(sequence) as fixed effects, and actual total dose as a covariate. Estimates of the within-subject

variance for these parameters will be obtained. The power will be estimated using this variance estimate from Stage 1, assuming an α level of 0.05 and a geometric mean ratio (GMR) of 0.95.

The power will be calculated using the below formulas:

t1 = tinv(**0.95**,df);

p1 = probt((ln(**1.25**)-ln(**0.95**))/StdErr - t1,df);

p2 = probt((ln(**0.8**)-ln(**0.95**))/StdErr + t1,df);

power = **100***abs(p1 - p2);

*where t1 is the 95$^{th}$ percentile of a Student's t density function with degrees of freedom df, StdErr is the estimated sample standard error, p1 and p2 are cumulative distribution function of Student's t-distribution.*

- If all power estimated from baseline-corrected sapropterin $AUC_t$, $AUC_{inf}$, and $C_{max}$ are greater than or equal to 80%, a 90% (α=0.05) CI for the $AUC_t$, $AUC_{inf}$, and $C_{max}$ true GMR and a point estimate will be calculated. The BE criteria will be evaluated based on the results of analysis from Stage 1 where the 90% CI for the baseline-corrected sapropterin $C_{max}$, $AUC_t$, and $AUC_{inf}$ true GMR has to fall completely between 80.00 and 125.00%. Regardless of the outcome of the BE evaluation, Stage 2 will not be required, and the study will be considered complete with the participants from Stage 1 only and a conclusion on BE will be made.
- If at least one power estimated from baseline-corrected sapropterin $AUC_t$, $AUC_{inf}$, and $C_{max}$ is less than 80%, a 94.12% (α=0.0294) CI for the $AUC_t$, $AUC_{inf}$, and $C_{max}$ true GMR will be calculated. If the results of the analysis from Stage 1 indicate that the 94.12% CI for the baseline-corrected sapropterin $AUC_t$, $AUC_{inf}$, and $C_{max}$ true GMR falls completely between 80.00 and 125.00%, Stage 2 will not be required, and the study will be considered complete with the participants from Stage 1 only. If the results from Stage 1 indicate that the 94.12% CI for the baseline-corrected sapropterin $C_{max}$, $AUC_t$, and $AUC_{inf}$ true GMR does not fall completely between 80.00 and 125.00%, Stage 2 will be initiated.
- If BE is not demonstrated, the study can continue with Stage 2. The sample size for Stage 2 is to be estimated using the variance at Stage 1 and an α level of 0.0294. The BE is evaluated at Stage 2 using data from both stages (α=0.0294) where the 94.12% CI for the baseline-corrected sapropterin $C_{max}$, $AUC_t$, and $AUC_{inf}$ true GMR has to fall completely between 80.00 and 125.00%.

Details of statistical analysis in Stage 2 can be found in section 10.2.2 *Stage 2*.

### 10.2.2 Stage 2

If Stage 2 is initiated based on the Stage 1 results, the sample size for Stage 2 is to be estimated using the variance at Stage 1, GMR of 0.95, and an α level of 0.0294. The number of subjects for Stage 2 would be the calculated sample size minus number of subjects in the Stage 1 statistical datasets. Once additional subject data becomes available, the BE is evaluated at Stage 2 using data from both stages' statistical datasets.

Analysis of co-variance (ANCOVA) will be applied for baseline-corrected and uncorrected sapropterin on log-transformed $AUC_t$, $AUC_{inf}$, and $C_{max}$ parameters. The model will include treatment, stage, period (stage), sequence, sequence*stage, subject(sequence*stage) as fixed effects, and actual total dose as a covariate.

The ratio of geometric least square means for treatments and the 94.12% CI for the ratio of geometric least square means, based on least squares means from the ANCOVA of the log-transformed data, will be calculated for $AUC_t$, $AUC_{inf}$, and $C_{max}$.

## 11.0 Safety Evaluation

### 11.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. A treatment emergent AE (TEAE) can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

A non-treatment emergent adverse event (NTEAE) is defined as any acute existing disease or symptom, which occurs during and after participants sign the ICF until first administration of the investigational medicinal product (IMP). Non-treatment emergent AEs will be reported separately from TEAEs in the study report. If, after administration of the IMP, a deterioration of the severity of the existing NTEAE is observed, this sign or symptom will be documented as a TEAE.

Treatment-related adverse events (TRAEs) will be defined as AEs assessed as possible or probable in relationship to the study drug in the study report.

Adverse event severity will be presented as mild, moderate, or severe.

A listing of all AEs (NTEAEs and TEAEs), SAEs, pregnancy and death, if any will be provided. The listing will include AEs onset and resolution date/time, duration, time from dosing, severity, relationship to the IMP, outcome, and the action taken to the IMP and to treat the AE.

All TEAEs and drug-related TEAEs will be summarized by relationship to IMP and/or the additional drug product, severity, and treatment as the number and percent of subjects experiencing the AE and the number of incidences reported.

All TEAEs and drug-related TEAEs will be summarized by system organ class, preferred term, severity, and treatment as the number and percent of subjects experiencing the AE and the number of incidences reported.

### 11.2 Vital Signs

A listing of all vital signs will be presented by parameter, visit, and timepoints, including the assessment of clinical significance for abnormal results.

Descriptive statistics for all vital sign parameters will be reported by visits/timepoints and treatments. Descriptive statistics will include number of observations, mean, SD, median, minimum, and maximum values.

Repeat and unscheduled vital signs measurements will be presented in listings only and will not be used in the descriptive statistics.

### 11.3 Clinical Laboratory Parameters

All individual clinical laboratory measurements will be listed by parameter and visit. A listing of abnormal clinical laboratory parameters will also be presented.

### 11.4 Electrocardiograms (ECGs)

All ECG parameters with the interpretation of result and description of abnormality for abnormal results will be listed by visit and timepoints for all subjects in the safety dataset.

Descriptive statistics for all ECG parameters will be reported by visits/timepoints and treatments. Descriptive statistics will include number of observations, mean, SD, median, minimum, and maximum values.

### 11.5 Physical Examination

Individual physical examinations will be listed by parameter and visit, including the assessment of clinical significance and description of abnormality for abnormal results.

## 11.6 Concomitant Medication

Concomitant medication taken by subjects outside of the study drug/additional drug product will be presented for each individual subject in a listing. A table summarizing the concomitant medication use will also be provided.

## 11.7 Other Data Reporting

Other individual data including participant demographics, participant disposition, treatment administration, and protocol deviations will also be listed. Demographics, and disposition will be summarized.

### 11.7.1 Demographics

Individual subject demographic data for the safety analysis set will be provided in a listing.

Summary tables including age, body mass index (BMI), weight and height, gender, race, and ethnicity for each analysis set will be provided.

Descriptive statistics for continuous variables (e.g., age, weight, height, and BMI) will include n, mean, SD, median, minimum, and maximum, whereas for categorical variables (e.g., ethnicity, race, and gender) frequency counts and percentages will be provided.

### 11.7.2 Disposition

The number and percent of participants enrolled in the study, completed the study and discontinued from the study based on total number of participants in the study will be summarized for each treatment and overall.

The participants who discontinue the study will be presented in a separate table with the reason for discontinuation.

The participants excluded from the PK dataset will also be reported in a listing.

# 12.0 References

[1] US Department of Health and Human Services. *Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA – Draft Guidance*. Washington, DC: Center for Drug Evaluation and Research; August 2021.

[2] Food and Drug Administration. *Draft Guidance on Sapropterin Dihydrochloride.* Washington, DC: Office of Generic Drugs; Published September 2008. Revised October 2024.

[3] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated *Guideline for bioequivalence for immediate release solid oral dosage forms* M13A. 2024.