# Statistical Analysis Plan

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| Protocol Title: | A Randomised, Controlled, Open-Label Parallel Arm Study of the Safety, Pharmacokinetics and Ammonia Control of RAVICTI® (Glycerol Phenylbutyrate [GPB]) Oral Liquid and Sodium Phenylbutyrate (NaPBA) in Phenylbutyrate Treatment Naïve Patients with Urea Cycle Disorders (UCDs) |
| Protocol Number: | HPN-100-021 |
| Compound: | RAVICTI® (glycerol phenylbutyrate) Oral Liquid |
| Phase: | 4; Post Marketing Requirement 2013-4 and post-authorisation study in the European Medicines Agency (EMA) Risk Management Plan |
| Sponsor: | Horizon Therapeutics, LLC<br>1 Horizon Way Deerfield, IL 60015<br>USA |
| SAP Author: | PPD<br>Horizon Therapeutics |
| SAP Version: | Final Version 2.0 |
| SAP Date: | 19-DEC-2022 |

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## DOCUMENT HISTORY

| Version | Date | Author | Description |
|---|---|---|---|
| 1.0 | 11-JUL2018 | PPD | Final Version |
| 2.0 | 16-DEC-2022 | PPD | The SAP has been updated for the following reasons:<br>• Reflect the changes made in protocol amendment<br>• Provide standard normal reference range for ammonia by age category<br>• Support an abbreviated clinical study report (CSR) instead of a full CSR |

# SIGNATURE PAGE AND APPROVALS

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# ABBREVIATIONS

| ABBREVIATION | DEFINITION OR DESCRIPTION |
|---|---|
| ABCL | Adult Behavior Checklist |
| AE | Adverse Event |
| ASR | Adult Self-Report |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Curve |
| BSA | Body Surface Area |
| CBCL | Child Behavior Checklist |
| CGI-I | Clinical Global Impression - Improvement |
| CGI-S | Clinical Global Impression - Severity |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| HAC | Hyperammonemic Crises (HAC) |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified Intent-To-Treat |
| NaBz | Sodium Benzoate |
| NaPBA | Sodium Phenylbutyrate |
| PAA | Phenylacetic Acid |
| PAGN | Phenylacetylglutamine |
| PBA | Phenylbutyric acid |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SI | Standard International |
| SOC | System Organ Class |
| TEAE | Treatment-emergent Adverse Event |
| UCD | Urea Cycle Disorder |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |

# 1. Overview

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Horizon Therapeutics protocol HPN-100-021, "A Randomised, Controlled, Open-Label Parallel Arm Study of the Safety, Pharmacokinetics and Ammonia Control of RAVICTI® (Glycerol Phenylbutyrate [GPB]) Oral Liquid and Sodium Phenylbutyrate (NaPBA) in Phenylbutyrate Treatment Naïve Patients with Urea Cycle Disorders (UCDs)", Version 12, Amendment 11, dated 23-Sep-2022.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. An abbreviated CSR will be submitted for this study, therefore certain analyses described in this SAP will not be performed. The clinical outcome assessment endpoints (excluding the hedonic scale) will not be summarized, and z-scores for the vital signs parameters will not be calculated. Some subgroup analyses may not be performed for efficacy variables due to the small number of enrolled subjects. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- Case report forms (CRFs) for Protocol HPN-100-021.
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

# 2. Study Objectives and Endpoints

## 2.1 Study Objectives

The objective of this study is to assess the safety, tolerability, pharmacokinetics (PK), and ammonia control of RAVICTI as compared to sodium phenylbutyrate (NaPBA), in urea cycle disorder (UCD) subjects not currently or previously chronically treated with phenylacetic acid (PAA) prodrugs.

## 2.2 Efficacy, Safety, and PK/PD Endpoints (Target Variables)

### 2.2.1 Efficacy Variables

#### 2.2.1.1 Initial Treatment Period (RAVICTI vs NaPBA)

- The primary efficacy variable is the rate of treatment success (see section 6.2.1 for definition of treatment success).
- Drug discontinuation due to any reason

#### 2.2.1.2 Transition, Maintenance, and Safety Extension Periods (RAVICTI only)

- Annualised rate of hyperammonemic crises (HAC).
- Fasting (for those who can tolerate fasting) plasma ammonia concentrations at the end of the transition period, weeks 4 and 8 of the maintenance period, at safety extension visits 1 and 2, and at the end of study visit.

### 2.2.2 Safety Variables

- Adverse events (AEs)
- Clinical laboratory tests
- Amino acid panel
- Rate of discontinuations due to AEs

### 2.2.3 Pharmacokinetic Variable(s)

- Plasma concentrations of phenylbutyric acid (PBA), phenylacetatic acid (PAA) and phenylacetylglutamine (PAGN )
- Urinary excretion of PAGN

### 2.2.4 Clinical Outcome Assessment Variables

- Palatability of study drug (Hedonic Scale)
- Changes in clinical global impression (CGI) scales (Investigator)
- Neuropsychological assessments: Child Behavior Checklist (CBCL) or Adult Behavior Checklist (ABCL) or Adult Self Report (ASR)
- EQ-5D-5L health status quality of life assessment
- Subject preference for study drug (Arm 2 after exposure to both RAVICTI and NaPBA)

## 3. Overall Study Design and Plan

This is a randomised, controlled, open-label parallel arm study of RAVICTI compared with NaPBA in UCD patients who are not currently and have not been chronically treated with PAA prodrugs. Subjects will be randomised to one of two treatment arms in which they will receive either RAVICTI or NaPBA at a dose that corresponds to their disease and treatment

status at entry as follows: 1) presenting with hyperammonemic crisis (HAC) requiring a dose at the high end of the recommended and approved range; 2) inadequately controlled with diet and supplements requiring a dose in the middle of the recommended and approved range; or 3) stable on sodium benzoate (NaBz) or needing additional scavenging while on NaBz treatment, requiring transition from NaBz to PBA at an equivalent dose. At the discretion of the investigator and considering the clinical status of the subject, the dose may be adjusted after initial dosing.

The study design includes a baseline period, initial treatment period, transition period, maintenance period and a safety extension period. Before entering the initial treatment period, subjects will be randomised 2:1 to either Treatment Arm 1 (RAVICTI) or Treatment Arm 2 (NaPBA).

Subjects will receive their assigned study drug treatment (either RAVICTI or NaPBA) in the initial treatment period for a period of approximately 4 weeks. Subjects who have reached and maintained a stable dose for at least 7 consecutive days by the end of the initial treatment period will complete 8-hour plasma ammonia, amino acid panel, glutamine, PK, and spot urine collections. Blood PK and Urine samples will also be taken if patients experience an HAC or PAA toxicity at any time throughout the study.

Subjects on NaBz entering the baseline period will have their NaBz treatment titrated down and simultaneously replaced with the randomized study drug (RAVICTI or NaPBA).

Treatment Arm 1 subjects who do not meet the criteria for treatment success (defined in Section 6.2.1) and all Treatment Arm 2 subjects may enter the 7 day Transition Period if the investigator considers continued treatment with RAVICTI to be an appropriate course of therapy. Treatment Arm 1 subjects who achieve treatment success will proceed directly to the Maintenance Period.

Following successful completion of the initial treatment period and/or transition period, subjects will begin the maintenance period and be treated with RAVICTI for 8 weeks. Subjects will continue at the stable dose of RAVICTI they were receiving at the end of the prior period.

Subjects will be monitored in the RAVICTI maintenance period for adequate plasma ammonia control and clinical stability.

Following completion of the maintenance period, subjects will begin the safety extension and be treated with RAVICTI for 12 weeks. All subjects will continue at the dose of RAVICTI they were receiving at the end of the maintenance period. Subjects will continue to be monitored during phone and onsite visits that will include plasma ammonia and amino acid assessments.

For subjects who were taking NaBz at study entry, the NaBz treatment may be resumed during the safety extension period at the discretion of the investigator. The dose of NaBz cannot be greater than the PBA equivalent of the dose of RAVICTI that the subject is taking.

After completion of the safety extension period, subjects will complete their participation in the study. The investigator may prescribe RAVICTI where it is commercially available or may contact the administrator of the Managed Access Program or Named Patient Program in countries where RAVICTI is not commercially available.

For further details of the study design, please see the protocol.

## 4. Analysis and Reporting

### 4.1 Interim Analysis

No formal interim analysis is planned for this study.

### 4.2 Final Analysis

The final analysis for the study will be performed once all subjects have completed participation in the study, and all relevant study data have been processed and integrated into the analysis database.

## 5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety population:** The safety population includes all subjects who receive any amount of study medication, and will be analysed based on treatment as received. This will be the primary population for all safety analyses.
- **Modified intention-to-treat population (mITT):** The mITT population includes all randomized subjects with 1) no major eligibility violations, 2) who have received at least one dose of study drug and 3) have a data point (ammonia value) post randomisation. Subjects will be analysed based on the treatment the subject was randomized to during the Initial Treatment Period. This will be the primary population for efficacy analyses.
- **Pharmacokinetic population (PK):** The PK population includes all subjects who have at least one dose of study drug and have a valid PK measurement. This will be used for all PK analyses. Subjects will be analysed based on treatment as received.

## 6. General Issues for Statistical Analysis

### 6.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables summarizing data for the Initial Treatment Period will be summarized by randomized treatment group for efficacy analyses and by actual treatment received for safety analyses. All tables (for both mITT and Safety populations) summarizing data from the Transition Period, Maintenance Period, and Safety Extension Period will be summarized by the actual treatment received (RAVICTI).

Baseline and safety tables will be completed for the safety population unless otherwise specified. Efficacy tables will be presented for the mITT population and pharmacokinetic tables will be presented for the PK population.

Continuous, quantitative variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation, median, minimum, and maximum, unless otherwise specified.

Categorical, qualitative variable summaries will include the frequency and percentage of subjects who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group, unless otherwise specified.

All analyses will be performed using SAS® Software version 9.3 or later.

### 6.1.1 Determination of Sample Size

Approximately 16 subjects will be enrolled in this study. This is a safety, efficacy, and tolerability study and no formal sample size calculation has been performed. The sample size of 16 subjects was chosen considering the number of subjects with this orphan disease and the criteria of the study. Sixteen subjects meeting the entry criteria will be enrolled and expected to complete the initial treatment period (including assessment of the primary endpoint). The study is expected to have approximately 30% drop out rate after the initial treatment period, due to liver transplant or other reasons and therefore approximately 12 subjects are expected to complete the study.

### 6.1.2 Handling of Missing Data

Any subject who withdraws from the study will be asked to undergo early termination procedures which include efficacy and safety data.

In general, missing data will not be imputed. However, the following exceptions are made.

If AEs are missing data on severity or relationship to study medication, a plausible worst-case approach will be taken: thus missing severity will be imputed as CTC grade 3, and missing relationship will be imputed as probably related. If dates are missing or partial for AEs, then those AEs will be assumed to be treatment emergent unless it can be definitively shown otherwise. See section 9.1 for further details.

Similarly, if dates are missing or partial for other medications taken by subjects, it will be assumed that they are concomitant unless it can be definitively shown otherwise. See section 9.5 for further details.

If subjects have missing data at the 4 h timepoint for calculation of the ammonia 8 h AUC but have values available at the 0 and 8 h timepoint, then AUC will be calculated using the available values, which is equivalent to linear interpolation of the missing value.

If subjects are missing ammonia measurements for either the 0 h or the 8 h timepoint then the AUC will not be calculated.

If data on variables contributing to the primary endpoint of treatment success are missing, a worst case approach will be taken and missing values will be assumed not to meet the criteria for success (see section 6.2.1).

No other missing data will be imputed.

### 6.1.3 Definition of Baseline

For all safety and efficacy variables, the baseline value will be the last measurement taken before the first dose of study medication. This will in general be the pre-dose measurement

on day 1, but if a measurement is not collected or is missing at that timepoint, then the most recent value from the baseline or screening periods will be used instead.

### 6.1.4 Pooling of Centers

All centers will be pooled for analysis. No analyses will adjust for center effects.

### 6.1.5 Visit Windows

Study visits are expected to occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. For subjects who discontinue prematurely, data from the early termination (ET) visit will be summarized separately according to the treatment period during which the early termination occurred for summaries by visit.

In data listings, the relative study day of all dates will be presented.

## 6.2 Derived and Computed Variables

The following derived and computed variables will be used for the analysis of efficacy.

### 6.2.1 Treatment Success

After the completion of the initial treatment period of the study, a subject will be considered a treatment success for NaPBA or RAVICTI if the subject has not experienced an unprovoked HAC (i.e., a HAC that cannot be attributed to one or more specific precipitating factors such as infection, intercurrent illness, diet noncompliance, treatment noncompliance, etc.) on the assigned treatment and has met at least 2 of the following 3 criteria at the end of the initial treatment period:

- Standardized absolute values at the 3 time points (pre-dose, after dose at 4 hours and 8 hours) of plasma ammonia levels which do not exceed the upper limit of normal (ULN) at the end of the initial treatment period (missing values will be assumed to exceed the ULN)
- Has normal (≤ ULN) glutamine levels at the End of Initial Treatment Period visit at time point 0 Hour
- Has normal (≤ ULN) essential amino acids including branched chain amino acid levels (threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) at the End of Initial Treatment Period visit at time point 0 Hour

### 6.2.2 Normalisation of Ammonia Concentrations

Since ammonia data will be collected through local laboratories that may have different normal ranges, all ammonia analyses will use ammonia results standardised to a common unit (µmol/L) and normalised to a common ULN. All data will be converted to SI units (µmol/L) before the normalisation, imputation and calculation of the AUC. The conversion formula is µg/dL * 0.5872 = µmol/L.

The standard normal reference range to be used will depend on the age of the subject. For subjects ≤ 1 month old the ULN is 107 umol/L; for subjects > 1 month to 18 years old, the

ULN is 57 µmol/L; for adult subjects > 18 years old the ULN is 35 umol/L (Chernecky CC, Berger BJ. Laboratory Tests and Diagnostic Procedures. 2013. 6th ed. St. Louis, MO: Saunders).

Normalization will be done by applying the scale normalization approach (Juha Karvanen, "The Statistical Basis of Laboratory Data Normalization", Drug Inf J. 2003; vol. 37:pp. 101-107), using the following formula:

$s = x * (U_s / U_x)$,

where s is the normalized laboratory value, x is the original laboratory value, $U_x$ is the upper limit of the normal reference range from the original laboratory, and $U_s$ is the upper limit of the normal reference range for the standard laboratory. For example, if a value of 10 was obtained from a local laboratory with a normal range of 5 to 25, and we want to normalize this value to the standard reference range which was established to be 28 to 57, then by applying the above formula, we would obtain a normalized value of 22.8 as detailed below:

$s = 10 * (57 / 25) = 22.8$

### 6.2.3 Calculation of Ammonia 8 h AUC

Ammonia 8 h AUC will be calculated from the values recorded at 0 h, 4 h, and 8 h, using the linear trapezoidal rule. If any of those values are missing, the AUC will be imputed as described in section 6.1.2.

### 6.2.4 Calculation of Clinical Outcome Assessment Scores

The clinical outcome assessment scores (the clinical global impression-severity scale, the clinical global impression-improvement scale, palatability using the hedonic scale and assessment of drug preference) will be assessed as observed, no imputation will be performed for missing data.

For the CBCL, ABCL/ASR and EQ-5D-5L questionnaires, scores will be calculated and missing data will be handled according to the validated questionnaire manual. Certain questionnaires are only validated for particular age ranges. Questionnaires are not collected or analysed for subjects outside of the validated age ranges.

## 7. Study Subjects and Demographics

### 7.1 Disposition of Subjects and Withdrawals

The number and percent of subjects in each study population (safety, mITT, and PK) will be summarized by treatment group and overall. The number and percent of the subjects who enrolled in the study, completed the study, who withdrew from the study and their reasons for withdrawal will also be tabulated by treatment group and overall for the safety population.

The number and percent of subjects who entered and completed each period will also be summarized for the mITT population.

### 7.2 Protocol Deviations

The number and percent of subjects who experienced a protocol deviation and type of protocol deviation will be summarized for all enrolled subjects.

### 7.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the safety population by treatment group, unless otherwise specified.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, age groups, sex, race, ethnicity, height, weight, body mass index [BMI] body surface area [BSA], head circumference (if applicable), starting dose category)
- Medical History
- Prior Medications
- UCD history (UCD diagnosis type, time since first diagnosis [years], previous use of gastric or nasogastric tube, whether family members have been diagnosed with UCD, whether family members have been diagnosed with neoplasms or malignancies, number of hospitalisations due to UCD in the previous 12 months, number of hyperammonemic crises in the last 12 months, medications used for UCD management)

Medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.1). Incidences of findings in medical history will be summarized by system organ class (SOC) and preferred term by treatment group, unless otherwise specified.

Note that all concomitant medications and concomitant medications used for UCD management will be coded using the World Health Organization (WHO) Drug Dictionary (Version September 2017). The frequency and percentage of all prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification and preferred term for all subjects in the safety population by treatment group, unless otherwise specified.

Prior medication is defined as medications recorded on the concomitant medication log with a start date earlier than the date of first treatment. If it cannot be determined whether medications are prior medications because of missing or incomplete start dates, they will be assumed to be both prior and concomitant medications. Note that medications will also be considered both prior and concomitant if the start date is before the date of first study medication dose and the medication continues after the first study medication dose.

Age groups are defined as: 2 months – < 2 years, 2 years - 12 years inclusive, > 12 -16 inclusive and ≥ 17 inclusive.

## 8. Efficacy and Pharmacokinetic Analysis

This study will examine the efficacy of RAVICTI compared to NaPBA in UCD patients who are not currently and have not been chronically treated with PAA prodrugs.

It may be necessary to complete additional exploratory analyses after the planned analyses are completed. Full details of additional analyses will be presented in the CSR, and any such additional analyses not specified in this SAP will be clearly identified as post-hoc.

Efficacy analyses will use the mITT population.

Statistical significance will be accepted at the level of 0.05 based on 2-sided tests.

All efficacy and pharmacokinetic data will be displayed in data listings.

### 8.1 Primary Efficacy Variable Analysis for the Initial Treatment Period

The primary efficacy variable is treatment success, which is defined in section 6.2.1. To compare the rate of treatment success between the 2 treatment groups, the odds ratio for treatment success of RAVICTI vs NaPBA will be presented together with its 95% confidence interval. The statistical significance of the difference will be determined with Fisher's exact test.

Also, subgroup analysis by age group (birth – < 2 years, 2 years – 12 years inclusive, > 12 – 16 inclusive and >= 17 inclusive), NaBz use at baseline, starting dose category (stable, not adequately controlled, on NaBz), region (US, Europe; provided sufficient number of subjects in each treatment group), and by gender and race (white, non-white) for the primary endpoint will be performed. The subgroup analysis will use the same methods as the primary analysis provided at least 2 subjects are in each category for each treatment group.

### 8.2 Secondary Efficacy Variable Analysis for the Initial Treatment Period

Plasma ammonia AUC to 8 h and the peak ($C_{max}$) will be compared between the treatment groups. The data for AUC will first be assessed by a Shapiro-Wilk test. If the Shapiro-Wilk p-value is >0.01 the data will be considered to not violate normality assumptions and will be compared with a 2-sample t-test. The difference in means and its 95% confidence interval and p-value will be presented.

If the normality assumption is violated, then a log transformation will be derived. If the log-transformed data appear to be approximately normally distributed, then a t-test will be done on the log-transformed data, and the difference between means and its 95% confidence interval will be back-transformed to give the ratio of the geometric means.

If the data still violates normality assumptions after the log transformation, the difference between the treatment groups will be tested with the Wilcoxon rank sum test, and the difference between medians and its 95% confidence interval will be estimated with the Hodges-Lehmann estimator.

Normalized fasting plasma ammonia change from baseline concentrations at weeks 1, 2, 3, and 4 of the initial treatment period will be analysed using the same method.

The number of subjects who discontinued treatment as well as the reasons for discontinuation will be summarized in the disposition table.

### 8.3 Efficacy Variable Analysis for the Transition, Maintenance and Safety Extension Periods

The number of HAC prior to enrollment and while taking RAVICTI (all periods) and NaPBA (initial treatment period only) during each period will be summarized with descriptive statistics (number of subjects, mean, SD, median, min, max) and by number and percent of subjects with 0, 1, 2, 3, and 4 or more HAC. A summary for overall HAC while taking RAVICTI will be included as well.

The rate of HAC overall while taking RAVICTI or NaPBA will be calculated across subjects as

- Rate of HA crises = ∑number of HA crises between first and last dose of [RAVICTI or NaPBA] / ∑of number days on [RAVICTI or NaPBA].

The overall rate for all subjects while taking RAVICTI will be summarized. The rate of HAC while taking NaPBA will be calculated and summarized similarly for the initial treatment period.

The rate of HAC during the first year prior to enrollment will be calculated across all subjects as

- Rate of HA crises/year prior to enrollment = ∑number of HA crises during the year prior to enrollment / ∑365.25 days.

If a subject has an age of 365 days or less, their age in days will be used as the denominator for the rate of HAC prior to enrollment. The overall rate for all subjects prior to enrollment will be presented.

Subgroup analysis by age group (2 months – < 2 years, 2 years - 12 years inclusive, > 12 – 16 inclusive and >= 17 inclusive), race, gender, starting dose category (stable, not adequately controlled, on NaBz), region (US, Europe), and NaBz use at baseline for the HAC analysis described above will be presented. Hypothesis testing will not be conducted.

The fasting normalized plasma ammonia concentrations measured during the transition, maintenance, and safety extension periods will be presented along with change from baseline using descriptive statistics for overall subjects and by subgroup.

The number and percentage of abnormal ammonia values (≥ULN) and ammonia values ≥2 times the ULN will be summarized by visit.

Plots will be provided for individual subject normalized ammonia concentrations over time and mean normalized ammonia concentrations by age groups for each treatment group over time.

### 8.4 Pharmacokinetic Analysis

Plasma concentrations of PBA, PAA and PAGN, and urinary excretion of PAGN will be summarised by treatment group and timepoint using descriptive statistics. Data will be presented using the number of subjects (N) with non-missing values, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum.

Results of PK samples taken in response to HAC or PAA toxicity will be tabulated in the same manner, but all combined into a single virtual timepoint, irrespective of the time they are taken.

### 8.5 Clinical Outcome Assessment Analysis

Results of the hedonic scale to assess palatability will be presented by tabulating the number of responses in each category at the end of the initial treatment period for both treatment arms and in the transition period day 7 for Treatment Arm 2 (NaPBA) subjects. In addition, for subjects in the Treatment Arm 2, responses to the hedonic scale for NaPBA at the end of the

initial treatment period will be cross-tabulated in a shift table against the responses for RAVICTI at the end of the transition period.

The VAS score change from baseline of the EQ-5D-5L will be compared between treatment groups at the end of the initial treatment period using the same t-test/Wilcoxon analysis method described in section 8.2, and the difference between means will be presented along with its 95% confidence interval and p-value. The p-value will be interpreted in an exploratory sense only. The EQ-5D-5L VAS will also be presented with descriptive statistics only for the maintenance and safety extension periods.

Individual question responses to the EQ-5D-5L will be summarized using frequencies and percentages for the initial treatment, maintenance, and safety extension periods.

Observed t-scores (for domains for which a t-score is calculated) will be summarized for the CBCL, ABCL, and ASR questionnaires at the baseline, end of maintenance period, and end of study visits as well as the change from baseline to each visit.

Other data collected on the CBCL 1.5Y – 5Y, CBCL 6Y – 18Y, ABCL 19Y – 59Y, and ASR 19Y – 59Y assessments will be listed only.

A summary of Treatment Arm 2 (randomized to NaPBA for the Initial Treatment Period and then received RAVICTI in the Transition Period) subjects' drug preference will be provided.

## 9. Safety and Tolerability Analysis

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject in the safety population:

- Adverse Events
    - Treatment-emergent AEs (TEAEs) and treatment-emergent serious adverse events (TESAEs)
    - AEs leading to withdrawal of study drug
    - Any deaths
- Clinical laboratory investigations (chemistry and haematology)
- Amino acid panel
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, body weight)
- Concomitant Medications
- Study Drug Exposure

Safety data will be presented separately for each of the following study periods:

- Baseline Period (Subject may experience AEs prior to receiving actual treatment or IMP)
- Initial treatment period
- Transition period
- Maintenance and Safety Extension Periods

- Overall RAVICTI

For the Baseline Period safety data will be presented separately by Treatment Arm. For the initial treatment period, safety data will be presented separately by treatment assignment. Transition period data will be summarized separately from other periods. For the maintenance and safety extension periods, safety data will be presented for all patients combined. A summary for all AEs and SAEs occurring while on RAVICTI will be included as well.

### 9.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (Version 20.1).

TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication and up to the end of study for non-serious AEs and up to 30 days after the end of the last administration of study medication for SAEs. However, all AEs considered to be related to the study medication are defined as treatment-emergent whenever they occurred.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates and times will not be replaced.

The following are used for guidance for programmers.

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end day of the treatment-emergent period, or if the start day is the same day as the first treatment and the stop date/time is before the first treatment.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of treatment-emergent period or if the stop date/time is before the start of first treatment.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end year of treatment-emergent period or if the stop date/time is before the start of first treatment.
- If the start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date/time is before the start of first treatment.

AEs will be assigned to study periods based on the start date of the AE. If the missing data in the start date of an AE does not allow it to be unambiguously assigned to one of the 3 study periods, then it will be counted in the earliest treatment period in which it might have occurred, though no earlier than the initial treatment period.

For each of the ~~3~~ 4 study periods described above, all AEs will be summarized in a table whose rows give the number of subjects for each of the following:

- All TEAEs

- Serious TEAEs
- Drug-related TEAEs
- TEAEs leading to discontinuation of study drug

Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum intensity, and TEAEs by strongest relationship to study drug.

Each subject will be counted only once within each preferred term in each study period. If a subject experiences more than one TEAE within a preferred term for the same study period, only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

No inferential statistical tests will be done.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

TEAEs by SOC and preferred term will also be tabulated by subgroups of NaBz use at baseline, region, age group, race and gender.

All AE tables will include columns for RAVICTI and NaPBA during the initial treatment period, RAVICTI during the transition period, a combined column for RAVICTI during the maintenance and safety extension periods, and an overall RAVICTI column.

### 9.1.1 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term, will be prepared for the safety population for each study period. No inferential statistical tests will be done.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

### 9.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages) of TESAEs by treatment group, SOC, and preferred term will be prepared for the safety population for each study period. No inferential statistical tests will be done.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

## 9.2 Clinical Laboratory Evaluations

Descriptive summaries of observed values and changes from baseline will be presented by visit for clinical chemistry and haematology for each study period for the safety population. Laboratory values will be presented in standard international (SI) units.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

For each laboratory variable, shifts in assessments of abnormality from baseline to each visit within that study period will be presented in shift tables.

### 9.3 Amino Acid Panel

Descriptive summaries of observed values and changes from baseline will be presented by visit for amino acid values for each study period for the safety population.

Amino acid values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

For each amino acid laboratory variable, shifts in assessments of abnormality from the start of each study period to each visit within that study period will be presented in shift tables.

### 9.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), temperature, height, weight, BSA, and head circumference. These summaries will be presented by visit for the safety population in each study period.

Descriptive summaries for height, weight, head circumference, and BMI z-scores based on age will be derived using normative growth charts from the CDC website published in May 2000. BSA z-scores derived using weight-for-length charts will also be summarized.

### 9.5 Concomitant Medication

Concomitant medications will be analysed similarly as prior medications.

A concomitant medication is defined as any medication taken after the start of study treatment and up to end of study. The frequency and percentage of all concomitant medications will be summarized by ATC class and preferred term for subjects in the safety population by study period. The ATC level 4 terms will be used in the summary. If the level 4 term is not available, the level 3 term will be used and so on. Additionally, NaBz medications will be summarized by ATC class and preferred term. All medication tables will include columns for RAVICTI and NaPBA during the initial treatment period, RAVICTI during the transition period, a combined column for RAVICTI during the maintenance and safety extension periods, and an overall RAVICTI column. A listing of all medications and a separate listing for NaBz medications will be provided.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

Thus, the following approach will be taken for exclusion from concomitant medications because of discontinuation before start of treatment:

- If the stop day is missing but the month is complete, then the medication will be excluded from concomitant medications only if the stop month is before the month of treatment start.
- If the stop day and month are missing but the year is complete, then the medication will be excluded from concomitant medications only if the stop year is before the year of treatment start.

- If the stop date is completely missing, then the medication will not be excluded.

For concomitant medication exclusion (because of the late start after the end of the treatment period):

- If the start day is missing but the month is complete, then the medication will be excluded from concomitant medications only if the start month is after the end month of the treatment period.
- If the start day and month are missing but the year is complete, then the medication will be excluded from concomitant medications only if the start year is after end year of the treatment period.
- If the start date is completely missing, then the medication will not be excluded.

### 9.6 Exposure and Compliance

Overall exposure to study treatment will be summarized in terms of exposure duration and average daily dose in milliliters (mL, mL/$m^2$, g, g/$m^2$, and mg/kg) by actual treatment group for each study period and overall. Average daily dose will be calculated by taking sum of daily dose between the period start and end dates divided by the duration. Duration will be calculated as follows:

$$\text{Duration (days)} = \text{End date} - \text{Start date} + 1.$$

The dose of RAVICTI in grams/day and the amount of PBA ingested (g) (via RAVICTI) will be summarized as well. Each mL of RAVICTI delivers 1.02 g of PBA and the density of RAVICTI is 1.1 g/mL. The number of dose changes will be summarized. Frequencies and percentages of subjects exposed to RAVICTI for ≥ 2 weeks, ≥ 1 month, ≥ 3 months, and ≥ 6 months will be presented for the overall treatment period. The route and frequency will be summarized for each visit.

Exposure duration will be summarized categorically (≥2 weeks; ≥1 month; ≥6 months) using frequencies and percentages. A numeric summary of total years of exposure will also be provided. Total years of exposure will be calculated by duration/365.25.

Data for subjects who took NaPBA will be summarized in a similar manner during the initial treatment period.

Study drug exposure and route of drug administration (oral or through feeding tubes) will be listed. A listing containing demographic data, disease type, dosing data, protein intake data, PBA, PAA, PAGN, ammonia data and TESAEs will also be presented.

## 10. Changes from Protocol Planned Analysis

Age, gender, region and race subgroup analyses have been added to some of the efficacy assessments and adverse event tables.

## 11. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services:

Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
4. Chernecky CC, Berger BJ. Laboratory Tests and Diagnostic Procedures. 2013. 6th ed. St. Louis, MO: Saunders.
5. Karvanen J. The statistical basis of laboratory data normalization. *Drug information journal*. 2003;37(1):101–7.
6. Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. http://www.cdc.gov/growthcarts/

## 12. Tables, Listings, and Figures

A list of all planned tables, listings, and figures will be provided as a separate document.