Statistical Analysis Plan

PROTOCOL NUMBER: HPN-100-011

LONG TERM USE OF HPN-100 IN UREA CYCLE DISORDERS

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Contents

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BRIEF	Behavior Rating Inventory of Executive Function
BSA	Body Surface Area
CVLT-II	California Verbal Learning Test
CBC	Complete Blood Count
CBCL	Child Behavior Checklist
CI	Confidence Interval
CRF	Case Report Form
g	Gram
HPN-100	Glyceryl tri-(4-phenylbutyrate), GT4P
kg	Kilogram
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
m^2	Square meter
mg	milligram
Min	Minimum
mL	millilitre
NP	Neuropsychological
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UCD	Urea Cycle Disorder
ULN	Upper Limit of Normal
WASI	Wechsler Abbreviated Scale of Intelligence

1 Introduction

This document presents the statistical analysis plan (SAP) for Horizon Therapeutics, Inc. (Horizon) formerly Hyperion Therapeutics, Inc. (Hyperion), Protocol HPN-100-011: Long Term Use of HPN-100 in Urea Cycle Disorders.

This analysis plan is based on protocol Version 4.0 Final (Amendment 3), Version 2.0 Final (Amendment 1), Version 3.0 (Canada) Amendment 2, 4.0 Final (Amendment 3), and 4.0 (Canada) Amendment 03, Administrative Change 1.

The SAP provides the description of the final data analysis.

2 Study Objectives

The purpose of this protocol is to provide study subjects completing Protocols HPN-100-005, HPN-100-007, or HPN-100-012 continued access to HPN-100 in the context of a protocol designed to collect safety information with extended treatment.

The objective of this study is to evaluate the long-term safety of HPN-100 and its control of venous ammonia in the management of UCDs.

2.1 Endpoints

The primary endpoint is the rate of adverse events.

The secondary endpoints are the following:

- Venous ammonia levels
- Number and causes of hyperammonemic crises
- Neuropsychological testing

3 Study Design

3.1 Discussion of Study Design

This is a long-term safety study of HPN-100 in UCD subjects. Subjects will be assessed regularly for safety. Unscheduled visits (clinic visits/hospitalization/emergency room visits) will be assessed and hyperammonemic crisis events will be characterized with respect to contributing factors.

As in Studies HPN-100-005, HPN-100-007, and HPN-100-012, the dose of NaPBA and thus HPN-100 is chosen based on the severity of the enzyme deficiency, on the content of the subject's diet, and on the intake of amino acids or other supplements. The dose will therefore vary among subjects.

Subjects who have completed Study HPN-100-005, HPN-100-007, or HPN-100-012 will initially receive open-label HPN-100 at the same dose that they were receiving when they completed Study HPN-100-005, HPN-100-007, or HPN-100-012.

The investigator may subsequently adjust the dose for any subject if judged clinically appropriate [the dose should not exceed the equivalent of 20 g/day of NaPBA (~17.4 mL total daily dose of HPN-100)].

Subjects will stay on this study until the subjects can be transitioned to commercially available HPN-100 or until alternate approved treatment is available.

3.2 Study Schedule

For subjects who completed HPN-100-005, HPN-100-007, or HPN-100-012 and with the exception of the SF-36 or SF-15 questionnaire, the Month 0 visit of this study may be combined with the Month 12/Termination visit of the HPN-100-005, HPN-100-007, or HPN-100-012 study if conducted on the same day or within 14 days of the termination of either study. Common assessments between these visits (including neuropsychological battery) do not have to be repeated. However, these data must be recorded on both the Month 12 CRF for HPN-100-005, HPN-100-007, or HPN-100-012 and the Month 0 CRF for HPN-100-011.

Subjects should visit the clinic as prescribed by the Investigator, but at a minimum a visit must occur every 6 months until HPN-100 is commercially available to the subject or the subject terminates HPN-100 for other reasons.

Data will also be recorded for unscheduled visits (e.g., unscheduled clinic visit, emergency room visit, or hospitalization).

Assessments for every 12 months or the final visit are the same as the 6 month visits, with the exception of performing neuropsychological battery tests.

Full details of the study schedules can be found in the study protocol. Details will not be duplicated within the SAP.

3.3 Concomitant Medications and Diet

Medications being used at the time of study initiation may be continued with the permission of the investigator. All concomitant medications, including dose adjustments, and their indications must be recorded on the CRF.

The following prohibited medications may not be used during the study:

- Drugs known to cause hyperammonemia, such as valproate
- Drugs known to significantly affect renal clearance, such as probenecid

All subjects should adhere to the diet (e.g. low protein, amino acid supplements) prescribed for them by the investigator. The diet chosen for each individual depends on age and residual enzyme activity and should not be altered for this study. At the discretion of the investigator, changes in dietary protein may be prescribed as necessary. Changes in prescribed protein and/or calories will be recorded on the CRF.

3.4 Study Analysis Population

Only one analysis population will be evaluated for this study, the safety population.

All subjects who receive any amount of study medication will be included in the safety population. This is the primary population for all analyses performed for this study.

3.5 Withdrawn Subjects

Subjects may be withdrawn for any of the following reasons:

- Voluntary withdrawal
- At the discretion of the investigator if it is in the best interest of the subject
- Lost to follow-up

Subjects who exit the study will not be replaced.

3.6 Randomization and Blinding

Not applicable – This is a non-randomized and open-label study.

3.7 Sample Size

No formal sample size or power calculations were performed for this long-term safety study. Subjects who completed protocols HPN-100-005, HPN-100-007, or HPN-100-012 will be eligible for enrollment in this study.

4 Statistical Methodology

4.1 Planned Analyses

Summary statistics [number of subjects (n), mean, standard deviation (SD), median, minimum and maximum] will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables. Unless otherwise noted, percentages will be calculated using the total subjects per treatment group in the appropriate population and/or subgroup.

All summary tables will include separate statistics for adults (>=18 years) and pediatric patients (<=17 years). Totals for all patients will also be presented.

Final analyses will occur upon data cutoff from the last monitoring visit (paper case report forms) at the single remaining open site in 2015. This data cut will initiate a full analysis. Any additional data collected after this data cut-off will be summarized in a CSR addendum.

4.2 Interim Analysis

All Canadian patients enrolled in HPN-100-011 will continue to be followed under the protocol schedule of assessments until commercial access, or access through Health Canada Special Access Program or alternate treatment is available to them.

All US patients will be terminated from the study after 30June2013. All data from US patients will be cleaned and locked upon completion of the final US patient. Data from these patients will be analyzed according to the plans detailed within this SAP.

4.3 Significance Levels

If statistical significance testing is performed, it will be performed for exploratory purposes only. Tests will be evaluated at the two-sided 0.05 level of significance and/or using two-sided CIs. No adjustments for multiple testing will be made for this study.

4.4 Baseline and Demographic Characteristics

Demographic data including age, race, ethnicity, and gender as well as UCD history will be summarized using descriptive statistics. UCD history data will be obtained from the original study (HPN-100-005, HPN-100-007, or HPN-100-012) databases.

Baseline variables including medical history, physical and neurological examinations, vital signs, laboratory data, and other baseline disease characteristics will be summarized using descriptive statistics.

Unless otherwise noted, baseline will be defined as the last non-missing value prior to the first dose of study treatment as part of protocol HPN-100-011. Additional analyses may be performed using the baseline value from the original study (HPN-100-005, HPN-100-007, or HPN-100-012).

4.5 Safety Analysis

The primary objective of this study is to evaluate the safety and tolerability of HPN-100. Safety will be evaluated in the safety population using adverse event reporting, laboratory tests, vital signs, hyperammonemic events, and concomitant medications.

4.5.1 Adverse events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). If a patient experiences multiple events that map to a single preferred term, the greatest severity and most conservative relationship will be assigned for the applicable summaries.

A treatment-emergent AE is an AE that begins (or a pre-existing condition that worsens) after receiving the study medication as part of HPN-100-011. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

Treatment-emergent AEs will be summarized by system organ classification, preferred term, and treatment. Treatment-emergent serious adverse events (SAEs) will also be summarized by system organ classification, preferred term, and treatment. A similar summary will also be prepared for AEs leading to discontinuation of study treatment.

Treatment-emergent AEs will also be presented by maximum severity/intensity and by most conservative relationship to study medication.

Adverse events will also be tabulated by total exposure to HPN-100 treatment during HPN-100-011 (0-3 months, >3-6 months, >6-9 months, >9-12 months, and >12-months exposure).

The number and percentage of patients with at least one qualifying adverse event will be tabulated for all summaries.

4.5.2 Laboratory and amino acid data

Laboratory samples (blood and urine) were collected in accordance with the schedule of assessments, and at the investigator's discretion. The safety laboratory assessments will be defined as:

- Hematology: complete blood count (CBC) with differential and platelet count
- Coagulation: prothrombin time and international normalized ratio (INR)
- Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, and glucose
- Liver function tests: ALT, aspartate aminotransferase (AST), albumin, total bilirubin, and alkaline phosphatase
- Amino acid panel: ornithine, aspartic acid, serine, threonine, glutamic acid, asparagine, proline, glutamine, alanine, glycine, valine, citrulline, methionine, cystine, leucine, isoleucine, phenylalanine, tyrosine, lysine, tryptophan, arginine, and taurine.

Laboratory test results and their changes from baseline will be summarized using descriptive statistics by study visit. Laboratory results will be classified relative to the normal reference range and will be summarized by study treatment and visit. A shift table showing the shift from baseline to each study visit, relative to the normal range, will be prepared.

The amino acid data collected for each study period will be summarized similarly. Glutamine and glutamate results as well as the sum of glutamine and glutamate values

will be summarized in a separate table. Glutamine values will be plotted (mean ± standard error) by study visit. Branched chain amino acids will be summarized separately in a similar manner.

4.5.3 Vital signs

Results for systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature will be summarized, along with the change from baseline, by treatment and visit. Body surface area (BSA) will be calculated as

$$BSA(m^2) = \sqrt{\frac{weight(kg) \times height(cm)}{3600}}$$

4.5.4 Hyperammonemic events

The number of hyperammonemic (HA) crises and the number of subjects with at least one crisis will be summarized by study and age group (pediatric and adults). Peak observed ammonia during the crises will also be summarized. Precipitating factors and symptoms recorded as suggestive to hyperammonemia will be summarized. The duration of the crisis in hours will be calculated as stop date/time minus start date/time. If time is not known, then it will be assumed to be 12:00pm. A correlation analysis will be performed to determine if the ammonia value at admission is a determining factor on the length of the crisis. Spearman's rank-order correlation will be used.

HA crisis history data will be obtained from the databases of the original studies (HPN-100-005, HPN-100-007, or HPN-100-012) and summarized similarly.

4.6 Exploratory Efficacy Analyses

Blood samples will be collected for assessment of venous ammonia levels at office visits in accordance with the study protocol. Ammonia data will be summarized by study visit and relative to the baseline value in order to evaluate the long-term benefit of HPN-100 on controlling blood ammonia levels.

All analyses of ammonia data collected as part of this protocol will be considered exploratory in nature and will be used as supportive to data collected under prior HPN-100 studies.

Ammonia data will be presented using the normalized values described below as well as the raw or non-normalized results.

4.6.1 Standardization and Normalization of the Ammonia Level Data

Two units are used for the ammonia data, µmol/L and µg/dL. All data will be converted to SI unit (µmol/L) before the normalization, imputation and calculation of the AUC. The conversion formula is µg/dL * 0.5872 = µmol/L.

The ammonia level data are obtained from different local laboratories and each laboratory may use a slightly different normal reference range. Therefore, the ammonia level data will be normalized to a standard laboratory reference range before

performing any analysis of ammonia data. This normalization will be done by applying the scale normalization approach, 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 – 25, and we want to normalize this value to a standard reference range, that was established to be 10 – 35, then by applying the above formula, we would obtain a normalized value of 14 as detailed below:

$$s = 10 *(35 / 25) = 14$$

These standardized and normalized values will be used in summaries of ammonia data. In addition to the normalized data, selected ammonia analyses may be repeated using raw/non-normalized results.

4.6.2 Analysis of Ammonia Data

Ammonia values will be summarized with descriptive statistics, along with the change from baseline for each study visit.

Changes in average ammonia values from baseline to the average ammonia obtained during the entire study period will be analyzed. For this analysis, all available ammonia data obtained after beginning treatment under protocol HPN-100-011 will be averaged (including the values obtained while the subject was in hyperammonemic crisis) and compared to the baseline value.

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

4.7 Disposition of Patients

The number and percentage of patients receiving study treatment who completed or prematurely discontinued the study and the reasons for any premature discontinuation will be presented. In addition to study completion, the number of subjects who completed 3, 6, 9, 12 and >12 months of treatment with HPN-100 under this protocol will be summarized.

4.8 Concomitant Medication

Incidence of concomitant medications will be presented by therapeutic area and preferred drug name. Medications will be coded using the WHO Drug dictionary.

Concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

4.9 Exposure to HPN-100

The number of patients treated with HPN-100 will be summarized. The dose of HPN-100 in mL/day, grams/day, grams/m^2, and mg/kg will be summarized. Date of last dose of study drug will be derived from the last daily dose date and compared to last dose captured from the CRF when available. The total duration of HPN-100 treatment will also be summarized. Duration will be calculated as follows:

Duration = Date of Last Dose – Date of First Dose +1.

The duration of treatment will be summarized based on treatment under protocol HPN-100-011 as well as total treatment with HPN-100 based on data from the original studies the subjects participated in (HPN-100-005, 007, and 012).

Data on dose modifications will be listed.

4.10 Neuropsychological Testing

Neuropsychological (NP) battery testing will be performed at study entry, every 12 months (or early termination visit), and at the End of Study. For adults, the following tests will be performed:

- Wechsler Abbreviated Scale of Intelligence (WASI)
- Digit span
- Grooved pegboard
- California Verbal Learning Test (CVLT-II)

For pediatric patients, the following tests will be performed:

- Wechsler Abbreviated Scale of Intelligence (WASI)
- Child Behavior Checklist (CBCL)
- Behavior Rating Inventory of Executive Function (BRIEF)

Results will be summarized and listed by subject.

Tests are to be administered by a properly trained medical professional. Instructions to administer these tests, including individual test manuals and kits, will be provided in the Study Manual.

For the WASI test, the vocabulary T score, matrix reasoning T score, and full scale IQ standard score will be summarized using descriptive statistics.

For the CBCL form, the T-score for each item will be summarized.

The T-score for each item will be summarized for the BRIEF tests.

Change from baseline will be compared using paired t-tests for all NP tests.

The Scaled Score for the Digit Span will be summarized. The Z scores for the dominant and non-dominant hands will be summarized for the Grooved Pegboard test.

The T score for the CVLT-II List A Total 1-5 and the Z score for rows 1-6 will be summarized using descriptive statistics.

Summaries for adult and pediatric patients will be produced separately.

4.11 Protocol Violations or Deviations

Violations and deviations from the protocol will be documented on an ongoing basis by the study monitors and project managers throughout the study period. These violations/deviations will be included in the clinical study report.

4.12 Deviations from SAP

Any deviations from the final SAP will be described and justified in the final clinical study report.

4.13 Changes in Conduct or Planned Analyses from the Protocol

Paired t-tests for the neuropsychological tests were added to the SAP.

5 Tables and Listings

All output will be produced using SAS version 9.1.3 or later. In general, outputs will be prepared in the following manner.

5.1 Format

At the top of each table/listing/figure, a number followed by the title will be presented. After the title line, optional sub-title or population information will be presented. Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be put under the main body of text.

The sponsor name, protocol number, programmer ID, status of the output (i.e. draft or final), SAS program name, and the date and time of creation will be on the output. The page number will appear on the bottom right corner of each output (Page X of Y).

Outputs will be prepared in landscape layout unless otherwise specified. All margins will be a minimum of 1 inch. In general, Courier New, 8 point font will be used for tables and listings. If necessary for formatting, an alternate font type or size may be used.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible, data will be decimal aligned.

Unless otherwise specified, frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the date9. format (e.g., 01JAN2012). In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

Listings will be sorted by site, patient and visit, as appropriate.

The mock ups and table of contents (Final Version 1 dated 15Feb2013) as part of this SAP provide the expected layout and titles of the tables, listings, and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation.