Study: HPN-100-014

NCT#: 01948427

TITLE:
SAP
Long-Term Registry of Subjects with Urea Cycle Disorders (UCDs)

Date of Document:
SAP: 08 January 2020

Statistical Analysis Plan (SAP)

Study Title:	Long-Term Registry of Subjects with Urea Cycle Disorders (UCDs)
Study No:	HPN-100-014
Date of Protocol:	11 February 2013 (Amendment 1)
Clinical Phase:	4
Study Sponsor:	Horizon Therapeutics USA, Inc. 150 S. Saunders Road South Lake Forest, IL 60045
Compound:	RAVICTI™ (glycerol phenylbutyrate) Liquid
SAP Status/Version:	Final 1.0
SAP Date:	08 Jan 2020

1. Statistical Analysis Plan Signature Page

Statistical Analysis Plan Final V1.0 (Dated 08JAN2020) for Study Number HPN-100-014

Author

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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2. Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version

3. List of Abbreviations and Definitions of Terms

AE	adverse event
ARG	arginase
ASL	argininosuccinate lyase
ASS	argininosuccinate synthetase
BCAA	branched-chain amino acid
BMI	body mass index
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CITRIN	aspartate glutamate transporter
CPS	carbamyl phosphate synthetase
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
HHH	ornithine translocase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minumum
n	Number of subjects
NAGS	N-acetylglutamate synthetase
NaPBA	sodium phenylbutyrate
NDA	New Drug Application
NICU	neonatal intensive care unit
OTC	ornithine transcarbamylase
PAA	phenylacetate
PBA	phenylbutyrate
PK	pharmacokinetic
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	system organ class
UCD	urea cycle disorder

4. Table of Contents

5. Introduction

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of data for Study HPN-100-014 dated on 11 February 2013 (Amendment 1).
Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the Protocol.

6. Study Design

This is a non-interventional, multi-centre registry to be conducted in subjects with UCDs. Investigators will prescribe treatments based on usual clinical practice, and there will be no restrictions on the use of commercially available medications. As an observational study, this study will not change the patient/ healthcare provider relationship, nor influence the healthcare provider's drug prescription or the therapeutic management of the patient.
Study visits, procedures, and evaluations are summarized in the Schedule of Assessments and described in detail in the Appendix A and in Sections 5.2 in HPN-100-014 Registry Protocol. Subjects with UCDs will be recruited and invited to attend a Baseline visit. After eligible subjects are enrolled, retrospective and baseline data will be collected.
Subjects will be followed for up to 10 years, during which time they will be assessed by their healthcare provider. Subjects and healthcare provider will be asked to report episodes of hyperammonemic crisis, available ammonia values, and other information. Assessments of follow-up information, data points of interest (Appendix B in HPN-100-014 Registry Protocol), and age-appropriate neuropsychological testing (Appendix C in HPN-100-014 Registry Protocol) will be performed annually. SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual.
Subjects who become pregnant during this registry will be invited to participate in the UCD pregnancy registry (Protocol HPN-100-018)

6.1 Study Objectives

- To characterize the demographics and clinical course of the patient population diagnosed with UCD
- To track growth and neurocognitive outcomes in subjects with UCD.
- To generate comparative effectiveness data in UCD subjects

6.2 Hypothesis

Not applicable.

6.3 Sample Size

Up to 500 subjects of whom at least 100 subjects are being treated with RAVICTI. According to Wolters Kluwer data received by Hyperion in September 2010, there were an estimated 406 subjects on NaPBA during the time period of 01 April 2009 through 31 March 2010. The enrollment target of at least 100 subjects receiving glycerol phenylbutyrate was selected due to feasibility, and an attempt to capture a significant portion of the probable glycerol phenylbutyrate patient population, which is estimated, at peak, to be similar to the number of subjects on NaPBA.

6.4 Randomization

Not applicable for this study.

6.5 Unblinding Plan

Not applicable for this study.

6.6 Schedule of Assessments

Please refer to APPENDIX A. SCHEDULE OF ASSESSMENTS in the protocol.

6.6.1 Study Visits

As defined in the protocol, the following visits will be used for reporting purposes:

- Retrospective
- Baseline/Enrollment
- Day 7 to 30
- Standard Visits
- Year 1 to Year 10 Annual Visits

7. Changes to Analysis from Protocol

There are no changes from the analysis mentioned in the protocol.

8. Treatment Arms

For reporting purposes the following treatment arms (Ammonia-Scavenging Medication) will be used:

- Sodium Phenylbutyrate
- Raviciti
- Sodium Benzoate
- Carglumic Acid

[redacted]

- Other

9. Statistical General Considerations

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor and in consistency with this SAP.
Coding of AEs and medical history will be done by Medical Dictionary for Regulatory Activities (MedDRA) directory Version 19.1 and medications data by the World Health Organization (WHO)-drug dictionary dated Mar2019 by UBCTM.
The default summary statistics for continuous variables includes number of contributing observations (n), mean, standard deviation (SD), median, minimum and maximum or as described in the respective section in the mocks-up documents.
For categorical variables, the number and percentage (the percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number of subjects in the relevant analysis set, with assessments available in each category will be the default summary presentation.

9.1 Planned Analysis

Annual reports will be created using all data available.

9.2 Analysis Sets

The following study population will be used for reporting purposes:

Table 1 Analysis Sets

Analysis Set	Description
All Patients Enrolled Set (ENR)	The ENR will include all subjects who signed informed consent/enrolled in the registry.
All Patients who Attended a Baseline Visit (All)	The All analysis set will include all subjects in the ENR who attended and provided data at Baseline visit.

9.3 Software Version

All analyses, statistics, and graphics reported in the clinical study report will be conducted using Statistical Analysis System® (SAS) Version 9.3 or higher (SAS-Institute, Cary, North Carolina, USA).

9.4 Multicenter Studies

This is a multicentre study. Data from all sites will be pooled for analysis.

9.5 Missing Data

Only partial dates will be imputed as per APPENDIX 1.

9.6 Statistical Test, Testing Strategy and Adjustment for Multiplicity

This is an observational study, hence hypothesis testing or alpha adjustment are not required. Any inferential analysis (if done) will be exploratory in nature.

9.7 Windowing Conventions

Please see APPENDIX A, B, C and D. SCHEDULE OF ASSESSMENTS in the protocol. Special consideration to Neuropsychological tests which may be performed ≤6 months before, or ≤2 months after enrollment.

9.8 Common Calculations

Duration in Days:

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study treatment at baseline (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1
- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date)
- In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

Weeks	Duration = duration in days / 7
Months	Duration = duration in days / 30.4
Years	Duration = duration in days / 365.25
Minutes	Duration = duration in days / 60

1 pound = 0.454 kg.
1 inch = 2.54 cm.

Age The subject's age is calculated as the number of years from the subject's date of birth to the date of enrollment into the study if a date of birth is available:

Age = ([Enrollment Date - Date of Birth] / 365.25).

If only the year of birth is available, the age is calculated as follows:

Age = Enrollment Year – Birth Year.

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

Percentage change from baseline will be calculated as:

(Test Value at Visit X – Baseline Value) *100/ Baseline Value

9.9 Patients Background information

For reporting purposes in addition to patient disposition status, the following study assessments in section 6 the protocol will be considered as patient background information using the default summary statistics for continuous and categorical variables as described in Section 9, unless otherwise specified:

(a) Patient Disposition (Using All patient enrolled analysis set)

(b) Demographic and Clinical Assessments (Using the all patient who attended a baseline visit analysis set)

- Demography
- Urea Cycle Disorder History
- Urea Cycle Disorder (UCD) Cancer History
- Past and Current Treatments
    - Ammonia-Scavenging Medications
    - Prescribed Daily Protein/Calorie Intake
- Prior and Concomitant Medications
- Patient Clinical Status
    - Vitals
    - Cancer History
    - Chemistry
    - Hematology
    - Data Points of interest
- Additional data points
    - Plasma and Urine PK (Patients on sodium phenylbutyrate or glycerol phenylbutyrate)
    - Actual Dietary Intake

Table 2 below summarize how this data will be tabulated (using descriptive statistics) and listed.

Table 2. Patients Background Information (part 1 of 8)

Assessment	Categories	Subcategories	Additional details
Patient Disposition and Withdrawals	○ Total number of patients screened ○ Total number of patients enrolled ○ Total number of patients who attended baseline visit	- Continuous variable	Table by Ammonia-Scavenging Medication (ASM) - ASM at baseline by visit (using All Patient enrolled) - Listing - Population used: All patients who attended baseline visit
	○ Patient Disposition	- Completed - Discontinued - Serious Adverse Event - Investigator request - Lost to follow-up (patient could not be contacted by phone or other means) - Patient no longer willing to participate in study - Other	
Patient Demographics	○ Sex	- Male - Female	- Table by ASM at baseline - Listing - Population used: All patients who attended baseline visit
	○ Age (years)	- Continuous variable	
	○ Age Groups at Screening	- ≤ 2 years old (infants) - > 2 to ≤ 12 years old (children) - > 12 to ≤ 21 years (adolescences) - > 21 years old (adults)	
	○ Race	- White - Black or African American - Asian - American Indian or Alaska Native - Native Hawaiian or Other Pacific Islander - Other - Not reported	
	○ Ethnicity	- Hispanic or Latino - Not Hispanic or Latino - Not Reported	

Table 2. Patients Background Information (part 2 of 8)

Assessment	Categories	Subcategories	Additional details
Urea Cycle Disorder (UCD) History	o Time since first presentation of UCD symptoms (years)	- Continuous variable	- Table by ASM at baseline - Listing - Population used: All patients who attended baseline visit
	o Time since first presentation of UCD symptoms (years)		
	o UCD Presentation	- Newborn screening - Clinical symptoms - Prenatal diagnosis - Abnormal lab tests - Other	
	o Time since UCD Diagnosis in years	- Continuous variable	
	o Method of diagnosis	- Amino acid analysis - DNA mutation analysis - Enzyme analysis on fibroblast - Enzyme analysis on liver - Enzyme analysis on RBC - Other - Not available	
	o UCD subtype	- ARG Deficiency - ASL Deficiency - ASS Deficiency - CITRIN Deficiency - CPS Deficiency - HHH Syndrome - NAGS Deficiency - OTC Deficiency - Not available	
	o GI or NG tube placement?	- Yes - No	

Table 2. Patients Background Information (part 3 of 8)

Assessment	Categories	Subcategories	Additional details
Glutamine/Amino Acid Pane	o Blood sample collected, n (%)	- Yes - No - Unknown - Missing	- Table by ASM at baseline (retrospective values) - Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	o Patients Fasting o Patients No Fasting o Patients Fasting (unknown)	- Glutamine - Leucine - Isoleucine - Valine	
Past and current treatments: Ammonia-Scavenging Medication Use and Primary reason for discontinuation	o Patient with any retrospective ammonia-scavenging medication	- Yes - No - Missing	- Table by ASM at baseline (retrospective values) - Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	o Ammonia-Scavenging Medication - prior baseline	- Sodium phenylbutyrate - Ravicti - Sodium benzoate - Carglumic acid - Other	
	o End date known	- Yes - No - Missing	
	o Primary reason medication changed or discontinued	- Condition resolved/no longer needed - Lack of efficacy - Participation in clinical trials - Patient decision - Patient death - Physician decision - Pregnancy - Side effects - Tolerability - Other	

Table 2. Patients Background Information (part 4 of 8)

Assessment	Categories	Subcategories	Additional details
Past and current treatments: Treatment Switchers	Ammonia-Scavenging Medication Post Baseline o Sodium Phenylbutyrate o Raviciti o Sodium Benzoate o Carglumic Acid o Other	- Continuous variable	- Table by ASM at baseline and changes of ASM by Visit - Population used: All patients who attended baseline visit
Past and current treatments: Prescribed Daily Protein/Calorie Intake	o Number of patients on a prescribed diet	- Yes - No - Missing	- Table by last known ASM (by visit) - Change from Baseline in Prescribed Daily Protein/Calorie Intake - Listing - Population used: All patients who attended baseline visit
	o Prescribed dietary protein (per kg of body weight)	- Continuous variable	
	o Total prescribed dietary protein (per day)		
	o Prescribed calorie intake (per kg of body weight)		
	o Total prescribed calorie intake (per day)		
	o Compliant with the prescribed diet	- Yes - No - Unknown - Missing	

Table 2. Patients Background Information (part 5 of 8)

Assessment	Categories	Subcategories	Additional details
Prior and Concomitant Medications	o Number of Patients Reported Concomitant Medication of Interest, n (%)	- Continuous variable	- Table by last known ASM using ATC and preferred Term and by Visit - Listing - Population used: All patients who attended baseline visit
	o Amino Acids and Derivatives, n (%) o Amino Acids, Incl. Combinations with Polypeptides, n (%) o Amino Acids/Carbohydrates/Minerals/Vitamins, Combinations, n (%) o Vitamins, Other Combinations, n (%)		
Patient Clinical Status: Vitals	o Weight (kg) o Height (cm) o Body Mass Index (BMI [kg/m^2]) o BSA(m^2)		- Table by ASM at baseline (retrospective) - Listing - Population used: All patients who attended baseline visit
Patient Clinical Status: Urea Cycle Disorder (UCD) Cancer History	o Number of patients with any history of cancer diagnosis, n (%)		- Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	o Cancer Status, n (%)	- Malignant - Benign	
	o Resolved, n (%)	- Yes - No - Unknown	

Table 2. Patients Background Information (part 7 of 8)

Assessment	Categories	Subcategories	Additional details
Patient Clinical Status: Data points of interest	o Attention- deficit/hyperactivity disorder (ADHD) o Learning disability o Cerebral palsy o Mental retardation o Hypertension o G-tube or nasogastric tube o Menstrual cycle disorder o Other developmental disabilities o Cancer Diagnosis	- Yes - No - Not available	- Table by last known ASM (by Visit) - Listing - Population used: All patients who attended baseline visit
	o Use of gastrostomy or nasogastric tube for nitrogen scavenging agent administration o Use his/her gastrostomy or nasogastric tube for food administration o Use of gastrostomy or nasogastric tube for administration of dietary supplements o Vomiting upon or after taking NSA o Body odor o Gastrointestinal o Nausea upon or after taking nitrogen scavenging agent o Refusal to eat due to taste or smell of nitrogen scavenging agent o Decreased appetite o Recurrent abdominal pain o Burning sensation in mouth or throat o Irritability/agitation/excessive crying o Heartburn o Neurological o Lethargy or sleepiness o Chronic or recurrent headache	- No - Rarely, once a month - Sometimes, almost once a week - Frequently, 2-3 times a week - Always, almost daily - Not Available	
	o NSA Type at the time of assessment	- Buphenyl - Ravicti - Ammunol - Carbaglu - Other	
	o Family history of similar cancer? o Receiving any NS	- Yes - No	

Table 2. Patients Background Information (part 8 of 8)

Assessment	Categories	Subcategories	Additional details
Additional data points: Plasma and Urine PK (Patients on sodium phenylbutyrate or glycerol phenylbutyrate)	o Blood sample collected, n (%) o Urine sample collected, n (%)	- Yes - No - Missing	- Table by last known ASM by visit - Listing - Population used: All patients who attended baseline visit
	o Plasma PAA result o Plasma PAGN result o Urine PAGN result	- Continuous variable	
Additional data points: Actual Dietary Intake	o Number of patients on actual diet	- Yes - No - Missing	
	o Actual dietary protein (per kg of body weight) o Total actual dietary protein (per day) o Actual calorie intake (per kg of body weight) o Total actual calorie intake (per day) o Number of days the diet was collected	- Continuous variable	

9.10 **Effectiveness**

For reporting purposes, the following study outcomes variables in section 2.2 in the protocol will be summarized (using the default summary statistics for continuous and categorical variables as described in Section 9, unless otherwise specified), and listed using All Patients who Attended a Baseline Visit analysis set:

a) Growth and Development Outcomes (pediatric patients)
b) Neurocognitive Outcomes (Adaptive Behavior Assessment System, second edition (ABAS-II) and The Behavior Rating Inventory of Executive Function for Adults (BRIEF-A) and for Pediatrics (BRIEF-P)

Notes:

- The two sided 90% CI for the mean raw and T Scores in the Brief summary tables will be computed using Proc means.
- The 95% CI in the BAS and the 90% CI in the Brief listings will not be derived (computed) and the value displayed are the ones collected via the electronic Data Capture System.

See table 3 below for details.

Table 3. Effectiveness part 1 of 3

Outcome	Categories	Subcategories	Additional details
Growth and Development Outcomes (pediatric patients)	○ Number of patients with Growth and Development assessments to report, n (%)	- Continuous variable	- Table by last known ASM (by Visit) - Table Change from Baseline in Growth and development by ASM. - Listing - Population used: All patients who attended baseline visit
	○ Age ≤ 2 years old (Infancy) ○ Age > 2 to ≤ 12 years old (Childhood) ○ Age > 12 to ≤ 21 years old (Adolescence)	- Girls - Boys	
	○ Weight for High Z Score (All) ○ Weight for High Z Score by Gender ○ Weight for length (All) ○ Weight for length Z Score by Gender ○ Length for-age z-score ○ Length for age Z Score by Gender ○ BMI [kg/m2]) for Age Z-Scores (All) ○ BMI [kg/m2]) for Age Z-Scores by Gender		- Table by last known ASM (by Visit) for the change from baseline in Growth and development Note: weight and age for length only for Infancy subjects - Listing - Population used: All patients who attended baseline visit
Neurocognitive Outcomes: ABAS – admin / intro report	○ Patient with any retrospective ABAS-II record, n (%)	- Yes - No - Missing	- Adaptive Behavior Assessment System, second edition (ABAS-II) Part I - Retrospective values - Population used: All patients who attended baseline visit
	○ ABAS II Type, n (%)	- Parent/Primary Caregiver (Ages 0-5) - Parent (Ages 5-21) - Adult (Ages 16-89)	- This is an intro table using ASM at baseline for all patients - Population used: All patients who attended baseline visit
	○ Adult Rater Type, n (%)	- Rater-Self - Rater-Other	
	○ ABAS-II submission options, n (%)	- Completed at the site and the site returned questionnaires - Completed off site and returned the questionnaires to the site - Completed off site and returned the questionnaire to UBC	
	○ Language the questionnaires was collected, n (%)	- English - Spanish	

Table 3. Effectiveness part 2 of 3

Outcome	Categories	Subcategories	Additional details
ABAS Scores Parent/Primary Caregiver (Ages 0-5)	○ Patient with any retrospective ABAS-II record, n (%)	- Yes - No - Missing	- Table by ASM at baseline (retrospective) - Table by last known ASM (by visit) Which also will include the admin /intro table for each visit (two reports by age group) - Listing by form type Parent/Primary Caregiver (Ages 0-5) Parent (Ages 5-21) Adult (Ages 16-89) - Population used: All patients who attended baseline visit
	○ ABAS-II submission options, n (%)	- Completed at the site and the site returned questionnaires - Completed off site and returned the questionnaires to the site - Completed off site and returned the questionnaire to UBC	
	○ Language the questionnaires was collected, n (%)	- English - Spanish	
	○ Sum of Scale Scores - Composite, mean (SD) ○ Composite Scores, mean (SD) ○ Composite Scores, SEM	- General Adaptive composite - Conceptual Domain - Social Domain - Practical Domain	
	○ Raw Score to Scaled Score Conversions ○ Skill Area - Scaled Scores, mean (SD)	- Communication (Com) - Community Use (CU) - Functional Academics (FA) - Home Living (HL) - Health and Safety (HS) - Leisure (LS) - Self-Care (SC) - Self-Direction (SD) - Social (Soc) - Motor (MO)	
ABAS Scores Parent (Ages 5-21) and Adult (Ages 16-89)	Same as for Patients using the Parent/Primary Caregiver (Ages 0-5) form (above)	- Add Work (WK) to Raw Score to Scaled Score Conversions And Skill Area - Scaled Scores, mean (SD)	
For all groups	○ In addition to all categories and subcategories for the ABAS – admin / intro report the following will be added: Raw Scores, Scaled Scores and Motor	- General Adaptive composite - Skill Area and each particular domain under it	- Change from Baseline in Adaptive Behavior Assessment System, second edition (ABAS-II) for each form type - Population used: All patients who attended baseline visit

Table 3. Effectiveness part 3 of 3

Outcome	Categories	Subcategories	Additional details
Neurocognitive Outcomes: Adults (BRIEF-A)	○ Patient with any retrospective BRIEF-A® record, n (%)	- Yes - No - Missing	- Table by ASM at baseline (retrospective) - Table by last known ASM (by visit) Note: descriptive statistics will include n (%), mean, SD and 90% CI as captured in the eCRF - Listing - Population used: All patients who attended baseline visit
	○ Summary Table completed by, n (%)	- Parent - Teacher	
	○ BRIEF-A® Test submission options, n (%)	- Completed at the site and the site returned questionnaires - Completed off site and returned the questionnaires to the site - Completed off site and returned the questionnaire to UBC	
	○ Raw Score ○ T Score	- Emotional Control (EC) - Self-Monitor - Behavioral Regulation Index (BRI) - Initiate - Working Memory (WM) - Plan/Organize (PO) - Task Monitor - Organization of Materials - Metacognition Index (MI) - Global Executive Composite (GEC) (BRI + MI)	
	○ The following domain by visit: Inhibit, Shift, Self Monitor, Behavioral Regulation Index (BRI), Initiate, Working Memory (WM), Plan/Organize (PO), Task Monitor, Organization of Materials, Metacognition Index (MI) and Global Executive Composite (GEC) (BRI + MI)	- Continuous variable	- Change from Baseline in Behavior Rating Inventory of Executive Function Pediatrics (BRIEF-P) by Ammonia-Scavenging Medication at Baseline (Raw Scores) - Population used: All patients who attended baseline visit
Pediatrics (BRIEF-P)	○ Same as for adults using their respective categories	- Same as above	- Same as above

9.11 Safety

For reporting purposes, the following study outcomes variables in section 6.2 in the protocol will be summarized and listed using All Patients who Attended a Baseline Visit analysis set:

a) Ammonia-Scavenging Medication and Ammonia Control
   - Ammonia Levels by Ammonia-Scavenging Medication
   - Change from Baseline in Blood Ammonia Levels by Ammonia-Scavenging Medication at Baseline
   - Hyperammonemic Crisis (HAC)

b) Summary of Serious Adverse Events by Visit

c) Summary of Serious Adverse Events - PI Attestation by Visit

d) Listing of Urea Cycle Disorders (UCD) Related Hospitalizations

See table 4 below for details.

Table 4. Safety part 1 of 5

Outcome	Categories	Subcategories	Additional details
Patient Clinical Status: Vitals	o Weight (kg) o Height (cm) o Body Mass Index (BMI [kg/m^2]) o BSA(m^2)	Continuous variable	- Table by last known ASM (by visit - Population used: All patients who attended baseline visit - The Listing will include retrospective and post baseline vitals data.
Ammonia-Scavenging Medication and Ammonia Control: Ammonia Levels (umol/L)	o Blood sample collected, n (%)	- Yes - No - Unknown - Missing	- Table by ASM at baseline (retrospective values) - Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	o Patients Fasting o Patients No Fasting o Patients Fasting (unknown)	- NA for retrospective values For the by Visit report: - 0 to ≤ 0.49 ULN - ≥ 0.5 to ≤ 0.99 ULN - ≥ 1 ULN	
Ammonia-Scavenging Medication and Ammonia Control: Change from Baseline in Blood Amonia Levels by Ammonia-Scavenging Medication at Baseline	Continuous variable	Continuous variable	Change from baseline in blood ammonia levels by visit The table will be repeated for Patients Fasting Patients No Fasting Patients Fasting unknown Population used: All patients who attended baseline visit

Table 4. Safety part 2 of 5

Outcome	Categories	Subcategories	Additional details
Ammonia-Scavenging Medication and Ammonia Control: Hyperammonemic Crisis (HAC)	○ Patients with a HAC	- 0, 1, 2, 3 and 4 or more HACs	- Table by ASM at baseline (retrospective) - Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	○ Number of HAC episodes	- Continuous variable	
	○ HAC Crude Rate per 100 patients	- Continuous variable - Computed as the total of HACs divided by the total number of subject in each treatment group, multiplied by 100	
	○ Number of patients with at least one HAC ○	- by Gender - by Race - by Ethnicity - by Baseline Ammonia (umol/L) group: 0 to ≤ 0.49 ULN; ≥ 0.5 to ≤ 0.99 ULN and ≥ 1 ULN	
	○ Number of patient hospitalized	- Yes - No - Missing	
	○ Admission Ammonia Levels	- As continuous value and by result character (<, >, none and missing)	
	○ Peak Ammonia Levels	- Continuous variable	
	○ Discharge ammonia levels		
	○ Precipitation Factors	- Yes - No - Unknown	
	○ Type of Precipitation Factors	- Infection - Intercurrent illness - Change in diet (prescribed change by physician) - Non-compliance with diet - Non-compliance with UCD medication - Non-compliance with other medication - Other	

Table 4. Safety part 3 of 5

Outcome	Categories	Subcategories	Additional details
SAEs	○ Number of patients with Adverse Events, n (%)	- Yes - No	- Summary of SAE table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
	○ Outcome, n (%)	- Recovered - Not recovered - Recovered with sequelae - Fatal - Unknown	
	○ Severity, n (%)	- Grade 1 (Mild) - Grade 2 (Moderate) - Grade 3 (Severe) - Grade 4 (Life-threatening) - Grade 5 (Fatal)	
	○ Action taken, n (%)	- None - Medication withdrawn - Non-Drug Treatment - Other	
	○ Patient taking RAVICTI, n (%) ○ Patient taking sodium phenylbutyrate, n (%) ○ Patient taking sodium benzoate, n (%) ○ Taking any co-suspect medication, n (%)	- Yes - No	
	○ Dosage form, n (%)	- Tablet - Powder	
	○ Relationship to medication, n (%)	- Not Related - Possibly Related - Probably Related	
	○ SAE Criteria, n (%)	- Results in death - Is life-threatening - Requires hospitalization or prolongation of hospitalization - Results in disability/incapacity - Congenital anomaly/birth defect - Important medical event (required intervention to prevent one of the other outcomes above)	

Table 4. Safety part 4 of 5

Outcome	Categories	Subcategories	Additional details
SAEs - PI Attestation	Same as above but only the following categories post baseline o Patient taking RAVICTI, n (%) o Patient taking sodium phenylbutyrate, n (%)	Same as above	- Table by last known ASM (by visit) - Listing - Population used: All patients who attended baseline visit
SAE - Incidence Rates of Serious Adverse Events	o Serious Adverse Events, n(%)b o System Organ Class (SOC) o Preferred Term (PT)	- Number and percentage of all SAEs by treatment arm - SAE incidence rate (m) per system organ class and preferred term are computed using all new SAE cases divided by the total number of patients at risk (at each particular data cut off time). Subjects may contribute to more than one category	- Table: Summary of Incidence Rates of Serious Adverse Events by System Organ Class and preferred term.
Urea Cycle Disorders (UCD) Related Hospitalizations	o Subjid o Visit o Ammonia-Scavenging Medication at Baseline o Reason for hospitalization o Admission date o Discharge date		- Listing only - Population used: All patients who attended baseline visit
Patient Clinical Status: Chemistry Labs	o Blood sample collected, n (%)	- Yes - No - Missing	- Table by last known ASM (by visit) - Population used: All patients who attended baseline visit
	o AST o ALT o Total Proteins o Total Bilirubin o Direct Bilirubin o Albumin o Potassium o Sodium o Chloride	- Continuous variable	

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Assessment	Categories	Subcategories	Additional details
Patient Clinical Status: Hematology Labs	○ Blood sample collected, n (%)	- Yes - No - Missing	- Table by last known ASM by visit - Population used: All patients who attended baseline visit
	○ Hematocrit (HCT) ○ Hemoglobin (HGB) ○ Platelet Count (PLAT) ○ Red Blood Cell count (RBC) ○ White Blood Cell count (WBC) ○ WBC Differential ○ Neutrophils ○ Lymphocytes ○ Monocytes ○ Eosinophils ○ Basophils	- Continuous variable	

10. References

Protocol HPN-100-014. Long-Term Registry of Patients With Urea Cycle Disorders (UCDs). Version 2.0 Amendment 1. 11FEB2013

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 14.0 Reston, Virginia, USA; 2008.

WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. June 2012 B Format edition. Uppsala, Sweden; 2008.

APPENDIX 1. PARTIAL DATE CONVENTIONS

(1) Imputation of Dates

Adverse Event

If onset date is completely missing, onset date is set to the date of enrollment unless end date is before the date of enrollment, in which case the onset date is set to 28 days prior to end date.

If (year is present and month and day are missing) or (year and day are present and month is missing):

If year = year of enrollment, then set month and day to month and day of enrollment unless end date is before the date of enrollment, in which case the onset date is set to 28 days prior to end date.

If year < year of enrollment, then set month and day to December 31st.

If year > year of enrollment, then the following applies:

If year = year of first therapy switch, then set month and day to month and day of first therapy switch unless end date is before the date of therapy switch, in which case the onset date is set to 28 days prior to end date.

If there is no therapy switch, then set month and day to January 1st.

If month and year are present and day is missing:

If year=year of enrollment and if month = month of enrollment then set day to day of enrollment date unless end date is before date of enrollment, in which case the onset date is set to 28 days prior to end date.

If month < month of enrollment then set day to last day of month

If month > month of enrollment then the following applies:

If year=year of first therapy switch and if month = month of first therapy switch, then set the day to a day of therapy switch unless end date is before the date of therapy switch, in which case the onset date is set to 28 days prior to end date.

If there is no therapy switch, then set day to 1st day of month
For all other cases, set onset date to date of enrollment unless end date is before date of enrollment, in which case the onset date is set to 28 days prior to end date.
End date will not be imputed.

Therapy Switch

The following rules apply to start date.

If start date is completely missing: start date will be imputed as 60 days past enrollment date.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to the date of the first closest visit, unless another switch occurred before it. In such a case set the start date to the date of the previous visit.
If year and month are present and day is missing: set day to the date of the first closest visit, unless another switch occurred before it. In such a case set the start date to the date of the previous visit.

The following rules apply to end date.

If end date is completely missing: end date will not be imputed unless there is another therapy switch. In that case the end date is imputed as a day before that next therapy switch.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to the date of the last closest visit, unless another switch occurred. In such a case set the end date to the as a day before that next therapy switch.

If year and month are present and day is missing: set day to the date of the last closest visit, unless another switch occurred before it. In such a case set the end date to a day before that next therapy switch.
Any partial dates will be displayed in data listings without imputation of missing days and/or months.

Concomitant Medications

The following rules apply to start date.

If start date is completely missing: start date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to January 1.

If year and month are present and day is missing: set day to 1st day of month. The following rules apply to end date.

If end date is completely missing: end date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to December 31.

If year and month are present and day is missing: set day to last day of the month.
Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009). No other imputation of missing data will be performed.

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant