IND NUMBER:	073480
EudraCT NUMBER	2015-000075-27
STUDY NUMBER:	HPN-100-021
INVESTIGATIONAL DRUG:	RAVICTI® (glycerol phenylbutyrate) Oral Liquid
STUDY 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)
SPONSOR:	Horizon Therapeutics, LLC 1 Horizon Way Deerfield, IL 60015
Amendment 11:	Version 12.0 23Sep2022
Amendment 10:	Version 11.0 Administrative Change#1 22 April 2022
Amendment 10:	Version 11.0 12 November 2019
Amendment 9:	Version 10.0 28 August 2018
Amendment 8:	Version 9.0 15 June 2018
Amendment 7:	Version 8.0 31 May 2017
Amendment 6:	Version 7.0 19 January 2017
Amendment 5:	Version 6.0 27 October 2016
Amendment 4:	Version 5.0 22 June 2016
Amendment 3:	Version 4.0 23 September 2015
Amendment 2:	Version 3.0 07 August 2015
Amendment 1:	Version 2.0 17 December 2014
Initial Version:	Version 1.0 23 July 2014

PROTOCOL SIGNATURE PAGE

Protocol Number:	HPN-100-021
Version:	12.0, incorporating Amendment 11
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)

DocuSigned by:

Horizon Therapeutics, LLC

PPD

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	HPN-100-021
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Horizon Therapeutics, LLC

I have read this protocol and agree to conduct this trial in accordance with this protocol, any future amendments, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

Investigator's Signature	Date
Investigator's Printed Name	

STUDY PERSONNEL CONTACT INFORMATION

Name Title Organization Telephone E-mail	PPD
Name Title Organization Telephone Fax E-mail	PPD
Name Title Organization Telephone Fax E-mail	PPD
Name	Sponsor Contact for Emergency or Serious Adverse Event Reporting
Organization Fax E-mail	PPD

CONTACT IN THE EVENT OF AN EMERGENCY

Any death, life threatening event, or other Serious Adverse Event experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contact numbers provided above.

SUMMARY OF CHANGES

Protocol HPN-100-021

Version 11.0 (22 April 2022) to Version 12.0 (23 September 2022)

This amendment incorporates the following changes to the prior protocol:

- Synopsis: Number of Subjects, Study Rationale: Updated to: 16 subjects
- Synopsis; Sample Size and Statistical Considerations and Protocol Section 15.1: A sample size of 16 subjects rather than 18 will be enrolled. Approximately 12 subjects will complete the study
- Administrative changes on pages 1, 2, 3, 4, 33, 43, 94, 95
- Protocol Section 15.2 Interim Analysis: updated to read: There will be no formal interim analysis.
- Protocol Section 20: References; Lee 2015, corrected to Lee 2014

Version 11.0 (12 November 2019) to Version 11.0 (22 April 2022)

This amendment incorporates the following changes to the prior protocol:

- Administrative changes on pages 1, 2, 4 of this protocol document
- Section 7.1.5.1. Added the fax and email address for reporting SAE

Version 10.0 (28 August 2018) to Version 11.0 (12 November 2019)

This amendment incorporates the following changes to the prior protocol:

- Administrative changes on pages 1 and 2 of this protocol document
- Protocol Section 1, Prior studies with RAVICTI text replaced with the Benefit Risk Analysis from the EU PBRER (DL31Jan2019) section 18.2
- Protocol list of abbreviations, VHP removed
- Synopsis, Protocol Section 3.3, 5.2.2.1: Clarifies the requirement to assign the initial dose of study drug according to the disease/treatment status on entry as set out in protocol section 3.3
- Synopsis, Protocol Section 15.1: Reduces the Number of Subjects to 18
- Protocol section 15.4: Removes age range for sub-groups, these will be defined in the Statistical Analysis Plan.
- Synopsis, Protocol Section 4.1, 6, 9, 15.4, Reduces age at entry to Birth

Version 9.0 (15 June 2018) to Version 10.0 (28 August 2018)

This amendment incorporates the following changes to the prior protocol:

- Synopsis Dosage and Regimen Transition Period, Protocol Sections 3.4, 5.2.2.3, 6.1.4: Provides a visit window of 2 days from End of Initial Treatment Period (EITP) visit to assignment to the next study period in order to evaluate ammonia and amino acid results from EITP, for subjects in Treatment Arm 1
- Appendix A, Schedule of Assessments: added footnote #22 to EITP visit

Version 8.0 (31 May 2017) to Version 9.0 (15 June 2018)

This amendment incorporates the following changes to the prior protocol:

- Updated Horizon signature page in line with Horizon internal procedures
- Synopsis Study Procedures section, Protocol Sections 3.2.1, 6.1.3, 15.4.2, and Appendix A, Schedule of Assessments, updated to clarify the timing of randomisation ie. Following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1, subjects will be randomised
- Amino Acid Panel for analysis at study visits has been updated
- Treatment Success clarified to include:
  - specific timepoint (Hour 0) to assess glutamine levels
  - specific timepoint (Hour 0) to assess amino acids
  - specific Amino Acids which contribute to Treatment Success are listed: Essential amino acids and branch chain amino acids: threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine
- Study Endpoints in Protocol Synopsis, Protocol section 2.2 and Protocol section 15.3 have been revised for consistency.
- Section 15.4.2 mITT population has been updated per SAP
- Updated sponsor contact for SAE reporting
- Section 7: Updated SAE reporting process
- Section 8: corrected order of priority for blood samples
- Administrative Changes as appropriate

Version 7.0 (19 January 2017) to Version 8.0 (31 May 2017)

This amendment incorporates the following changes to the prior protocol:

- Clarifies that NaPBA powder and NaPBA granules are the same product
- Adds requirement to collect AST, ALT and total bilirubin at Unscheduled visits throughout the study when subjects experience hyperammonemia, HAC or PAA toxicity

and when PK sampling occurs at unscheduled visits due to signs and symptoms of HAC or PAA toxicity

- Corrects the prior summary of changes, protocol version 4 to protocol version 5 to include: Removal of the requirement for the subject to complete the Clinical Global Impression scale

Version 6.0 (27 October 2016) to Version 7.0 (19 January 2017)

This amendment incorporates the following changes to the prior protocol:

- Revises the inclusion criteria to allow subjects ≥ 2 months of age and older
- Updates the age range for measurement of head circumference
- Updates the age range for administration of CBCL
- Includes a recommendation for step-wise reduction of the dose of phenylbutyric acid (PBA)
- Adds stopping rule relating to adverse clinical and laboratory parameters
- Adds stopping rule relating to pregnancy
- Removes the statement in section 5.7 "The randomisation will be stratified by NaBz use at study entry"
- Adds an anticipated dropout rate and rationale for sample size calculations

Version 5.0 (22 June 2016) to Version 6.0 (27 October 2016)

This amendment incorporates the following changes to the prior protocol:

- Corrects the prior summary of changes to include removal of the inclusion criterion of weight > 15 Kg
- Clarifies that "normal" as used in the definition of Treatment Success means < the upper limit of normal (ULN)
- Adds collection of plasma and urine for pharmacokinetic (PK) assessments whenever a subject presents at the study center with hyperammonemic crisis (HAC) or potential phenylacetic acid (PAA) toxicity and as feasible when subjects present at other health care facilities
- Adds the signs and symptoms of PAA toxicity to section 1.2.1
- Revises the dose adjustment algorithm in section 3.8 to:
    - Add specificity regarding plasma ammonia > ULN when the subject is asymptomatic
    - Include the maximum daily doses of study drugs
    - Provide definitions of terms used in the algorithm

- Adds dietary protein adjustment guidelines to section 5.6 and capture of dietary changes to each relevant visit
- Corrects typographical and formatting errors

Version 4.0 (23 September 2015) to Version 5.0 (22 June 2016)

This amendment incorporates the following changes to the prior protocol:

- Changes the design for the initial dosing period from a crossover to a parallel arm
- Adds information on the EMA approval of RAVICTI
- Replaces Crossover Periods 1 and 2 with a single parallel arm Initial Treatment Period (4 weeks)
- Adds a RAVICTI only Transition Period (1 week)
- Adds a RAVICTI only Maintenance Period (8 weeks)
- Changes the duration of the Safety Extension Period to 12 weeks
- Removes the Optional Long Term Safety Extension Period
- Removes pharmacokinetic (PK) analyses for sodium benzoate (NaBz)
- Removes inclusion criterion of weight > 15 Kg
- Limits analysis of serum phenylbutyric acid (PBA), phenylacetatic acid (PAA), and (phenylacetylglutamine) PAGN, as well as, urine PAGN to the End of Initial Treatment Period (EITP) visit
- Modifies the definition of Treatment Success
- Adjusts the PBA starting dose based on disease and treatment status at study entry
- Adds a dose adjustment algorithm
- Adds a process for product complaints
- Changes the entity responsible for receiving SAE reports
- Adds the maximum daily dose of study drug to all relevant sections
- Adds a contact at 30 days post study to check for SAEs and pregnancy

Protocol Version 4 was the first version approved via the Voluntary Harmonisation Procedure. Prior changes to the protocol are not addressed in this document.

SYNOPSIS

Title of Study	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
Study Drug	RAVICTI (glycerol phenylbutyrate) Oral Liquid (RAVICTI) and sodium phenylbutyrate (NaPBA)
Study Objective	To assess the safety, tolerability, pharmacokinetics (PK) and ammonia control of RAVICTI as compared to NaPBA in UCD subjects not currently or previously chronically treated with phenylacetic acid (also referred to as phenylacetate; PAA) prodrugs.
Study Rationale	The 2013 United States (US) Food and Drug Administration (FDA) approval of RAVICTI for UCD was based on clinical studies that included crossover comparison of ammonia control in stable UCD patients during equivalent steady-state dosing of NaPBA or RAVICTI, followed by long-term RAVICTI dosing studies. However, most UCD patients enrolled in these studies were already on a stable dose of NaPBA. This study is a FDA post-marketing requirement and is designed to assess the safety, efficacy and tolerability of RAVICTI as compared to NaPBA in patients who have not been treated chronically and presently are not being treated with oral phenylbutyrates (PAA prodrugs). This clinical study, HPN-100-021, is the first controlled and randomised study of RAVICTI in sixteen UCD patients who have not been exposed chronically to phenylbutyrate derivatives.
Study Design	The study design will include: 1) Baseline Period; 2) Initial Treatment Period; 3) a RAVICTI only Transition Period 4) a RAVICTI only Maintenance Period; and 5) a RAVICTI only Safety Extension Period (Study Schematic Figure 1). 1) Baseline Period: Prior to entering the Initial Treatment Period, subjects will be randomised at a 2:1 ratio (RAVICTI to NaPBA) into one of two treatment arms: • Treatment Arm 1: RAVICTI or • Treatment Arm 2: NaPBA 2) Initial Treatment Period: Subjects will receive their assigned treatment (either RAVICTI or NaPBA) for a period of 4 weeks. Subjects should have reached and maintained a stable dose for at least 7 consecutive days by the End of the Initial Treatment Period (EITP) and will complete an 8-hour ammonia, amino acid panel (including glutamine), PK and spot urine collections.

	Subjects on NaBz entering the Baseline Period will have their NaBz treatment titrated down as their assigned study drug is titrated up to replace NaBz and continue on study drug only during the Initial Treatment Period (see section 5.2.2.2 for titration steps). During the transition from NaBz, the dose of study drug will be adjusted to maintain subjects' clinical stability. See section 3.8 for Starting dose and dose adjustment guidelines. 3) Transition Period: Subjects in Treatment Arm 1 (RAVICTI) who meet the criteria for Treatment Success (see section 6.3 for definition of Treatment Success) will proceed directly to the Maintenance Period. Subjects in Treatment Arm 1 (RAVICTI) who do NOT meet the criteria for Treatment Success will have a 1 week Transition Period for additional adjustment of RAVICTI dose and then proceed to Maintenance Period. All subjects in Treatment Arm 2 (NaPBA) will have a 1 week Transition Period for changing from NaPBA to RAVICTI. Subjects who received NaPBA in the Initial Treatment Period and achieved Treatment Success will transition to an equivalent dose of RAVICTI to begin the Transition Period. Subjects who received NaPBA in the Initial Treatment Period and did NOT achieve Treatment Success will begin the Transition Period on a RAVICTI dose that constitutes an appropriate increase in PBA based on the EITP plasma ammonia results. See the Dose Adjustment algorithm in section 3.8. All who are adequately controlled (at minimum morning/fasting ammonia within normal limits) and should remain in the study based on the Investigator's judgment at the end of the Transition Period will proceed to the Maintenance Period. During the Transition Period, the RAVICTI dose should be adjusted as necessary to achieve or maintain plasma ammonia control and clinical stability. See the Dose Adjustment Algorithm in section 3.8. 4) Maintenance Period: This is an 8 week RAVICTI only period. Subjects who received RAVICTI in the Initial Treatment Period and achieved Treatment Success will continue on the dose they were stabilized on in that period. All others will start the Maintenance Period on the dose of RAVICTI that they were on at the end of the Transition Period. During the Maintenance Period, the RAVICTI dose may be altered as necessary to maintain plasma ammonia control and clinical stability. See the Dose Adjustment Algorithm in section 3.8. 5) Safety Extension Period: Following the Maintenance Period, subjects will enter the RAVICTI Safety Extension Period for an additional 12 weeks of treatment. During the Safety Extension Period, the RAVICTI dose may be altered as necessary to maintain plasma ammonia control and clinical stability. See the Dose Adjustment Algorithm in section 3.8. Subjects who were previously receiving NaBz may resume NaBz at the investigator's discretion, provided it is at a dose less than the phenylbutyrate equivalent of the RAVICTI dose that the subject is taking. RAVICTI must be the primary agent for ammonia control. This is to allow for real-world treatment adjustments.
Study Population	Subjects eligible for this study will have a suspected or confirmed UCD diagnosis of any subtype except n-acetylglutamate synthetase (NAGS)

	deficiency. Subjects must not be treated with oral PAA prodrugs (e.g. RAVICTI, NaPBA, Pheburane, or locally compounded mixture containing PAA prodrug) at the time of enrollment or for more than 14 consecutive days during the year prior to enrollment. For patients who are on NaBz at the time of enrollment, the Investigator must determine if transition from NaBz treatment and the use of PAA prodrugs (RAVICTI or NaPBA) will benefit the patient.
Duration of Study	Approximately 25 weeks: **Baseline:** Up to 3 days prior to Randomisation **Initial Treatment Period:** 4 weeks (± 8 days) (weekly visits are ± 2 days) **Transition Period**: 1 week (± 2 days) (visits as needed for plasma ammonia and dose adjustment with one scheduled visit at the end of the period) **Maintenance Period:** 8 weeks (every 4 week visits ± 7 days/ alternating with every 4 week phone/email contacts ± 4 days) **Safety Extension Period:** 12 weeks (every 4 weeks visits ± 7 days)
Number of Subjects	16 subjects will be enrolled.
Study Procedures	Baseline assessments and procedures will be conducted after obtaining informed consent and having completed successful screening (Schedule of Assessments: Appendix A). **Baseline (3 Days):** Physical and Neurological Examinations, Medical and UCD History, Safety Laboratory Assessments (including haematology and chemistry) , Amino Acid Panel and other assessments (Schedule of Assessments: Appendix A) **Randomisation:** Following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1, subjects will be randomised to Treatment Arm 1 (N=20) or Treatment Arm 2 (N=10) as follows: • Treatment Arm 1: RAVICTI • Treatment Arm 2: NaPBA **Initial Treatment Period - First Dose Initiation and Adjustment:** Subjects will initiate dosing with either RAVICTI or NaPBA at the 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; and 3) stable on NaBz or needing additional scavenging while on NaBz treatment, requiring transition from NaBz to PBA at an equivalent dose (See section 5.2.2.2). At the discretion of the Investigator, the dose may be adjusted after initiation of therapy to achieve plasma ammonia control and clinical stability. See the Dose Adjustment Algorithm in section 3.8. During the Initial Treatment Period, patients taking NaBz at Baseline will have their

	NaBz treatment titrated down and replaced with the assigned study drug (RAVICTI or NaPBA). Please see section 5.2.2.2 for guidance regarding the transition from NaBz. Every week during the Initial Treatment Period, subjects will return to the site for a fasting (or first morning for those who cannot fast) plasma ammonia, amino acids, and safety laboratories, as well as, assessment of dosing compliance and adverse events. After any dose or diet adjustment in the Initial Treatment Period, subjects will return to the site at an appropriate interval (See the Dose Adjustment Algorithm in section 3.8.) for assessment of morning/fasting plasma ammonia and amino acids (if indicated). All dose and diet adjustments will be recorded in the source documents and eCRF. All ammonia and amino acid results will also be recorded in the source and eCRF. The Initial Treatment Period is 4 weeks ±8 days (weekly visits are ±2 days as counted from the prior scheduled visit) in duration. Subjects should be treated for at least 7 days at a stable dose, and at 100% of the dose of study drug (i.e., without NaBz for subjects taking it at baseline), before undergoing the EITP visit procedures (i.e., 8-hour plasma ammonia, amino acid panel, PK and urine sample collections) and prior to starting the next study period. There will be an optional overnight hospital stay at the EITP visit for subject/caregiver convenience and/or investigator preference for subject observation and clinical management. Alternatively; subjects may be released from the clinic after completion of all visit procedures. Subjects in Treatment Arm 2, who received NaPBA in the Initial Treatment Period, will receive their first dose of RAVICTI in the clinic and be observed for at least 2 hours prior to release. The EITP visit will suffice as the end of the Initial Treatment Period and the start of the Transition or Maintenance Period. Treatment Arm 1 subjects who achieved Treatment Success will move directly to the Maintenance Period. All others will move to the Transition Period. **Transition Period:** Subjects who received NaPBA in the Initial Treatment Period and achieved Treatment Success will transition to an equivalent dose of RAVICTI to begin the Transition Period. Subjects who received NaPBA in the Initial Treatment Period and did NOT achieve Treatment Success will begin the Transition Period on a RAVICTI dose that constitutes an appropriate change in PBA based on the EITP plasma ammonia results. Subjects in Treatment Arm 1 (RAVICTI) who do NOT meet the criteria for Treatment Success will have a 1 week Transition Period for additional adjustment of RAVICTI dose. See the Dose Adjustment algorithm in section 3.8. Subjects will visit the clinic as needed for laboratory assessments (plasma ammonia and amino acid panel, if indicated) and dose adjustments. There will be a scheduled visit at the end of the week. All who are adequately controlled (at minimum morning/fasting ammonia within normal limits) and should remain in the study based on the Investigator's judgment at the end of the Transition Period will proceed to the Maintenance Period. **Maintenance Period:** All subjects will begin the Maintenance Period on the dose of RAVICTI they were stabilized on in the prior period (Initial Treatment or Transition). Subjects will be monitored in the RAVICTI Maintenance Period for

	adequate plasma ammonia control and clinical stability. The dose or diet or both may be adjusted to achieve adequate protein intake with adequate plasma ammonia control based on individual subject protein intake requirements and clinical status consistent with a personalized medical approach given the factors that impact UCDs. Multiple parameters around which RAVICTI doses can be adjusted must be considered relevant to dose adjustment including patient's baseline nutritional needs, dietary preferences, changes in BSA, fasting (or first morning for those who cannot fast) plasma ammonia and amino acids, concurrent illness, change in concomitant medications, and other stressors that can impact UCDs. See the Dose Adjustment Algorithm in section 3.8 for guidelines on dose increments and retesting. After any dose or diet adjustment in the Maintenance Period, subjects will return to the site (or to a more convenient local laboratory) at an appropriate interval (unscheduled visit not >7 days after the adjustment) for assessment of plasma ammonia and, if indicated, amino acids panel. All dose and diet adjustments and all laboratory results will be recorded in the eCRF. **Safety Extension** 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. During the Safety Extension Period, the dose of RAVICTI and/or diet may be adjusted at the discretion of the Investigator. See the Maintenance Period immediately above for details. For subjects 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 equivalent dose of RAVICTI that the subject is taking. Please see protocol Section 5.2.2.2 for dose equivalents of RAVICTI.
Hyperammonemic Crises	**Definition of Hyperammonemic Crisis:** A HAC is defined as signs and symptoms consistent with hyperammonemia (such as frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) that are associated with high blood plasma ammonia requiring medical intervention. Episodes of HAC may be controlled through standard-of-care measures, including parenteral administration of sodium phenylacetate (NaPAA)/NaBz and/or dialysis. A complete assessment of triggering factors and presenting signs and symptoms must be performed. The history and occurrence of hyperammonemia will be recorded and captured in the database throughout the study. Plasma ammonia values at admission, peak and discharge, along with glutamine levels (if performed as part of standard of care) will be captured on the electronic case report form (eCRF). Please see protocol Section 3.10 for further details regarding the management of HAC. **Management of Subjects with Hyperammonemic Crisis** Initial Treatment, Transition, and Maintenance Periods: If a HAC is experienced when subjects are receiving study drug during the Initial Treatment Period, medical management should be instituted and the

	study drug may be continued or temporarily stopped at the discretion of the Investigator and restarted after the subject is clinically stable. Subjects may continue in the study at the discretion of the Investigator; however, the subject should be clinically stable and on a stable dose of the study drug for 7 days prior to the EITP visit assessments. Safety Extension Period: If a HAC is experienced during the Safety Extension, the study drug may be discontinued or temporarily stopped at the discretion of the Investigator and medical management should be instituted. Study drug may be restarted after the subject is clinically stable and the presence of any factors contributing to the HAC have been identified and resolved. The dose of the study drug may be adjusted as needed. Temporary discontinuation of the study drug for this purpose will not constitute a withdrawal from the study and will be captured on the appropriate CRF.
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 EITP: • Has 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 ULN • Has normal (≤ ULN) glutamine levels at time point 0 Hour • Has normal (≤ULN) essential amino acids including branched chain amino acid levels at time point 0 Hour Essential amino acids and branch chain amino acids: threonine, Phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine
Study Endpoints	**Initial Treatment Period Endpoints (RAVICTI vs. NaPBA)** The efficacy endpoints that will be evaluated at the EITP are: • Rate of Treatment Success (Primary) • Drug discontinuation due to any reason **Transition, Maintenance and Safety Extension Periods (RAVICTI only)** The efficacy endpoints that will be evaluated during the Transition, Maintenance and Safety Extension Periods are: • Control of Plasma Ammonia • Annualized rate of HAC

	The clinical outcome assessments that will be evaluated throughout the study are: • Drug preference at TPD7 (questionnaire) (Treatment Arm 2 only) • 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)/Adult Self-Report (ASR) • EQ-5D-5L health status quality of life assessment
Study Endpoints	**Safety and Tolerability Endpoints** The endpoints that will be evaluated for safety and tolerability are: • Assessment of AEs • Standard clinical laboratory tests • Amino acid panel • Rate of drug discontinuation due to AEs
Pharmacokinetic Measures	**For all subjects in the Initial Treatment Period:** • Plasma PK parameters of PBA, PAA and phenylacetylglutamine (PAGN) • Urinary excretion of PAGN For any subject upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity: • Plasma PK parameters of PBA, PAA and PAGN • Urinary excretion of PAGN
Subject Selection Criteria	**Inclusion criteria:** • Signed informed consent given by the subject or the subject's parent/legal guardian for those under 18 years of age or the age of consent by local regulation • Male and female subjects with a suspected or confirmed UCD diagnosis of any subtype, except NAGS deficiency – Suspected diagnosis is defined as having experienced a HAC or a documented high ammonia of ≥100 µmol/L (see protocol Section 3.10 for HAC definition) – Confirmed diagnosis is determined via enzymatic, biochemical, or genetic testing • Requires nitrogen-binding agents according to the judgment of the Investigator • Birth and older

	• All females of childbearing potential and all sexually active males must agree to use an acceptable method of contraception from signing the informed consent throughout the study and for 30 days after the last dose of study drug. Appropriate contraceptive methods include hormonal contraceptives (oral, injected, implanted, or transdermal), tubal ligation, intrauterine device, hysterectomy, vasectomy, or double barrier methods. Abstinence is an acceptable form of birth control, though appropriate contraception must be used if the subject becomes sexually active.
	Exclusion criteria: • Subject has received chronic treatment with an oral phenylbutyrate (RAVICTI, NaPBA, Pheburane, or other) longer than 14 days within one year prior to enrollment – Temporary use of NaPBA for acute management of a hyperammonemic crisis in the past is acceptable. • Any concomitant illness (e.g., malabsorption or clinically significant liver or bowel disease) which would preclude the subject's safe participation, as judged by the Investigator • Has undergone liver transplantation, including hepatocellular transplant • Subjects on NaBz at Baseline will be excluded if they are viewed by the Investigator as being unable to undergo NaBz transition to a PAA prodrug during the Initial Treatment Period • Known hypersensitivity to PBA or any excipients of the NaPBA/PBA formulations. • Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed at the Baseline Visit prior to the start of study drug.

Dosage and Regimen	During the Initial Treatment Period, dose equivalents must be calculated to determine proper dosage. For ease of administration, each individual dose can be rounded up to the nearest 0.1 mL for RAVICTI, small spoon (spoons supplied with the drug) for NaPBA powder/granules, and single tablet for NaPBA tablets. **Initial Treatment Period** **Initial Dose** After randomisation, subjects will initiate dosing with either RAVICTI or NaPBA at the dose that corresponds to their disease and treatment status at entry as follows: 1) presenting with 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; and 3) stable on NaBz or needing additional scavenging while on NaBz treatment, requiring transition from NaBz to PBA at an equivalent dose (see section 5.2.2.2). The maximum daily doses of RAVICTI and NaPBA as stated in the current prescribing information should not be exceeded at any point during the study. The maximum total daily doses are: • RAVICTI - 17.5 mL • NaPBA in patients weighing < 20 Kg – 600 mg/Kg • NaPBA in patients weighing ≥ 20 Kg – 13 g/m^2 Subjects taking NaBz at Baseline will have NaBz titrated down and replaced completely by study drug (either NaPBA or RAVICTI) during the Initial Treatment Period. The transition from NaBz can be in one or multiple steps at the discretion of the Investigator. See section 5.2.2.2. **Dose Adjustment** After administration of the initial dose (See section 3.3 per protocol required ml/m2/day or g/m2/day for first dose) of study drug, during the Initial Treatment Period and throughout the study, the dose of study drug (RAVICTI or NaPBA) can be adjusted at the discretion of the Investigator. Adjustments may be indicated due to poor tolerability, to accommodate tapering the NaBz dose for those on NaBz at baseline, or to achieve the desired treatment effect and plasma ammonia control. See the Dose Adjustment Algorithm in Section 3.8 for guidelines on changes and related plasma ammonia assessment intervals. Maintenance is achieved when the subject is on a stable dose for 7 consecutive days with adequate ammonia control (at minimum morning/fasting plasma ammonia < ULN at the EITP visit) in the opinion of the Investigator. All such subjects, whether they achieve protocol defined treatment success or not, may proceed to the next study period (Transition or Maintenance). Subjects who cannot tolerate RAVICTI due to AEs or any other reason in the Initial Treatment Period must be discontinued. They should complete the EITP visit, as well as, Early Termination assessments. Subjects who cannot tolerate NaPBA during the Initial Treatment Period due to AEs or

for any other reason (palatability, dose volume, etc.) may enter the Transition Period on RAVICTI after they have completed the EITP visit.

Transition Period

Treatment Arm 1 subjects who achieved treatment success should proceed directly to the Maintenance Period. All others will receive RAVICTI in the Transition Period. For subjects in Treatment Arm 1, where Ammonia or Amino Acid panel (glutamine, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) results are not available on the day of EITP visit; the investigator will contact the subject (phone/email) within 2 days, to adjust the dose of RAVICTI if necessary, and to confirm whether the subject should proceed to the Transition Period or Maintenance Period 1.

Treatment Arm 1 treatment failures will have their RAVICTI dose or diet adjusted, if indicated to achieve ammonia control. See the Dose Adjustment Algorithm in section 3.8.

Treatment Arm 2 subjects who achieved treatment success will begin RAVICTI at a dose equivalent to the NaPBA dose they were receiving at the end of the Initial Treatment Period. The following formula should be used to calculate equivalent dose:

RAVICTI dose (mL) = NaPBA tablet dose (g) x 0.86

RAVICTI dose (mL) = NaPBA powder/granulesdose (g) x 0.81

Treatment Arm 2 treatment failures will begin RAVICTI at a dose that delivers an adjusted PBA dose, if indicated to achieve ammonia control. Alternatively, they may begin RAVICTI at a dose equivalent to their NaPBA ending dose and have diet adjusted, if indicated. See the Dose Adjustment Algorithm in section 3.8.

Dose Adjustment

During the Transition Period, the dose of RAVICTI can be adjusted at the discretion of the Investigator. See the Dose Adjustment Algorithm in Section 3.8 for guidelines on changes and related plasma ammonia assessment intervals.

All subjects with adequate ammonia control (at minimum morning/fasting plasma ammonia < ULN at the ETPD7 visit), in the opinion of the Investigator, may proceed to the Maintenance Period.

Maintenance Period

Subjects will receive RAVICTI in the Maintenance Period. All subjects will continue at the dose of RAVICTI they were receiving at the end of the prior study period.

Dose Adjustment

During the Maintenance Period, the dose of RAVICTI can be adjusted at the discretion of the Investigator. See the Dose Adjustment Algorithm in

	Section 3.8 for guidelines on changes and related plasma ammonia assessment intervals. **Safety Extension** After the completion of the Maintenance Period, subjects will receive RAVICTI in the Safety Extension. All subjects will enter the Safety Extension at the dose of RAVICTI they were receiving at the end of the Maintenance Period. **Dose Adjustment** During the Transition Period, the dose of RAVICTI can be adjusted at the discretion of the Investigator. See the Dose Adjustment Algorithm in Section 3.8 for guidelines on changes and related plasma ammonia assessment intervals. For subjects who were taking NaBz at study entry, NaBz may be resumed during the Safety Extension Period at the discretion of the Investigator, provided that the dose of NaBz is never greater than the equivalent of the dose of RAVICTI that the subject is taking. Please see protocol Section 5.2.2.2 for dose equivalents of RAVICTI. **Subjects with Gastrostomy Tubes (G-Tubes) or Nasogastric Tubes (NG Tubes):** Subjects who enter the study with a G-tube or NG tube who cannot tolerate the study drug via oral administration may remain in the study and continue receiving the study drug through a G-tube or NG tube. Oral administration should be attempted on Day 1 of the Initial Treatment Period (unless the subject has swallowing difficulty). If oral administration is not successful, the reason for failure will be captured in the eCRF.

Laboratory Sample Collection	**Safety Laboratory Assessment:** The following will be collected at Baseline, at weekly visits during the Initial Treatment Period, at the EITP (end of the Initial Treatment Period/start of the Maintenance Period), at the ETPD7 visit, and at each Maintenance Period and Safety Extension Period site visit • Haematology: complete blood count (CBC) with differential and platelet count • Chemistry: sodium, potassium, calcium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, and alkaline phosphatase The following will be collected at Unscheduled visits throughout the study when subjects experience hyperammonemia, or signs and symptoms of HAC or PAA toxicity. • Chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin **Amino Acid Panel:** Every amino acid panel will include glutamine and branched chain amino acids. The required Amino acid panel will include the following essential, non-essential and branched chain amino acid tests: threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine, glutamine. As available and required when the site has validated testing and reportable results are available: citrulline, arginine and ornithine. As available when the site has validated testing and reportable results are available: aspartic acid, serine, glutamic acid, asparagine, proline, alanine, glycine, cystine, tyrosine, taurine, phosphoserine, phosphoethanolamine, alpha-aminobutyric acid, 1-methylhistidine, 3-methylhistidine, and argininosuccinate. The fasting (first morning for those who cannot fast) panel (plasma or serum per clinical site standard) will be collected at Day 1, each scheduled Initial Treatment Period visit, the EITP visit, ETPD7 visit, at each scheduled Maintenance Period and Safety Extension Period visit, and, at the Investigator's discretion, at unscheduled visits that occur due to dose or diet adjustment. At the EITP visit, eight (8)-hour amino acid panel testing will occur at the following timepoints: • Hour 0 (just before the first main meal and dose after an overnight fasting or after 4-6 hours without high calorie and protein intake: i.e., 08:00 [8:00 am]) • Hour 8 (~2-4 hours after lunch or the after second main meal: i.e. ~16:00 [4:00 pm] prior to dosing) **Plasma Ammonia:**

	The fasting (first morning for those who cannot fast) plasma ammonia sample will be collected at Day 1, each scheduled Initial Treatment Period visit, the EITP visit, ETPD7 visit, at each scheduled Maintenance Period and Safety Extension Period site visit, and at unscheduled visits that occur due to dose or diet adjustment. At the EITP visit, eight (8)-hour plasma ammonia testing will occur at the following time points: • Hour 0 (just before the first main meal and dose - after an overnight fasting or after 4-6 hours without high calorie and protein intake for those who are physically able to fast or restrict intake: i.e., 08:00 [8:00 AM]) • Hour 4 (lunch: i.e. 12:00 [12:00 PM] prior to dosing) • Hour 8 (~2-4 hours after lunch or the second main meal: i.e., ~16:00 [4:00PM] prior to dosing) **PK Blood Collection:** Eight (8)-hour PK sampling will occur at the EITP visit: • Hour 0 (just before the first main meal and dose after an overnight fasting or 4-6 hours without high calorie and protein intake: i.e. 08:00[8:00 am]) • Hour 4 (lunch: i.e., 12:00 [12:00 pm] prior to dosing) • Hour 8 (~2-4 hours after lunch or the second main meal: i.e., ~16:00 [4:00 pm] prior to dosing) The EITP visit will also be the start of the next study period. Following completion of the Hour 8 sample collection, subjects in Treatment Arm 1 will continue on RAVICTI; subjects in Treatment Arm 2 will be given their first RAVICTI dose, at the final main meal of the day and be observed for at least 1 hour. This will complete the transition to the next period. **Spot PK Blood Collection:** A single sample will be collected upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity (see section 1.2.1). **8- Hour Spot Urine Collection:** Spot urine is defined as a single aliquot of urine from a void at a particular time point. The 8-hour spot urine collection is intended to capture metabolites excreted over 8 hours from the full daily dose of the study drug. They will be collected at the EITP visit at the following time points: • Hour 0 (just before the first main meal and dose after an overnight fasting or 4-6 hours without high calorie and protein intake: i.e. 08:00 [8:00 am]) • Hour 8 (~2-4 hours after lunch or the second main meal: i.e. ~16:00 [4:00 pm] prior to dosing) **Single Sample Spot Urine Collection:**

	A single sample will be collected upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity.
Drug Compliance	Assessment of drug compliance will be made during the study based on study drug accountability records and/or by subject or parent/legal guardian interviews.
Clinical Global Impression scales (CGI)	The **Clinical Global Impression - Severity** scale (CGI-S) is a 7-point scale that requires the Investigator to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating *relative to Baseline*. The **Clinical Global Impression - Improvement** scale (CGI-I) is a 7 point scale that requires the Investigator to assess how much the subject's illness has improved or worsened *relative to a Baseline state* at the beginning of the intervention.
Health Outcome Measures	EQ-5D-5L (http://www.euroqol.org/home.html) is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L is designed for self-completion by subjects or caregivers (EuroQol 1990). The EQ-5D-5L is appropriate for and will only be completed by subjects or caregivers of subjects who are ≥ 12 years of age.
Neuropsychological Testing	**Child Behavior Checklist (CBCL)** CBCL is a questionnaire by which parents rate a child's problem behaviors and competencies. This instrument can either be self-administered or administered through an interview. It is intended for use with children aged 18 months to 18 years in the following languages: English, Czech, Spanish, Italian, German, French, and Flemish. **Adult Behavior Checklist (ABCL) or Adult Self-Report (ASR)** The ABCL is a questionnaire used to obtain information about the individual's adaptive functioning and problems. It is completed by an observer who knows the individual well, such as a spouse, partner, family member, or friend. It is intended for use with adults aged 19 to 59 years. Alternatively, the ASR is a similar questionnaire that may be completed by those subjects able to self-complete the form. The ABCL and ASR are validated in US English and will be completed only by English speaking subjects or caregivers.
Diet and Nutrition	All subjects should adhere to the low-protein diet and amino acid supplements prescribed for them by the Investigator or Dietician. The diet chosen for each individual depends on age and residual enzyme activity. Meals provided during any inpatient visits in the Initial Treatment Period will be consistent with the subject's prescribed dietary protein intake. Subjects will follow the diet throughout the study as prescribed by the Investigator or Dietician and dietary compliance and prescription changes must be recorded on the appropriate eCRFs.

	At the discretion of the Investigator, changes in dietary protein may be prescribed, as necessary, during the study, followed by plasma ammonia check at an appropriate interval. See the Dietary Protein Adjustment Guidelines in section 5.6. The diet should be stable for at least 7 days prior to the EITP visit.
Sample Size and Statistical Considerations	This is a safety, efficacy and tolerability study and no formal sample size calculation has been performed. The sample size of 16 patients was chosen considering the number of patients 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 and other reasons therefore approximately 12 subjects will complete the study. The rate of treatment success will be presented for each treatment arm with appropriate statistical tests performed. Descriptive statistics for all endpoints will be presented. Further details of statistical analysis will be provided in the Statistical Analysis Plan (SAP).
Subject Stopping Rules	Subjects meeting any of the following criteria must stop receiving treatment (either RAVICTI or NaPBA) and be withdrawn from the study: • Clinically significant allergy or hypersensitivity reactions to study drug requiring medical intervention and leading to discontinuation of RAVICTI and/or NaPBA. • Liver transplant, including hepatocellular transplant • AE of Grade 4 or greater severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or lifethreatening AE if not covered by CTCAE except for events that are objectively unrelated to drug treatment. These patients must have been followed through resolution of the AE or up to 30 days after the completion of the study, whichever came first. • Pregnancy at any time during the study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ABCL	Adult Behavior Checklist
ADE	adverse drug experience
ADL	activities of daily living
AE	adverse event
ASR	Adult Self-Report
ASS	argininosuccinate synthetase
AUC	area under the curve
$AUC_{tn\ 0\text{-}8hr}$	8-hour time normalized area under the curve
BSA	body surface area
CBCL	Child Behavior Checklist
CGI	clinical global impression
CGI-I	clinical global impression – improvement
CGI-S	clinical global impression – severity
C_{max}	maximum plasma concentration
CPS	carbamyl phosphate synthetase
CRF	case report form
CTCAE	common terminology criteria for adverse events
eCRF	electronic case report form
EDC	electronic data capture
EITP	End of Initial Treatment Period
EOS	End of Study
ET	Early Termination
ETPD7	End of Transition Period Day 7
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPB	glycerol phenylbutyrate, HPN-100 (formerly GT4P)
G-tube	gastrostomy tube
HAC	hyperammonemic crisis
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
ITP	Initial Treatment Period
IV	Intravenous
mITT	modified intent-to-treat
MP	Maintenance Period
NaBz	sodium benzoate
NAGS	n-acetylglutamate synthetase
NaPAA	sodium phenylacetate
NaPBA	sodium phenylbutyrate
NG Tube	Nasogastric Tube
OTC	ornithine transcarbamylase
PAA	phenylacetatic acid (also referred to as phenylacetate)
PAGN	phenylacetylglutamine
PBA	phenylbutyric acid (also referred to as phenylbutyrate)
PK	Pharmacokinetic
RAVICTI	RAVICTI® (glycerol phenylbutyrate) Oral Liquid
SAE	serious adverse event
SAP	statistical analysis plan
SE	Safety Extension
SOP	standard operating procedure
TP	Transition Period
U-PAGN	urinary phenylacetyl glutamine
UCD	urea cycle disorder
ULN	upper limit of normal
US	United States

1. BACKGROUND INFORMATION

1.1. Introduction and Background

Urea cycle disorders (UCDs) are inborn errors of metabolism caused by a deficiency in one of six enzymes or two mitochondrial transport proteins involved in the production of urea, resulting in accumulation of toxic levels of ammonia in the blood (hyperammonemia). UCD subtypes are summarized in Table 1 (Seminara 2010, Orphanet 2013), along with estimated prevalence in the European Union (EU) and the United States (US). These are rare diseases, and a recently estimated overall incidence in the US of 1 in 35,000 live births (Summar 2013) likely applies to Europe as well (Dionisi-Vici 2002).

Table 1: Prevalence of Urea Cycle Disorders in the EU and US

Deficiency	Abbreviation	Inheritance Pattern	Estimated Prevalence in EU	Estimated Prevalence in US
Ornithine transcarbamylase	OTC	X-linked	1 in 69,904	1:14,000
Argininosuccinate synthetase	ASS	Autosomal recessive	1 in 50,800 (mild type) 1 in 189,740 (classic)	1:57,000
Carbamoyl phosphate synthetase	CPS	Autosomal recessive	1 in 142,857	1:62,000
Argininosuccinate lyase	ASL	Autosomal recessive	1 in 146,857	1:70,000
Arginase	ARG	Autosomal recessive	1 in 363,000 to 1 in 2,349,717	1:350,000
N-acetylglutamate synthetase	NAGS	Autosomal recessive	(unknown/very rare)	(unknown/very rare)
Ornithine translocase	HHH	Autosomal recessive	Exceedingly rare[1]	(unknown/very rare)
Aspartate glutamate transporter	CITRIN	Autosomal recessive	Exceedingly rare[1]	(unknown/very rare)

[1]These are exceedingly rare UCD subtypes for which precise incidence rates are not available, because they occur much less frequently than ASL (Dionisi-Vici 2002). Source: Horizon Therapeutics data on file.

The severity and timing of UCD presentation vary according to the severity of the deficiency, which may range from minor to extreme depending on the specific enzyme or transporter deficiency, and the specific mutation in the relevant gene. UCD patients may present in the early neonatal period with a catastrophic illness, or at any point in childhood, or even adulthood, after a precipitating event such as infection, trauma, surgery, pregnancy/delivery, or change in diet (Ah Mew 2015). Acute hyperammonemic episodes at any age carry the risk of encephalopathy and resulting neurologic damage that is sometimes fatal, but even chronic, sub-critical hyperammonemia can result in impaired cognition (Gropman 2007). UCDs are therefore associated with a significant risk of neurological abnormalities and intellectual and

developmental disabilities over all ages (Tuchman 2008, Krivitzky 2009). UCD patients with neonatal-onset disease are especially likely to suffer cognitive impairment (Krivitzky 2009) and death (Summar 2008) compared with patients who present later in life.

Management of acute hyperammonemic crises (HAC) may require haemodialysis and/or intravenous (IV) administration of sodium phenylacetate (NaPAA) and sodium benzoate (NaBz). Orthotopic liver transplantation may also be considered for patients with severe disease that manifests itself in the neonatal period. Long-term UCD management is directed toward prevention of hyperammonemia and may include the following treatment options:

- Restriction of dietary protein
- Arginine and/or citrulline supplementation, which can enhance waste nitrogen excretion for certain UCDs
- Sodium benzoate
- Oral nitrogen-binding drug therapy that provides an alternate path for waste nitrogen removal including sodium phenylbutyrate (NaPBA; marketed as AMMONAPS® in the EU and as BUPHENYL® in the US).

Despite dietary and pharmacologic management, UCD patients still experience episodes of hyperammonemia, which leads to further risk of hyperammonemic encephalopathy requiring aggressive medical intervention and chronic hyperammonemia leading to cumulative neurocognitive impairment (Krivitzky 2009).

The clinical trials leading to the 2013 US approval and 2015 EMA approval of RAVICTI (glycerol phenylbutyrate) Oral Liquid (RAVICTI, formerly known as HPN-100), which involved short-term comparison of ammonia control and pharmacokinetics (PK) during equivalent dosing of NaPBA and RAVICTI (Lee 2010, Lichter-Konecki 2011, Diaz 2013, Smith 2013, Berry 2014) as well as long-term open label RAVICTI dosing (Diaz 2013, Berry 2014), have also provided new information pertaining to the utility of fasting ammonia (Lee 2014), urinary phenylacetylglutamine (U-PAGN) (Mokhtarani 2012) and the ratio of phenylacetic acid (also referred to as phenylacetate; PAA) to PAGN (phenylacetylglutamine) in plasma (Mokhtarani 2013) as dosing biomarkers.

The development program of RAVICTI involved switching patients who were already on NaPBA to RAVICTI to establish the non-inferiority of RAVICTI to NaPBA in terms of ammonia control. As a consequence, no patients who were naïve to phenylbutyric acid (PBA) were enrolled in the controlled studies. In the long-term study, a very limited number of patients were enrolled who had been diagnosed with UCD that were not on NaPBA and started receiving RAVICTI. Therefore limited data is available on patients naïve to PBA being treated with RAVICTI.

RAVICTI, a prodrug of PBA and a pre-prodrug of the active compound phenylacetatic acid (PAA), has been approved in the US and Europe for use as a nitrogen-binding agent for chronic management of adult and paediatric patients from birth with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). The limitations of use are as follows:

- RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs.
- The safety and efficacy of RAVICTI for the treatment of Nacetylglutamate synthetase (NAGS) deficiency has not been established.

The current US RAVICTI Package Insert contains the following contraindications:

- Known hypersensitivity to PBA. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

1.2. Summary of Potential Risks and Benefits

.The clinical development program of RAVICTI, which comprised four short term and three long term studies including more than 100 UCD patients in the total study population, showed significant and clinically relevant efficacy of RAVICTI. The slow gastrointestinal absorption of RAVICTI, which presumably reflects the time required for digestion of RAVICTI by pancreatic lipases, leads to sustained levels of the active metabolites PAA and PAGN and results in evenly sustained release during the day, thus providing optimal reserve capacity to bind nitrogen between doses. This is the key to improved ammonia control and reduction in hyperammonemic events in UCD patients. Among all patient subgroups, RAVICTI demonstrated similar ammonia control independent of gender, age (2-11, 12-17, ≥18 years), UCD subtype (OTC vs. non-OTC) or age at onset. These lower ammonia levels were also maintained over 12 months of dosing in both adult and pediatric studies.

Furthermore, RAVICTI significantly reduces glutamine levels, which correlate with plasma ammonia levels and symptoms in UCD patients. Its intracellular accumulation in glial cells is believed to mediate cerebral edema [Butterworth et al., 2009, Maestri et al., 1992, Tuchman et al., 2008].

Approximately 50% of the UCD population is comprised of children, where compliance with treatment and sustained disease control are essential to provide normal growth and development. RAVICTI is an odorless, nearly tasteless liquid that requires no preparation and contains no sugar. RAVICTI is a palatable alternative for children that may increase compliance in this patient population. RAVICTI is also suitable for patients with hypertension due to the absence of sodium.

The clinical data in 49 pediatric patients treated with RAVICTI up to 12 months indicates a favorable safety profile and ammonia control. The rate of documented hyperammonemic events after switching to RAVICTI showed the greatest decrease among the youngest patients, so that the rate of such crises decreased from 1.44/patient to 0.63/patient during treatment with RAVICTI. The improvement in cognitive function and in common symptoms associated with UCD was sustained and clinically meaningful in the pediatric study population treated with RAVICTI.

Due to its liquid formulation, RAVICTI can also be administered via nasogastric tube or gastrostomy tube in patients with neurological impairment due to the underlying UCD. Overall, RAVICTI was shown to be well tolerated. ADRs believed to be unique to RAVICTI, such as flatulence, abnormal skin odor, decreased appetite or diarrhea, have been transient and mild.

The incidences of AEs were similar across the population subgroups including gender, race or UCD subtype. No trend towards an increase in the incidence of any treatment associated AE under long-term exposure with RAVICTI was identified.

Furthermore, the favorable benefit-risk profile is supported by the completion of long-term studies by 90% of patients and the fact that only two (2%) patients discontinued treatment due to experiencing ADRs in these long-term studies.

The use of RAVICTI is limited to the chronic management of UCD, and is not indicated for treatment of acute hyperammonemia, which requires emergency actions, such as hemodialysis for rapid ammonia detoxification.

Of note, in the EU and US the indication for RAVICTI was extended for the pediatric population from birth based on results from the study HPN-100-009.

There is limited information in relation to chronic use in subjects with UCDs. In long-term open label safety study HPN-100-011, RAVICTI was effective in maintaining ammonia control in adult and pediatric UCD subjects for up to 24 months. In addition, long-term treatment with RAVICTI was well tolerated, and the safety profile was consistent with the experience from the 12 months of safety extension studies. The 10-year USA registry (HPN-100-014) will provide further information on long-term safety in the post authorization setting.

The clinical findings collectively suggest that the benefits of RAVICTI substantially outweigh its risks, which are adequately addressed in the labeling. Furthermore, RAVICTI offers clinically meaningful advantages for UCD patients based on its slow-release formulation and improved tolerability. The slow-release formulation of RAVICTI allows for a more evenly waste nitrogen removal throughout the day, which results in better blood ammonia control with fewer hyperammonemic events, thus significantly contributing to the improvement of the subject's quality of life.

Prior Clinical Studies with NaPBA:

NaPBA tablets and powder/granules have been approved for marketing in the US since 1996 as an adjunctive therapy in the long-term management of patients with UCDs involving deficiencies of CPS, OTC, or ASS. It is also indicated in all patients with neonatal-onset deficiency (enzyme deficiency presenting in the first 28 days of life) and in patients with late-onset disease who have a history of hyperammonemic encephalopathy. NaPBA must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. NaPBA should not be used to manage acute hyperammonemia, which is a medical emergency.

For NaPBA, the assessment of clinical AEs was derived from 206 patients treated with NaPBA over a period of 20 years by many investigators across the US. AEs (both clinical and laboratory) were not collected systematically in these patients, but were obtained from patient-visit reports by the 65 co-investigators. In female patients, the most common clinical AE reported was amenorrhea/menstrual dysfunction (occurring in 23% of the menstruating patients). Decreased appetite, body odour (probably caused by the metabolite PAA), and bad taste or taste aversion were reported in 4%, 3%, and 3% of patients, respectively. A variety of laboratory abnormalities were also reported as AEs including acidosis, alkalosis, hyperchloremia, hypophosphatemia, hypoalbuminemia, decreased total protein, increased alkaline phosphatase and increased liver transaminases, anemia, leukopenia, leukocytosis, and thrombocytopenia

1.2.1. PAA Toxicity

The major metabolite of RAVICTI and NaPBA, PAA, is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity, including somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy, were observed at plasma PAA concentrations ≥500 µg/mL in a study of cancer patients who were administered IV PAA. In this study, adverse events were reversible. Although these have not been seen in clinical trials involving UCD patients, high PAA levels should be suspected in patients with unexplained somnolence, confusion, nausea and lethargy who have normal or low ammonia.

1.3. Study Rationale

The 2013 US approval of RAVICTI for UCDs was based on clinical studies that included cross-over comparison of ammonia control in stable UCD patients during equivalent steady-state dosing of NaPBA or RAVICTI, followed by long-term RAVICTI dosing studies. Most UCD patients enrolled in these studies were already on a stable dose of NaPBA and this study, which is a Food and Drug Administration post-marketing requirement, is therefore designed to assess the safety, efficacy and tolerability of RAVICTI as compared to NaPBA in patients who have not been treated chronically and are presently not being treated with oral phenylbutyrates (PAA prodrugs). This study is also an element of the RAVICTI Risk Management Plan filed with the EMA. This clinical study, HPN-100-021, is the first controlled and randomised study of RAVICTI in UCD subjects who have not been previously exposed chronically to phenylbutyrate derivatives.

1.4. Conduct of Trial and Compliance with Good Clinical Practice

This study will be conducted in compliance with the protocol, in accordance with the International Conference on Harmonisation (ICH) E6, and according to applicable regulatory requirements.

1.5. Study Population

Subjects eligible for this study will have a suspected or confirmed UCD diagnosis of any subtype except NAGS deficiency. Subjects must not be treated with PAA prodrugs (RAVICTI, NaPBA, Pheburane, or locally compounded mixture containing PAA prodrug) at the time of enrollment or for more than 14 consecutive days during the year prior to enrollment.

For patients who are on NaBz at the time of enrollment, the Investigator must determine if transition from NaBz treatment to the use of PAA prodrugs (RAVICTI or NaPBA) will benefit the patient.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Objective

The objective of this study is to assess the safety, tolerability, PK, and ammonia control of RAVICTI as compared to NaPBA, in UCD subjects not currently or previously chronically treated with PAA prodrugs.

2.2. Endpoints

2.2.1. Efficacy

2.2.1.1. Initial Treatment Period

- Rate of Treatment Success (Primary)
  (See Section 6.3 for definition of Treatment Success)
- Drug discontinuation due to any reason

2.2.1.2. Transition, Maintenance and Safety-Extension Periods

- Annualized rate of HAC
- Control of Plasma Ammonia

2.2.2. Safety and Tolerability

- Assessment of AEs
- Standard clinical laboratory tests
- Amino acid panel
- Rate of drug discontinuation due to AEs

2.2.3. Clinical Outcome Assessments

- Palatability of study drug (Hedonic Scale)
- Drug preference at TPD7 (questionnaire) (Treatment Arm 2 only)
- 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

2.3. Pharmacokinetics

For all subjects at the EITP visit:

- Plasma PK parameters of PBA, PAA and PAGN
- Urinary excretion of PAGN

For any subject upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity:

- Plasma PK parameters of PBA, PAA and phenylacetylglutamine (PAGN)
- Urinary excretion of PAGN

3. DESIGN AND PLAN

3.1. Description

This is a randomised, controlled, open-label parallel arm study of RAVICTI compared to 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 begin by receiving 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; and 3) stable on 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 approved dose of RAVICTI is 5-12.4 g/m^2/day (US RAVICTI package insert).

The recommended dose of NaPBA per its package insert is 450-600 mg/kg/day in patients weighing <20 kg or 9.9-13 g/m^2/day in larger patients.

The study design includes a Baseline Period, Initial Treatment Period, Transition Period, Maintenance Period and a Safety Extension Period. Prior to entering the Initial Treatment Period, subjects will be randomised 2:1 to Treatment Arm 1 (N=20) or Treatment Arm 2 (N=10) as follows:

Treatment Arm 1: RAVICTI

or

Treatment Arm 2: NaPBA

See Figure 1 for a schema of the overall study design.

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.

Subjects on NaBz entering the Baseline Period will have their NaBz treatment titrated down and simultaneously replaced with the assigned study drug (RAVICTI or NaPBA).

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:

- Has 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 ULN at the End of the Initial Treatment Period
- Has normal (≤ ULN) glutamine levels at the end of the Initial Treatment Period at time point

  0 Hour

- Has normal (≤ ULN) essential amino acids including branched chain amino acid levels

  (specifically, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) at the end of the Initial Treatment Period at time point 0 Hour.

Following successful completion of the Initial Treatment Period, subjects achieving a stable phenylbutyrate dose will begin the Maintenance Period and be treated with RAVICTI for 8 weeks. Treatment Arm 1 subjects will continue at the stable dose of RAVICTI they were receiving at the end of the Initial Treatment Period. Treatment Arm 2 subjects will begin RAVICTI at a dose equivalent to the NaPBA dose they were receiving at the end of the Initial Treatment Period; RAVICTI dose (mL) = NaPBA tablet dose (g) x 0.86 or NaPBA powder/granules dose (g) x 0.81.

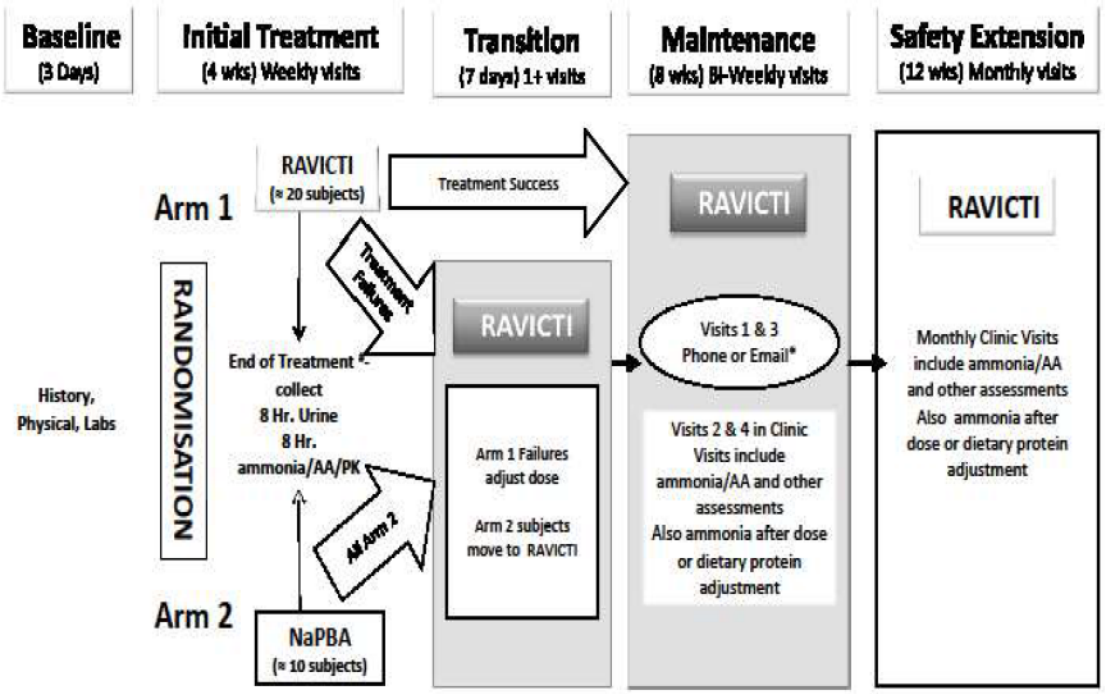
Subjects will be monitored in the RAVICTI Maintenance Period for adequate plasma ammonia control and clinical stability.

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 (MAP) in countries where RAVICTI is not commercially available.

Figure 1: Study Design: Schema



#Subjects should be on a stable dose of study drug and dietary protein prior to sample collection at the EITP visit.
*Phone/Email contact to inquire about ongoing AEs, new complaints, diet and dosing compliance.

See Protocol for important considerations regarding dosing and dose adjustments during all study periods, as well as steps to take if drug intolerance is evident.

3.2. STUDY SCHEDULE

The study schedule consists of the following:

Baseline (3 Days):

During the Baseline Period, subjects will:

- Provide informed consent
- Undergo screening procedures

3.2.1. Randomisation:

Following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1, subjects will be randomised, in an open-label fashion, to Treatment Arm 1 or Treatment Arm 2 as follows:

- Treatment Arm 1 (N=20):

  RAVICTI
- Treatment Arm 2 (N=10):

  NaPBA

3.3. Initial Treatment Period - First Dose Initiation and Adjustment:

After randomisation, subjects will receive either RAVICTI or NaPBA in the dose range corresponding to their disease/treatment status at entry:

Status at Entry	**Arm 1 – RAVICTI Starting Dose Range**	**Arm 2 – NaPBA Starting Dose Range**
Stable (ammonia < 50% ULN) after presenting with HAC acutely managed with Ammonul®/dialysis	11.2 mL/m^2/day	Subjects weighing < 20Kg – 0.6 g/kg/day All others – 13 g/m^2/day
Not adequately controlled with diet and nutritional supplements	8 ± 1 mL/m^2/day	Subjects weighing < 20Kg – 0.53 g/kg/day All others – 11.5 ± 0.5 g/m^2/day
On NaBz treatment	Gradual transition to equivalent dose (RAVICTI dose (mL) = NaBz dose (g) x 0.50 See section 5.2.2.1	Gradual transition to equivalent dose (NaPBA tablet dose (g) = NaBz dose (g) x 0.58 NaPBA powder/granules dose (g) = NaBz dose (g) x 0.63 See section 5.2.2.1

After administration of the initial dose (per protocol required ml/ m^2/day or g/ m^2/day for first dose) of study drug, at the discretion of the Investigator, the dose may be adjusted after initiation of therapy. See section 3.8 Patients taking NaBz at Baseline will have their NaBz treatment titrated down as the study drug dose is increased to achieve a complete transition from NaBz to study drug.

The Initial Treatment Period is 4 weeks (+/- 8 days) in duration. Subjects will visit weekly (+/- 2 days as counted from the prior scheduled visit) during this period. Subjects should be treated for at least 7 consecutive days at a stable dose, and at 100% of the dose of study drug (no NaBz), before undergoing 8-hour ammonia, amino acid panel, PK and spot urine sample collections at EITP prior to entering the next study period.

There will be an optional overnight hospital stay at the end of the Initial Treatment Period. Alternatively, subjects may be released from the clinic after completion of all EITP procedures.

Dose adjustments (changes in the total daily dose) in the Initial Treatment Period will be followed by repeat fasting/morning ammonia testing within an appropriate interval. See the Dose Adjustment Algorithm in section 3.8.

3.4. Transition Period:

Treatment Arm 1 (RAVICTI) subjects who meet the criteria for treatment success at the end of the Initial Treatment Period may proceed directly to the Maintenance Period. Treatment Arm 1 subjects who do not meet the criteria for treatment success 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. The Transition Period is 7 days in duration based on prior RAVICTI studies that have demonstrated this is an adequate period of time to move from NaPBA to RAVICTI and/or to stabilize on RAVICTI following a dose change. All subjects entering the Transition Period will receive RAVICTI.

- Treatment Arm 1 subjects entering Transition will have their RAVICTI dose adjusted, if indicated, by the laboratory results at the EITP visit. If in the Investigator's opinion the subject's plasma ammonia is adequately controlled (at minimum, fasting/morning was within the ULN at the EITP visit), the subject may enter Transition at the same dose of RAVICTI that he/she was receiving at the end of the Initial Treatment period.

  For subjects in Treatment Arm 1, where Ammonia or Amino Acid panel (glutamine, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) results are not available on the day of EITP visit; the investigator will contact the subject (phone/email) within 2 days, to adjust the dose of RAVICTI if necessary, and to confirm whether the subject should proceed to the Transition Period or Maintenance Period 1.

- Treatment Arm 2 (NaPBA) subjects who meet the criteria for treatment success at the end of the Initial Treatment Period will begin RAVICTI at a dose equivalent to the NaPBA dose they were receiving at the end of the Initial Treatment Period.

- Treatment Arm 2 (NaPBA) subjects who do not meet the criteria for treatment success at the end of the Initial Treatment Period will begin RAVICTI at a dose appropriately higher than the NaPBA dose they were receiving at the end of the Initial Treatment Period, if indicated. See the Dose Adjustment Algorithm in section 3.8. If in the Investigator's opinion the subject's plasma ammonia is adequately controlled (at minimum, fasting/morning was within the ULN at the EITP visit), the subject may enter Transition on RAVICTI at a dose equivalent to the NaPBA dose they were receiving at the end of the Initial Treatment Period.

All Treatment Arm 2 subjects must be observed in the clinic for at least 1 hour after their first dose of RAVICTI.

Dose adjustments (changes in the total daily dose) in the Transition Period will be followed by repeat fasting/morning ammonia testing within an appropriate interval. See the Dose Adjustment Algorithm in section 3.8. All subjects in the Transition Period will have morning/fasting plasma ammonia reassessed at an appropriate interval, not later than 7 days after entering Transition. If ammonia is adequately controlled, subjects may proceed to the Maintenance Period after 7 (± 2) days.

3.5. Maintenance Period:

After completion of the Initial Treatment Period or Transition Period, subjects will receive RAVICTI in the Maintenance Period. All subjects will continue at the dose of RAVICTI they were receiving at the end of the prior period. Subjects will alternate between phone/email and clinic visits every 2 weeks in the Maintenance Period.

Dose adjustments (changes in the total daily dose) in the Maintenance Period will be followed by repeat fasting/morning ammonia testing within an appropriate interval. See the Dose Adjustment Algorithm in section 3.8.

3.6. Safety Extension:

Following completion of Maintenance Period, subjects will receive RAVICTI in the Safety Extension for 12 weeks. All subjects will enter the Safety Extension at the dose of RAVICTI they were receiving at the end of the Maintenance Period. During the Safety Extension Period, subjects will visit every 4 weeks.

Dose adjustments in the Safety Extension Period will be followed by repeat fasting/morning ammonia testing within 3-5 days.

For subjects taking NaBz at study entry who transitioned from NaBz treatment during the Initial Treatment Period, the NaBz treatment may be resumed during the Safety Extension Period at the discretion of the Investigator, provided that the dose of NaBz is never greater than the equivalent of the dose of RAVICTI that the subject is taking. Please see protocol Section 5.2.2.2 for dose equivalents of RAVICTI.

Completion of the Safety Extension is the end of the study for all subjects. Investigators may prescribe RAVICTI for study subjects thereafter in regions where it is commercially available. Where RAVICTI is not commercially available, Investigators may apply to the MAP.

3.7. Duration of the Study

The study duration is approximately 25 weeks including:

- **Baseline Period**: Up to 3 days prior to Randomisation
- **Initial Treatment Period:** 4 weeks (± 8 days -weekly visits are ± 2 days)
- **Transition Period:** 7 days (± 2 days - All Treatment Arm 2 and Treatment Arm 1 treatment failures)
- **Maintenance Period:** 8 weeks (q 4week visits ± 7 days/ alternating with q 4 week phone/email contacts ± 4 days)
- **Safety Extension Period:** 12 weeks (q 4 week visits ± 7 days)

3.8. Dose Adjustment

Throughout the study, the dose of study drug (RAVICTI or NaPBA) can be adjusted at the discretion of the Investigator. Adjustments may be indicated due to poor tolerability, to accommodate tapering the NaBz dose for those on NaBz at baseline, or to achieve the desired treatment effect and plasma ammonia control. The Dosing Adjustment Algorithm below provides guidance on dose adjustments. Whenever dose is adjusted, morning or fasting ammonia

is to be repeated at an appropriate interval, generally within 3-5 days but as early as clinically warranted and in no case > 7 days. An amino acid panel may also be repeated at the discretion of the investigator.

Figure 2: Starting Dose Schema

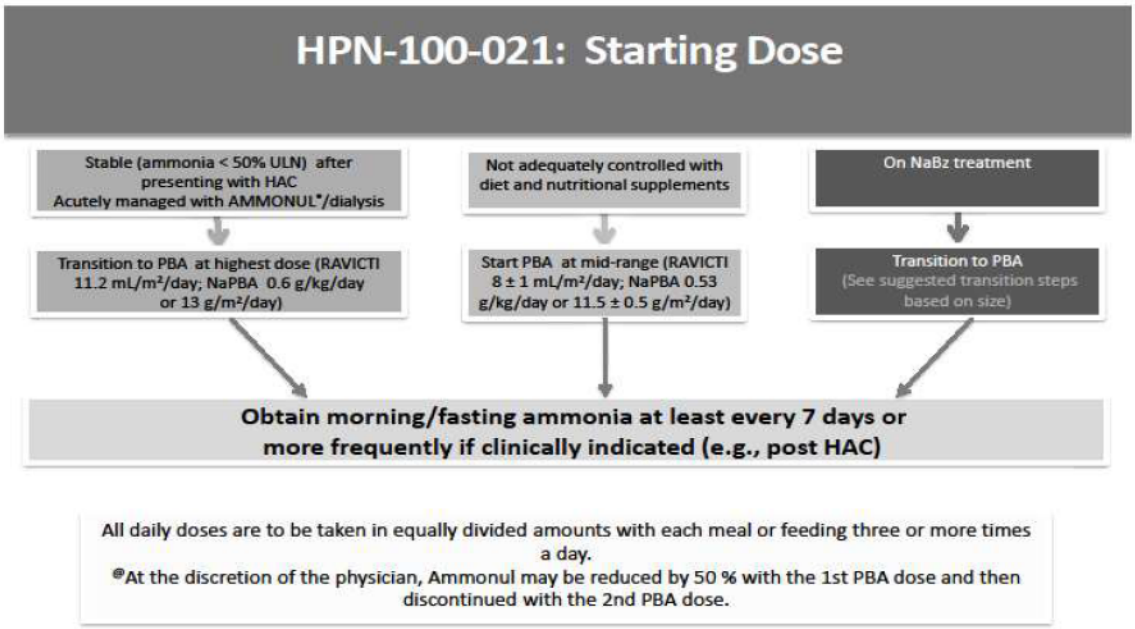


Table 2: Dose Adjustment Algorithm

<table>
<tr><th colspan="5">HPN-100-021: Dose Adjustment Algorithm</th></tr>
<tr><th>Morning/fasting ammonia < 50% ULN</th><th>Morning/fasting ammonia 50-100% ULN</th><th>Morning/fasting ammonia > ULN , asymptomatic[1]</th><th>Hyperammonemic Crisis (HAC) see section 3.10</th><th>Signs/Symptoms of PAA toxicity see section 1.2.1</th></tr>
<tr><td rowspan="4">Maintain current PBA dose</td><td rowspan="4">Increase PBA dose by 5%
Repeat morning/fasting ammonia within 7 days</td><td>If ammonia is < 110% of ULN AND < 1.5 times the most recent prior value→
Increase PBA dose by 10%
Repeat morning/fasting ammonia in 12-24 hours</td><td rowspan="4">Obtain blood and urine for PK assessments, AST,ALT, total bilirubin, if possible.
Manage with additional measures as necessary. PBA may be continued at the discretion of the investigator. Once the subject is stable[2], PBA may be maintained at the previous dose if a trigger or precipitating event for HAC has been identified and corrected. If no precipitating event has been identified, the PBA dose should be increased by 25%.</td><td rowspan="4">Obtain blood and urine for PK assessments, AST,ALT, total bilirubin,if possible.
Hold and/or reduce PBA dose by 10% and reassess.</td></tr>
<tr><td>If ammonia is < 110% of ULN AND > 1.5 times the most recent prior value→
Increase PBA dose by 15%
Repeat morning/fasting ammonia in 12-24 hours</td></tr>
<tr><td>If ammonia is >110% of ULN AND < 1.5 times the most recent prior value→
Increase PBA dose by 20%
Repeat morning/fasting ammonia in 12-24 hours</td></tr>
<tr><td>If ammonia is >110% ULN and > 1.5 times the most recent prior value→Investigate/treat for impending HAC[3] and/or instruct patient to seek hospital evaluation. Obtain blood for AST,ALT, total bilirubin, if possible</td></tr>
<tr><td colspan="5">The maximum daily doses of study medication must not be exceeded. Per section 3.8, they are: RAVICTI - 17.5 mL; NaPBA in patients weighing < 20 Kg – 600 mg/Kg; NaPBA in patients weighing ≥ 20 Kg – 13 g/m^2
Otherwise, this algorithm is intended to serve as guidance for the PI. However, adjustment of PBA dose often involves multiple factors and decisions regarding dose of PBA are ultimately at the discretion of the PI.</td></tr>
<tr><td colspan="5">See protocol section 5.6 for guidelines on dietary protein adjustment and related laboratory assessments</td></tr>
<tr><td colspan="5">PBA dose reduction: with ammonia adequately controlled and no evidence of PAA toxicity, if the investigator determines that PBA dose reduction may be in the best interest of the subject, the reason for dose change must be recorded and reductions of not > 5% should be followed by repeat morning/fasting ammonia (and amino acids if appropriate) at an appropriate interval that is no later than 7 days after the dose change</td></tr>
<tr><td colspan="5">[1] Asymptomatic means exhibiting no symptoms (physical indications) of hyperammonemia</td></tr>
</table>

[2] Stable means plasma ammonia < ULN and asymptomatic
[3] Impending HAC means confirmed rising or elevated ammonia warranting intervention to prevent HAC and close observation for symptoms of hyperammonemia

Dose adjustment may be based on the following PBA equivalents for RAVICTI and NaPBA:

- Each gram of NaPBA in tablet form contains approximately 0.880 g of PBA.
- Each gram of NaPBA in powder/granules form contains approximately 0.818 g of PBA.
- Each milliliter (mL) of RAVICTI delivers 1.1 g of GPB and 1.02g of PBA.

The maximum daily doses of RAVICTI and NaPBA as stated in the current prescribing information should not be exceeded at any point during the study. The maximum total daily doses are:

- RAVICTI - 17.5 mL
- NaPBA in patients weighing < 20 Kg – 600 mg/Kg
- NaPBA in patients weighing ≥ 20 Kg – 13 g/m2

3.8.1. Dose Adjustments

Dose adjustments must be followed by repeat fasting/morning plasma ammonia assessment within an appropriate time frame based on the reason for the adjustment. See the Dose Adjustment Algorithm in section 3.8. Amino acids may also be collected at the Investigator's discretion. These laboratory assessments will be captured as Unscheduled Visits and should occur at the study site during the Initial Treatment and Transition Periods. Thereafter, they may be done at an appropriate laboratory more conveniently located near the subject's residence.

3.9. Stopping Rules

3.9.1. Stopping Rules for Individual Subjects

Subjects meeting any of the following criteria must stop receiving treatment (either RAVICTI or NaPBA) and be withdrawn from the study:

- Clinically significant allergy or hypersensitivity reactions to study drug requiring medical intervention and leading to discontinuation of RAVICTI and/or NaPBA
- Liver transplant, including hepatocellular transplant
- AE of Grade 4 or greater severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or life-threatening AE if not covered by CTCAE except for events that are objectively unrelated to drug treatment. These patients must have been followed through resolution of the AE or up to 30 days after the completion of the study, whichever came first.
- Pregnancy at any time during the study.

3.10. Hyperammonemic Crises

A HAC is defined as signs and symptoms consistent with hyperammonemia (such as frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) which are

associated with high plasma ammonia requiring medical intervention. Episodes of HAC may be controlled through standard-of-care measures, including parenteral administration of NaPAA/NaBz and/or dialysis. A complete assessment of presenting signs and symptoms must be performed. In addition, all triggering factors of the HAC must be assessed and treated until resolution at the discretion of the Investigator. All interventions to treat HAC will be recorded on the appropriate eCRF.

The history and occurrence of hyperammonemia will be recorded and captured in the database throughout the study.

The following must be captured at a minimum:

- Precipitating factors (e.g., infection, intercurrent illness, change in diet, noncompliance with the study drug, noncompliance with other UCD medication)
- If due to noncompliance, reasons for noncompliance
- Ammonia level at hospital admission, peak and discharge
- Glutamine levels at admission, peak, and discharge (if performed as part of standard of care)
- Single samples of blood and urine should also be collected upon presentation at the study center (and as feasible at other health care facilities) for PK analysis
- AST, ALT, total bilirubin
- Signs and symptoms suggestive of hyperammonemia

3.10.1. Management of Subjects with Hyperammonemic Crisis

Initial Treatment, Transition, and Maintenance Periods:

If a HAC is experienced when subjects are receiving study drug during the Initial Treatment, Transition, or Maintenance Periods, medical management should be instituted and the study drug may be continued or temporarily stopped at the discretion of the Investigator and restarted after the subject is clinically stable. Subjects may continue in the study at the discretion of the Investigator. However, the subject must be clinically stable and should be on a stable dose of the study drug (except if on NaPBA and transitioning early) for at least 7 consecutive days before undergoing the EITP procedures (8-hour PK, amino acid panel, and ammonia).

Safety Extension Period:

If a HAC is experienced during the Safety Extension, the study drug may be discontinued or temporarily stopped at the discretion of the Investigator and standard medical management should be instituted. If stopped, study drug may be restarted after the subject is clinically stable and the presence of any factors contributing to the HAC have been identified and resolved. The dose of the study drug may be adjusted as needed. Temporary discontinuation of the study drug for this purpose will not constitute a withdrawal from the study and will be captured on the appropriate eCRF.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Subject Inclusion Criteria

Inclusion criteria are as follows:

- Signed informed consent given by the subject or the subject's parent/legal guardian for those under 18 years of age or the age of consent by local regulation
- Male and female subjects with a suspected or confirmed UCD diagnosis of any subtype, except NAGS deficiency
  - Suspected diagnosis is defined as having experienced an HAC or a documented high ammonia of ≥100 µmol/L (see Section 3.10 for HAC definition)
  - Confirmed diagnosis is determined via enzymatic, biochemical, or genetic testing
- Requires nitrogen binding agents according to the judgment of the Investigator
- Birth and older
- All females of childbearing potential and all sexually active males must agree to use an acceptable method of contraception from signing the informed consent throughout the duration of the study and for 30 days after the last dose of study drug. Appropriate contraceptive methods include hormonal contraceptives (oral, injected, implanted, or transdermal), tubal ligation, intrauterine device, hysterectomy, vasectomy, or double barrier methods. Abstinence is an acceptable form of birth control, though appropriate contraception must be used if the subject becomes sexually active.

4.2. Subject Exclusion Criteria

Exclusion criteria are as follows:

- Subject has received chronic treatment with an oral phenylbutyrate (RAVICTI, NaPBA, Pheburane, or other) longer than 14 consecutive days within one year prior to enrollment
  - Temporary use of oral PBA for acute management of a hyperammonemic crisis in the past is acceptable.
- Any concomitant illness (e.g. malabsorption or clinically significant liver or bowel disease) which would preclude the subject's safe participation, as judged by the Investigator
- Have undergone liver transplantation, including hepatocellular transplant
- Subjects on NaBz at Baseline will be excluded if they are viewed by the Investigator as being unable to undergo NaBz transition to a PAA prodrug during the Initial Treatment Period
- Known hypersensitivity to PBA or any excipients of the NaPBA/PBA formulations
- Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed at the Baseline Visit prior to the start of study drug.

4.3. Subject Withdrawal Criteria

Subjects may be withdrawn for any of the following reasons:

- Voluntary withdrawal
- Noncompliance as determined by the Investigator
- At the discretion of the Investigator, if it is in the best interest of the subject
- Having met any of the subject stopping rules (Section 3.9.1)
- If pregnancy occurs at any time during the Initial Treatment Period in a subject receiving NaPBA (Section 7.1.8)
- If lost to follow-up

Please refer to Section 6.1.8 for additional details on the study procedures in the instance of Early Termination.

4.4. Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information regarding the safety or efficacy of the study drug indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- There is a significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

5. TREATMENT OF SUBJECTS

5.1. Description of Study drug

5.1.1. RAVICTI (glycerol phenylbutyrate) Oral Liquid

RAVICTI is a clear, colorless to pale yellow oral liquid. It is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide and >65% acetonitrile.

RAVICTI is a nitrogen-binding agent. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone, the chemical name of which is benzenebutanoic acid, 1', 1' '-[1,2,3-propanetriyl] ester. It has a molecular formula of $C_{33}H_{38}O_6$ and a molecular weight of 530.67 g/mol.

RAVICTI contains no inactive ingredients.

Each milliliter (mL) of RAVICTI delivers 1.1 g of GPB and 1.02g of PBA. The density is 1.1 g/mL.

5.1.2. NaPBA (sodium phenylbutyrate) Tablet or Powder/Granules

NaPBA is a prodrug and is rapidly metabolized to PAA, the metabolically active compound that conjugates with glutamine via acetylation to form PAGN, which is excreted by the kidneys.

NaPBA is an off-white crystalline substance, which is soluble in water. NaPBA is also freely soluble in methanol and practically insoluble in acetone and diethyl ether. It is known chemically as 4-phenylbutyric acid, sodium salt. It has a molecular formula of $C_{10}H_{11}O_2Na$ and a molecular weight of 186 g/mol.

Each gram of NaPBA in tablet form contains approximately 0.880 g of PBA.

Each gram of NaPBA in powder/granules form contains approximately 0.818 g of PBA.

5.2. Study drug Dosage and Administration

5.2.1. Preparation

No special preparation is needed for RAVICTI. The dose should be drawn directly from the bottle and administered orally. It is recommended that subjects be fed immediately after dosing to ensure complete absorption of the drug.

For infants and toddlers, RAVICTI should not be added to the feeding bottle or mixed with a large amount of formula or other liquids. Due to its higher specific gravity, adding RAVICTI to formula in a bottle may cause it to settle to the bottom, thereby not allowing for adequate mixing or delivery of the full dose. If needed, the dose can be added to small amount of formula in a small syringe, nipple or other age-appropriate dosing instrument and delivered orally followed by feeding.

5.2.2. Dose and Administration

The study drugs (NaPBA and RAVICTI) will be administered orally three or more times daily with meals.

Subjects will be randomly assigned in a 2:1 (RAVICTI N=20; NaPBA N=10) ratio to one of two treatment arms and will receive the assigned treatment for approximately 28 days in the Initial Treatment Period.

Treatment Arm	Initial Treatment Period (approximately 28 days)	Transition Period (7 days)	Maintenance Period (approximately 8 weeks)	Safety-Extension (12 weeks)
1	RAVICTI	RAVICTI	RAVICTI	RAVICTI
2	NaPBA	RAVICTI	RAVICTI	RAVICTI

In Treatment Arm 2, whether tablet or powder/granules form of NaPBA is used will be at the Investigator's discretion.

5.2.2.1. Initial Treatment Period

Initial Dose

After randomisation, subjects will receive either RAVICTI or NaPBA in the dose range corresponding to their disease/treatment status at entry:

Status at Entry	Arm 1 – RAVICTI Starting Dose Range	Arm 2 – NaPBA Starting Dose Range
Stable (ammonia < 50% ULN) after presenting with HAC acutely managed with Ammonul®/dialysis	11.2 mL/m^2/day	Subjects weighing < 20Kg – 0.6 g/kg/day All others – 13 g/m^2/day
Not adequately controlled with diet and nutritional supplements	8 ± 1 mL/m^2/day	Subjects weighing < 20Kg – 0.53 g/kg/day All others – 11.5 ± 0.5 g/m^2/day
On NaBz treatment	Gradual transition to equivalent dose (RAVICTI dose (mL) = NaBz dose (g) x 0.50 See below	Gradual transition to equivalent dose (NaPBA tablet dose (g) = NaBz dose (g) x 0.58 NaPBA powder/granules dose (g) = NaBz dose (g) x 0.63 See below

After administration of the initial dose (per protocol required ml/ m^2/day or g/ m^2/day for first dose) of study drug, the investigator can adjust the dose.

For ease of administration, the individual dose can be rounded up to the nearest 0.1 mL for RAVICTI. Each Individual dose can be rounded up to the nearest small spoon (spoons supplied with the drug) for NaPBA powder/granules, and to the nearest tablet for NaPBA tablet. Subjects will be observed for at least 1 hour in the clinic after the initial dose of study drug.

5.2.2.2. Titrating NaBz

Subjects taking NaBz at Baseline will have their NaBz treatment titrated down and replaced completely by study drug (either NaPBA or RAVICTI) during the Initial Treatment Period.

Assuming 70% conversion of RAVICTI to PBA and excretion of 2 moles of nitrogen in the form of PAGN per each mole of PBA delivered (compared to 70% conversion of NaBz to urinary hippuric acid scavenging 1 mole of nitrogen per mole of hippuric acid delivered as benzoate), 0.5 mL of RAVICTI should replace 1 gram of NaBz. The following dose equivalents of RAVICTI and NaPBA should be considered when transitioning subjects from NaBz:

- RAVICTI dose (mL) = NaBz dose (g) x 0.50
- NaPBA tablet dose (g) = NaBz dose (g) x 0.58
- NaPBA powder/granules dose (g) = NaBz dose (g) x 0.63

A gradual transition from NaBz to PBA is suggested as follows:

- Based on the dose equivalents above, calculate the target daily PBA dose based on the current NaBz dose.
- Day 1 – 75% current NaBz dose and 25% target PBA dose
- Day 2 - 50% current NaBz dose and 50% target PBA dose
- Day 3 - 25% current NaBz dose and 75% target PBA dose
- Day 4 - 25% current NaBz dose and 100% target PBA dose
- Day 5 and ongoing -0 % current NaBz dose and 100% target PBA dose

Throughout the transition, check plasma ammonia and amino acid panel as needed. Record all transition steps and laboratory results in the source and eCRF.

Dose Adjustment in the Initial Treatment Period

During the Initial Treatment Period, the dose of study drug (RAVICTI or NaPBA) can be adjusted at the discretion of the Investigator. Adjustments may be indicated due to poor tolerability, to accommodate tapering the NaBz dose for those on NaBz at baseline, or to achieve the desired treatment effect and plasma ammonia control. Dose adjustments will be individualized at the discretion of the Investigator and according to the needs of each subject and accounting for the subject's expected level of growth and development, BSA, and ammonia control. If the subject's weight/BSA and/or metabolic needs increase, the study drug dose may be increased accordingly. No reduction in dose below the equivalent of 5 grams/m^2/day of PBA is recommended; however it can be done if it is considered absolutely necessary by an Investigator. All dose adjustments will be followed by a repeat fasting/morning plasma ammonia

at an appropriate interval and no more than 7 days following the adjustment. All dose and diet adjustments will be captured in the eCRF. See the Dose Adjustment Algorithm in section 3.8.

Subjects in Treatment Arm 1 who cannot tolerate RAVICTI due to AEs or any other reason in the Initial Treatment Period must be discontinued (complete early termination visit). The 8-hour ammonia, amino acid panel, PK, and spot urine collections should be completed if possible. Subjects in Treatment Arm 2 who cannot tolerate NaPBA during the Initial Treatment Period due to AEs or for any other reason (palatability, dose volume, etc.) may enter the Transition Period on RAVICTI after they have completed the 8-hour ammonia, amino acid panel, PK and spot urine sample collections at the EITP visit.

Subjects who cannot achieve 7 consecutive days at a stable dose of RAVICTI or NaPBA (without NaBz) should complete the EITP visit. At the Investigator's discretion, these subjects may proceed to the Transition Period.

5.2.2.3. Transition Period

Subjects in Treatment Arm 1 who were treatment successes at the EITP visit, should proceed to the Maintenance Period. Subjects in Treatment Arm 1 who were treatment failures at the EITP Visit may proceed to the Transition Period to optimize dose based on the Dose Adjustment Algorithm. For subjects in Treatment Arm 1, where Ammonia or Amino Acid panel (glutamine, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) results are not available on the day of EITP visit; the investigator will contact the subject (phone/email) within 2 days, to adjust the dose of RAVICTI if necessary, and to confirm whether the subject should proceed to the Transition Period or Maintenance Period 1.

All Treatment Arm 2 subjects should enter the Transition Period. Those who were treatment successes should receive the dose of RAVICTI equivalent to their NaPBA dose at the end of the Initial Treatment Period. Those who were treatment failures should receive a RAVICTI dose corresponding to an appropriate change in PBA. See the Dose Adjustment Algorithm in Section 3.8. The following formula should be used to calculate equivalent dose:

- RAVICTI dose (mL) = NaPBA tablet dose (g) x 0.86
- RAVICTI dose (mL) = NaPBA powder/granules dose (g) x 0.81

For ease of administration, the individual dose can be rounded up to the nearest 0.1 mL for RAVICTI.

5.2.2.4. Maintenance Period

At the end of the Initial Treatment Period or the Transition Period subjects will continue on the same dose of RAVICTI.

The dose of RAVICTI may be adjusted during the Maintenance Period at the discretion of the Investigator. See the Dose Adjustment Algorithm in section 3.8. After any dose or diet adjustment in the Maintenance Period, subjects will return to the site (or a local laboratory) at an appropriate interval (unscheduled visit) for assessment of plasma ammonia and amino acids (if indicated). All dose and diet adjustments will be recorded in the eCRF.

5.2.2.5. Safety Extension Period

Following completion of the Maintenance Period, subjects will receive RAVICTI in the Safety Extension at the same dose they received at the end of the Maintenance Period.

During the Safety Extension Period, the dose of RAVICTI can be adjusted at the discretion of the Investigator. See the Dose Adjustment Algorithm in section 3.8.

After any dose or diet adjustment in the Safety Extension Period, subjects will return to the site (or a local laboratory) at an appropriate interval (unscheduled visit) for assessment of plasma ammonia and amino acids (if indicated). All dose and diet adjustments will be recorded in the eCRF.

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 equivalent dose of RAVICTI that the subject is taking. Please see protocol Section 5.2.2.2 for dose equivalents of RAVICTI.

Subjects with Gastrostomy Tubes (G-Tubes) or Nasogastric Tubes (NG Tubes):

While it is highly recommended that RAVICTI be administered orally, a G-tube or NG-tube may be used for RAVICTI or NaPBA administration for subjects unable to tolerate oral dosing. RAVICTI administered through a G-tube or NG-tube should be followed by one or two small flushes each of at least 10 mL of water or formula, administered through the same port as RAVICTI, as detailed in the Study Pharmacy Manual.

A G-tube or NG-tube should only be used if the individual dose of RAVICTI is > 0.5 mL. The individual dose of RAVICTI should be rounded up to the nearest 0.1 mL, for ease of administration.

Subjects who enter the study with a G-tube or NG-tube who cannot tolerate the study drug via oral administration may remain in the study and continue receiving the study drug through a G-tube or NG-tube. Oral administration should be attempted on Day 1 of the Initial Treatment Period (unless the subject has known swallowing difficulty). If oral administration is not successful, the reason for failure will be captured in the eCRF.

5.3. Study Drug Materials and Management

5.3.1. Study Drug Packaging and Labeling

NaPBA tablets will be supplied in 250 cc bottles containing 250 NaPBA tablets. The bottles are equipped with child-resistant caps. Each tablet is off-white, oval, embossed with "UCY 500" and contains 500 mg of NaPBA. Doses in tablet form should be rounded up to the full tablet.

NaPBA powder/granules will be supplied in 500 cc bottles, with 266 g of powder/granules, containing 250 g of NaPBA. The bottles are equipped with child-resistant caps.

RAVICTI will be supplied in 1 ounce glass bottles with child resistant screw caps. Disposable oral syringes will be provided for measuring and administering RAVICTI.

Bottles will be labeled with study identification information and other pertinent information (contents, storage information, regulatory text, etc.) as necessary.

5.3.2. Study Drug Storage

The storage conditions for NaPBA tablets and powder/granules are 15° – 30°C (59° – 86°F).

RAVICTI storage conditions are 20° – 25°C [68° – 77°F] with excursions permitted to 15° – 30°C (59° – 86°F). After opening, keep the bottle tightly closed after each use.

5.3.3. Study Drug Accountability

The Sponsor or designee will supply RAVICTI and NaPBA for this study. These medications will be dispensed to the Investigator or designee at each site. The site will maintain the following records: receipt of shipments, dispensing to subjects, and return of empty, partially used, and unopened bottles, conditions of storage. Study medication should not be returned to the Sponsor or designee before the study monitor has checked the drug accountability records with the site personnel. These records will be made available to study monitor for the purpose of accounting for RAVICTI and NaPBA.

Study drug will be assigned and dispensed per the Study Pharmacy Manual and Schedule of Assessments (Appendix A: Schedule of Assessments). Subjects will return any empty bottles and/or unused or partially used study drug at each visit and at Early Termination or End of Study.

5.3.4. Study Drug Handling and Disposal

At the completion of the study, all unused study medication, including partially used and unopened bottles, will be returned to the Sponsor's designee or disposed of at the site as applicable (see Study Pharmacy Manual for complete instructions). Subjects are not allowed to dispose of any study drug containers (empty or full) and must return empty or partially used bottles to the study clinic.

Please reference the Study Pharmacy Manual for more detailed information on study drug packaging, labeling, and storage.

5.4. Treatment Compliance

Assessment of drug compliance will be made during the study based on study drug accountability records and/or by subject or parent/legal guardian interviews.

5.5. Concomitant Medications

Medications used at the time of study initiation may be continued at the discretion of the Investigator.

The use of corticosteroids, valproic acid, or haloperidol may increase plasma ammonia levels. Therefore, ammonia levels should be monitored closely, as deemed appropriate by the Investigator, if the subject is on one of these medications.

Probenecid may inhibit the renal excretion of metabolites of RAVICTI, including PAGN and PAA, and therefore this factor should be considered when assessing PK results.

Information about administered medications at Baseline and during the study will be collected on source documents and the appropriate CRFs. All concomitant medications used for any duration to treat an AE will be collected on source documents and the appropriate eCRFs. The

information to be collected on concomitant medications includes name of drug, indication, start date and stop date. The following guidelines are applied to the types of concomitant medications recorded on the CRF.

- All administered concomitant medications and their indication for use including any treatment for an AE will be collected.
- Information on dietary supplements prescribed to treat or manage UCD (such as amino acid and protein formula) will not be collected on the concomitant medications CRF. These will be recorded on a separate CRF page that will capture the total daily dose of such supplements.
- Vitamins or minerals used prophylactically or for "general health", IV fluids; fat emulsions and vaccines will not be collected unless they are used to treat an episode of acute hyperammonemia. Vitamins or minerals used to treat known deficiencies, such as vitamin D deficiency or iron deficiency, should be recorded on the concomitant medications CRF.

5.6. Nutrition

All subjects should adhere to the low-protein diet and amino acid supplements prescribed for them by the Investigator or Dietician. The diet chosen for each individual depends on age and residual enzyme activity.

Meals provided during any inpatient visits will be consistent with the subject's prescribed dietary protein intake.

Subjects will follow the diet throughout the study as prescribed by the Investigator or Dietician and dietary compliance must be recorded on the appropriate CRF.

At the discretion of the Investigator, changes in dietary protein may be prescribed, as necessary, during the study. However, the diet should remain unchanged for at least 7 days prior to the EITP visit.

Table 3: Dietary Protein Guidelines

HPN-100-021: Dietary Protein Adjustment Guidelines	
Dietary Protein Increases	**Dietary Protein Decreases**
Dietary protein (g/Kg body weight) may be increased at the discretion of the investigator during the trial. Any single increment should not exceed 10% of the current prescription unless the investigator's judgment indicates otherwise. The baseline protein prescription and any changes to the prescription as well as the reason or combination of reasons must be recorded in the source document and eCRF throughout the trial.	Dietary protein (g/Kg body weight) may be decreased and/or protein may be temporarily withheld at the discretion of the investigator during the trial. Any single increment should not exceed 10% of the current prescription unless the investigator's judgment or clinical picture (i.e., HAC) indicates otherwise. The baseline protein prescription and any changes to the prescription as well as the reason or combination of reasons must be recorded in the source document and eCRF throughout the trial.
Reasons for increasing dietary protein include: Inadequate growth/growth rate	Reasons for decreasing or withholding dietary protein include:

Intercurrent illness/trauma/or other physical event – (specific details to be captured in the source and eCRF) Subject's dietary preference Laboratory parameter – (specific details to be captured in the source and eCRF) Change in physical activity-(specific details to be captured in the source and eCRF) Other – Investigator discretion (specific details to be captured in the source and eCRF)	Elevated or rising plasma ammonia or glutamine Signs and symptoms of HAC Inadequate nitrogen scavenging at maximum dose of assigned PBA Intercurrent illness/trauma/or other physical event – (specific details to be captured in the source and eCRF) Change in physical activity (specific details to be captured in the source and eCRF) Other – Investigator discretion (specific details to be captured in the source and eCRF)
After any change in dietary protein prescription, morning/fasting plasma ammonia and any other clinically relevant laboratory assessments must be repeated in an appropriate interval not > 7 days after the date of the change.	

5.7. Randomisation and Blinding

This is a randomised, open-label study. After study eligibility is confirmed, subjects will be randomly assigned on a 2:1 (RAVICTI N=20: NaPBA N=10) ratio to one of the following Treatment Arms for the Initial Treatment Period:

Treatment Arm 1: RAVICTI

or

Treatment Arm 2: NaPBA

6. STUDY PROCEDURES

The schedule of assessments for subjects is provided in Appendix A-Schedule of Assessments.

6.1. Study Visits

6.1.1. Screening Assessments (Performed within 30 days of Baseline)

Subjects will be screened for the study and will complete the following procedures:

- Provide written informed consent either from the subject or the subject's parent/legal guardian, as appropriate
- Assessment by the Investigator that they have met the inclusion/exclusion criteria

6.1.2. Baseline (Day -3 to -1)

The following procedures should be completed at Baseline:

- Perform physical and neurological exam
- Record medical and UCD history

  UCD history includes the following information which may be recorded within 2 weeks of study entry, if necessary:

  - UCD subtype, if established
  - Date and method of UCD diagnosis, including newborn screening and prenatal diagnosis
  - Family history of UCD
  - Ammonia values for all HAC in the preceding 12 months or, depending on age, for as long as available up to 12 months. For each HAC, the peak ammonia level will be collected. Additional data, such as presenting symptoms, triggering factors, and glutamine levels (if available) will be collected for all historical HAC.
  - All episodes of hospitalizations due to UCD in the 12 months prior to enrollment, including reasons for hospitalization, ammonia levels (if available), and dates of admission and discharge
  - Medication(s) and dietary supplements (including arginine and citrulline) used for management of UCD
  - Insertion, removal and/or use of G-tube or NG-tube along with dates and reasons for their use for the 12 months prior to enrollment
  - Family history of neoplasm and malignancy
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Measure height, weight and calculate BSA using the following equation:

  BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)½

  - Measure head circumference (Birth -10 years of age only)

- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Perform urine pregnancy test for female subjects with childbearing capability
- Record concomitant medications
- Record AEs that occurred after signing the Informed Consent
- Perform CBCL (for subjects 18months to 18 years of age) or ABCL/ASR (for subjects 19 to 65 years of age)
- Record insertion, removal and/or use of G or NG tube
- Evaluate CGI–Severity (Investigator)
- Administer and collect EQ-5D-5L (for ≥ 12 years of age)

NOTE: Baseline Period may last up to 3 days to complete all of the required assessments

6.1.3. Initial Treatment Period

Following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1 subject will complete:

- Randomisation to one of two treatment arms:

  Treatment Arm 1:
  RAVICTI in the Initial Treatment Period (approximately 28 days)

  or

  Treatment Arm 2:
  NaPBA in the Initial Treatment Period (approximately 28 days)

6.1.3.1. Day 1

The following procedures should be completed at Day 1:

- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect single blood sample for fasting (or first morning for those who cannot fast) ammonia level assessment and amino acid panel prior to first dose
- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the subject's compliance with the diet prescribed prior to study entry
- Record the reason for any change to the prescribed diet
- Dispense study drug according to the randomised assignment. Study drug dose should be calculated as described in section 3.8 based on the subject's status at study entry
  - During the Initial Treatment Period, the dose of study drug (RAVICTI or NaPBA) can be adjusted at the discretion of the Investigator. See the Dose Adjustment

Algorithm in section 3.8 for recommendations on dose change increments and follow-up assessment

- No reduction in dose below the equivalent of 5 grams of PBA/m^2 is recommended; however this can be undertaken if it is considered absolutely necessary by the Investigator.
- The total daily dose of study drug should not exceed the limits stated in the current prescribing information (see section 3.8)

- Initiate First Dose in the Initial Treatment Period (with a meal)
  - Subjects will be observed in the clinic for a minimum of 1 hour following the first dose of study drug administered in the Initial Treatment Period
- Record concomitant medications
- Record AEs

6.1.3.2. Days 2-6

After release from the clinic on Day 1, subjects are not scheduled to return to the clinic until the ITP 1 visit (approximately day 7). During Days 2-6, laboratory results from Baseline and/or Day 1 visits are to be evaluated as they become available. Dose adjustments, based on laboratory results, can be made as necessary on an outpatient basis during this period. However, unscheduled visits may occur as necessary for proper follow up during Days 2-6 at the discretion of the Investigator.

6.1.3.3. Initial Treatment Period Visits 1, 2, and 3 (Weekly)

Subjects will report to the study unit in the morning at ITP 1, 2, and 3 visits (weekly +/- 2 days) and undergo the required study assessments and procedures as noted below:

- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Physical and Neurological Exam
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Collect blood samples for fasting/morning amino acid panel and plasma ammonia prior to dosing
- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed
- Record insertion, removal and/or use of G or NG-tube along
- Record concomitant medications
- Record AEs
- Collect all unused study drug and empty bottles
- Assess study drug compliance

- Record any changes to prescribed study drug dose and the reason for change
- Dispense study drug

6.1.4. End of Initial Treatment Period (EITP - last day of the Initial Treatment Period/Start of the Transition or Maintenance Period – optional overnight stay)

Subjects will visit the study unit in the morning at the EITP visit (approximately Day 28 ± 8 days) and undergo 8-hour blood sampling and spot urine collections and complete the required study assessments as noted below:

- Perform physical and neurological exam
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Measure height, weight and calculate BSA using the following equation:

  BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)½

  - Measure head circumference (Birth -10 years of age at study entry only)
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Collect blood samples for amino acid panel (at Hour 0 and 8 only), ammonia level and PK at the following time points:
  - Hour 0 (just before the first main meal prior to dosing after an overnight fasting or after 4-6 hours without high calorie and protein intake: i.e., 08:00 [8:00 am])
  - Hour 4 (lunch: i.e., 12:00 [12:00 pm] prior to dosing)
  - Hour 8 (approximately 2-4 hours after lunch or after the second main meal: i.e., approximately 16:00 [4:00 pm] prior to dosing)
- Collect spot urine samples at the following timepoints:
  - Hour 0 (just before the first main meal prior to dosing after an overnight fasting or after 4-6 hours without high calorie and protein intake: i.e., 08:00 [8:00 am])
  - Hour 8 (approximately 2-4 hours after lunch or the after second main meal: i.e., approximately 16:00 [4:00 pm] prior to dosing)

    Spot urine is defined as a single aliquot of urine from a void at a particular time point.
- Perform urine pregnancy test for female subjects with childbearing capability
- Record actual protein and calorie intake during this visit, including all meals, snacks and supplements
- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed NOTE: The prescribed dietary intake of protein and calories, should be stable (unchanged) for at least 7 days prior to the EITP visit

- Record insertion, removal and/or use of G or NG-tube
- Record any changes to prescribed study drug dose and the reason for change
- Record concomitant medications
- Record AEs
- Collect all unused study drug and empty bottles
- Administer and collect EQ-5D-5L (subjects ≥ 12 years of age)
- Perform palatability assessment for all subjects (Appendix B: Hedonic Scale to Assess Palatability)
- Dispense study drug for the Transition or Maintenance period. Arm 2 subjects will remain in the clinic for at least 1 hour following their first dose of RAVICTI (for Subjects in treatment Arm 2, the first dose of RAVICTI will be taken on the evening of the EITP visit after the 8-hour ammonia, amino acid panel, PK and spot urine samples have been collected)

  For subjects in Treatment Arm 1, where Ammonia or Amino Acid panel (glutamine, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) results are not available on the day of EITP visit; the investigator will contact the subject (phone/email) within 2 days, to adjust the dose of RAVICTI if necessary, and to confirm whether the subject should proceed to End of Transition Period Visit or Maintenance Period Visit 1.

6.1.5. Transition Period (7 days ± 2 days)

The Transition Period is 7 days in duration for all Treatment Arm 2 subjects and Treatment Arm 1 subjects who were treatment failures.

- If the dose of RAVICTI was adjusted to deliver a different amount of PBA than the subject was receiving during the final week of the Initial Treatment Period, the subject must return at an appropriate interval (see the Dose Adjustment Algorithm in section 3.8) for fasting/morning plasma ammonia and, if indicated, amino acid panel.

6.1.5.1. End of Transition Day 7 (± 2 days)

Subjects will return to the clinic for:

- Fasting/morning plasma ammonia and amino acid panel prior to dosing
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed

- Record insertion, removal and/or use of G tube or NG tube along with dates and reasons for their use
- Record concomitant medications
- Record AEs
- Collect all unused study drug and empty bottles
- Assess study drug compliance
- Record any changes to prescribed study drug dose and the reason for change
- Dispense study drug
- Perform palatability assessment for Arm 2 subjects (Appendix B: Hedonic Scale to Assess Palatability)
- Assess Drug Preference for Arm 2 subjects (Appendix D: Drug Preference Assessment)

6.1.6. Maintenance Period (8 Weeks)

Visits will occur every 2 weeks and alternate between onsite and phone/email contacts.

6.1.6.1. Maintenance Period Visits 1 (Week 2) and 3 (Week 6) (± 4 days)

Subjects or caregivers will be contacted by phone or email to:

- Record AEs
- Assess compliance with study drug
- Assess compliance with prescribed diet
- Record Concomitant Medications

6.1.6.2 Maintenance Period Visits 2 (Week 4) and 4 (Week 8) (± 7 days)

Subjects will report to the study unit in the morning at Maintenance Period visits 2 and 4 and undergo the required study assessments and procedures as noted below:

- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Physical and Neurological Exam
- Perform urine pregnancy test for female subjects with childbearing capability
- Measure height, weight and calculate BSA using the following equation:

  BSA (m^2) = ([Height (cm) x Weight (kg)]/ 3600)½
- Measure head circumference (Birth -10 years of age at study entry only)
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Collect blood samples for fasting/morning amino acid panel and plasma ammonia prior to dosing
- Record the subject's diet as prescribed by the Investigator or Dietician

- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed
- Record insertion, removal and/or use of G-tube or NG-tube along with dates and reasons for their use
- Record concomitant medications
- Administer and collect EQ-5D-5L (≥ 12 years of age) – Maintenance Period visit 4 only
- Administer and collect CBCL/ABCL/ASR– Maintenance Period visit 4 only
- CGI Severity and Improvement (Investigator) – Maintenance Period visit 4 only
- Record AEs
- Collect all unused study drug and empty bottles.
- Assess study drug compliance.
- Record any changes to prescribed study drug dose and the reason for change
- Dispense study drug

6.1.7. Safety Extension Period (12 Weeks)

Monthly Visits scheduled during the Safety Extension Period are intended to assess safety and ammonia control. Additional visits may be scheduled at the discretion of the Investigator and the data will be captured as unscheduled visits. For subjects taking NaBz at study entry who transitioned from NaBz treatment during the Initial Treatment Period, NaBz may be resumed during the Safety Extension Period at the discretion of the Investigator. The dose of NaBz cannot be greater than the equivalent of the dose of RAVICTI that the subject is taking. Please see protocol Section 5.2.2.2 for dose equivalents of RAVICTI.

6.1.7.1. Safety Extension visits 1 and 2 (at 4 week intervals ± 7 days)

At Safety Extension Visits 1 and 2, the following will be performed:

- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Measure height for subjects with BSA <1.3 m^2
- Measure weight - calculate BSA using the following equation:

  BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)½
- Measure head circumference (for those who were Birth-10 years of age at study entry)
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Collect single blood sample for fasting ammonia level assessment and amino acid panel prior to dosing
- Perform urine pregnancy test for female subjects with childbearing capability

- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed
- Record concomitant medications
- Record AEs
- Record insertion, removal and/or use of G or NG-tube
- Collect all unused study drug and empty bottles
- Assess study drug compliance
- Record any changes to prescribed study drug dose and the reason for change
- Dispense RAVICTI

6.1.8. End of Study Visit or Early Termination

At the end of the Safety Extension Period or at Early Termination, subjects will undergo the assessments outlined below:

- Perform physical and neurological exam
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Measure height
- Measure weight
- Measure head circumference (for those who were Birth -10 years of age at study entry)
- Collect blood for safety laboratory assessments (Chemistry and Haematology)
- Collect single blood sample for fasting/morning ammonia level assessment and amino acid panel prior to dosing
- Perform urine pregnancy test for female subjects with childbearing capability
- Record the subject's diet as prescribed by the Investigator or Dietician
- Record the reason for any change to the prescribed diet
- Record the subject's stated compliance with the diet prescribed Record concomitant medications
- Record AEs
- Collect all unused study drugs and empty bottles
- Record date and time of last dose of study drug
- Record any changes to prescribed study drug dose and the reason for change
- Assess study drug compliance
- Record insertion, removal and/or use of G or NG-tube

- Perform CBCL (for subjects 18months to 18 years of age) or ABCL/ASR (for subjects 19 to 65 years of age)
- Administer and collect CGI–Severity and Improvement (Investigator)
- Record reason for termination
- Perform EQ-5D-5L (≥ 12 years of age)

6.1.9. 30 Day Follow-Up (+ 7 days)

Subjects or guardians/caregivers (as appropriate) will be contacted (phone, email, or visit) for the following assessments:

- Record and report to sponsor any SAEs that have started or become serious since the final study visit
- Record and report to sponsor any pregnancy (subject or subject's partner) that has occurred since the final study visit
- If SAEs or pregnancy have occurred, schedule follow-up visits or communications to obtain records and complete data collection and reporting as described in section 7

6.2. Early Termination Procedures

Subjects who discontinue treatment will complete end of study procedures designated as early termination assessments (see Section 6.1.8 End of Study Visit).

6.3. Assessment of Efficacy

Upon completion of the EITP visit, a subject will be considered a Treatment Success for the assigned treatment arm 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:

- Has 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 ULN at the End of Initial Treatment Period visit
- 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

During the Initial Treatment Period, blood samples will be collected for assessment of plasma ammonia levels in accordance with the schedule of assessments (Appendix A: Schedule of Assessments) and as indicated based on dose and/or diet adjustments. Serial samples for the measurement of ammonia level will be collected over an 8-hour period at the End of Initial Treatment Period visit (approximately Day 28). All plasma ammonias and amino acid panels obtained will be recorded in the eCRF.

During the Transition, Maintenance, and Safety Extension periods, plasma ammonia samples will be collected at study visits and as indicated based on dose and/or diet adjustments. These will be assessed as a measure of the subject's ammonia control. All plasma ammonias and amino acid panels obtained will be recorded in the eCRF. In addition, HACs will be captured and characterized throughout the study.

Global clinical impression of change based on the Investigator's assessment will be undertaken as an exploratory measure of the effects of treatment on the perceived improvement or worsening of the condition.

7. ASSESSMENT OF SAFETY

7.1. Adverse Events (AEs)

7.1.1. Definition of Adverse Event

As defined by the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product, whether or not the event is considered related to the investigational product. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product.

NOTE: the term "AE" includes both non-serious and serious AEs unless otherwise specified.

7.1.1.1. Examples of an AE

- Conditions newly detected or diagnosed after the signing of the informed consent, including conditions that may have been present but undetected prior to the start of the study.
- Conditions known to have been present prior to the start of the study that worsen after the signing of the informed consent.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se should not be reported as an AE).

7.1.1.2. Issues Not Considered AEs

- Conditions present at the start of the study should be recorded as medical history;
- Medical or surgical procedures (e.g., endoscopy, appendectomy); a condition that leads to a procedure is an AE if it qualifies according to the definitions above;
- Situations where an untoward medical occurrence did not occur (e.g., social, diagnostic, elective, or convenience admission to a hospital);
- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change from Baseline;
- Abnormal laboratory or test findings that are not assessed by the Investigator as a clinically significant change from Baseline;

Hyperammonemia should be considered an AE if clinically significant unless the Investigator determines that the abnormal result was due to an inaccurate test. If a HAC occurs, the Investigator will be asked to assess for a precipitating event, if known.

AEs are divided into the categories "serious" and "non-serious." This determines the procedures that must be used to report/document the AE.

7.1.2. Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE that:

a. Results in death
b. Is life threatening

   NOTE: The term 'life threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an inpatient for any length of time. Emergency room treatment does not qualify for this category, but may be appropriately included in category f (see below). Complications that occur during hospitalization are usually AEs. If a complication prolongs hospitalization or fulfills any other serious criterion, the event will be considered as serious. When in doubt as to whether 'hospitalization' occurred, consult the medical monitor.

   Hospitalization will not be considered an AE in itself. It will be considered an outcome of an AE. Therefore, if there is no associated AE, there is no SAE. For example, hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline will not be considered an AE.

d. Results in disability/incapacity

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

   NOTE: Medical and scientific judgment should be exercised in deciding whether reporting as serious is appropriate in other situations; specifically, important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an 'important medical event,' consult the sponsor's medical monitor.

AEs that do not result in any of these outcomes are considered non-serious.

Hyperammonemic episodes will be considered SAEs when they meet the criteria for an SAE as described above.

7.1.3. Assessment of Severity

All AEs, both serious and non-serious, will be assessed for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The CTCAE v4.03 scale displays Grades 1 through 5 with unique clinical descriptions of severity for each AE (including abnormal laboratory values) based on this general guideline.

Not all grades are appropriate for all AEs; therefore, some AEs are listed with fewer than 5 options for grade selection. In particular, Grade 5 (death) is not appropriate for some AEs and therefore will not be an option for those AEs.

AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the patient's ability to perform daily activities as defined below:

- Grade 1 (Mild) – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate) – Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate activities of daily living (ADL)
- Grade 3 (Severe) – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 (Life Threatening) – Life-threatening consequences; urgent intervention indicated
- Grade 5 (Fatal) – Death related to AE

Notes:

- Severity is a category for rating the intensity of an event in relation to other events of the same type, and both non-serious AEs and SAEs can be assessed as severe. An event will be defined as serious when it meets one of the outcomes described in Section 7.1.2, "Definition of Serious Adverse Event."
- Note that "life-threatening" in the criteria for "serious" has a more immediate definition than the CTCAE definition of "life-threatening". Thus, an AE may be CTCAE Grade 4 in severity and still not meet the SAE definition of "life-threatening".

7.1.4. Recording Adverse Events

Adverse event collection begins from the signature of the informed consent. Subjects/or caregivers will be questioned about AEs at each study visit, including at the Day 1 visit prior to the subject's first dose of study drug, using nonspecific questions, such as "How have/has you/your child been feeling since the last study visit?" AEs must be recorded on the AE eCRF and documented in the source record after the signing of the informed consent.

Non-serious AEs will be recorded through the last study visit. All SAEs that occur at any time beginning from the time informed consent is given until 30 days after the last dose of study medication should be recorded.

7.1.5. Procedures for Reporting Serious Adverse Events and Product Complaints

7.1.5.1. Serious Adverse Events

An SAE is reported **by entering the information in the eCRF within 24 hours** of becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by fax or email within 24 hours of the Investigator becoming aware of the event.

PPD

The event must be documented in source documentation as well as on the eCRF.

See the Study Reference Manual for complete instructions.

After receipt of the initial report, the information will be reviewed and the Investigator may be contacted with requests for additional information or for data clarification.

Follow-up will be obtained via fax and e-mail as necessary until the event has resolved or attained a stable outcome. Horizon is responsible for the preparation of MedWatch 3500 A/CIOMS I forms and analysis of similar events for individual occurrences (to be submitted as Investigational New Drug [IND] safety letters to the FDA and investigators according to 21 CFR 312.32 by Horizon) and suspected unexpected serious adverse reactions [SUSARs] according to Clinical Trial Directive 2001/20/EC and respective national legislation (to be submitted to European health authorities, IECs, and Investigators by Horizon).

7.1.5.2. Product Complaints

A product complaint process will be described in the Study Reference Manual. Any product complaint must be reported to the sponsor using this process.

7.1.6. Duration of Follow-up for Patients with Adverse Events

Once the study-defined non-serious AE and SAE reporting periods have passed (see Section 7.1.4), reporting is required only if an Investigator becomes aware of an SAE that he or she considers related to the study treatment.

After the initial recording of an AE, the Investigator should proactively follow the subject. Any non-serious AEs that are still ongoing at the end of the study should be reviewed to determine if further follow-up is required. The Investigator will document on the AE eCRF any/all ongoing non-serious AEs that will not be followed further after the subject exits the study. If in doubt, the Investigator should consult the sponsor's medical monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the subject is lost to follow-up. Once the SAE is resolved, the corresponding AE eCRF page should be updated.

7.1.7. Investigator Notification of Important New Safety Information

The sponsor will notify all Investigators involved in the clinical investigation of important safety information regarding the study treatment as required by the applicable regulations. Investigators will notify their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all such notifications as required by the IRB/IEC.

7.1.8. Pregnancy

Pregnancy, *per se*, will not be considered an AE in this study. However, a urine or serum pregnancy test should be performed if any female patient or partner of a male patient suspects that she has become pregnant during the time period of the study or within 30 days after the end of the study. If the test is positive, the pregnancy should be immediately reported to the Investigator and sponsor.

Because NaPBA is contraindicated for use during pregnancy and the effects of RAVICTI have not been determined the subject must be withdrawn from the study.

Complete pregnancy information, including the outcome of the pregnancy, should be collected in the source documents on the female patient or partner of a male patient (if she is willing). In the absence of complications, follow-up after delivery will be no longer than 8 weeks. Any stillbirths or premature terminations of pregnancies, whether elective, therapeutic, or spontaneous, should be reported on the pregnancy outcome form. Any pregnancy complications, including an elective termination for medical reasons, should be reported as an AE

A spontaneous abortion should always be considered a SAE, as should any congenital defects in the newborn. Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator should be reported to the sponsor.

7.1.9. Assessment of Relationship to Study drug

The Principal Investigator must review each AE and make a determination of relationship to study drug (i.e., whether the study drug caused the AE) using the following definitions:

- Not Related:

  The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or injury; does not follow a known response pattern to the study drug; and/or no temporal relationship exists with the study drug.

- Possibly Related:

  There is a reasonable temporal relationship between the event and the administration of the study drug, and the event cannot be readily explained by the subject's medical condition, other therapies, or injury; may not follow a known response pattern to the study drug.

- Probably Related:

  The event follows a reasonable temporal sequence from administration of the study drug and is part of a known or suspected response pattern to the medication, and a plausible alternative etiology cannot be identified.

The assessment of causality will be based on the information available, and may be changed upon receipt of additional information. The reference safety information is contained within the following documents for each respective study drug:

- RAVICTI: Investigator Brochure
- AMMONAPS: Summary of Product Characteristics (SmPC)
- BUPHENYL: Package Insert

8. LABORATORY ASSESSMENTS

Blood samples will be collected for assessment of subject safety at clinic visits in accordance with the schedule of assessments (Appendix A: Schedule of Assessments).

Safety laboratory assessments will include:

- Haematology: complete blood count (CBC) with differential and platelet count
- Chemistry: sodium, potassium, calcium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, and alkaline phosphatase

Safety laboratory assessments will be sent to the central laboratory. Safety laboratory assessments may be sent to the local laboratory in exceptional circumstances if deemed necessary by the study investigator.

Ammonia assessments:

- Blood samples to measure ammonia levels

Ammonia samples will be analysed at the local laboratory.

Amino Acid assessments

- Required Amino acid panel will include the following essential, non-essential and branched chain amino acid tests: threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine, glutamine
- As available and required when the site has validated testing and reportable results are available: citrulline, arginine and ornithine
- As available when the site has validated testing and reportable results are available: aspartic acid, serine, glutamic acid, asparagine, proline, alanine, glycine, cystine, tyrosine, taurine, phosphoserine, phosphoethanolamine, alpha-aminobutyric acid, 1-methylhistidine, 3-methylhistidine, and argininosuccinate

Amino acid assessments will be analysed at the local laboratory

Sampling Limitations:

Local IRB and institutional guidelines on pediatric patients involved in clinical trials must be followed regarding the maximum blood volume withdrawal allowed.

Per recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin (2006) the study-related blood loss should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per Kg body weight.

The Office of Human Research Protection (OHRP) provides guidance for “Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review”. Per the OHRP guidance for studies that represent no more than minimal risk to

paediatric subjects, the amount of blood drawn may not exceed the lesser of 50 mL or 3 mL/kg in an 8-week period.

Protocol-specified blood sampling should in no case exceed appropriate ethical and regulatory guidelines and institutional requirements and in all cases the risk/benefit assessment of subjects participating in clinical trials must be considered.

In cases where the blood limits are approached or met, or in cases where an insufficient amount of blood is drawn from the subject to run all protocol-required tests, blood samples should be collected for the following tests in order of priority:

1. Ammonia
2. Amino Acid panel
3. Safety labs (chemistry/hematology)
4. PK

Safety labs will be evaluated as part of medical management. The duration of ammonia monitoring will vary depending on the subject's age and their presenting conditions,

It is the investigator/site's responsibility to track blood volumes.

Urine pregnancy tests will be performed in women of childbearing potential.

9. VITAL SIGNS, HEIGHT, WEIGHT, AND HEAD CIRCUMFERENCE

Blood pressure, respiratory rate, temperature, and pulse as well as height and weight will be measured according to the schedule of assessments (Appendix A: Schedule of Assessments). Measure length for infants who cannot yet stand. Height measurements must be made with the use of a stadiometer. Head circumference will be measured in children who are Birth -10 years of age at study entry.

10. PHYSICAL EXAMINATION

Physical examinations will be performed using the normal study site procedures according to the schedule of assessments. (Appendix A: Schedule of Assessments).

11. CLINICAL GLOBAL IMPRESSION (CGI) SCALES

The **Clinical Global Impression - Severity** scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating relative to Baseline.

- 1 normal, not at all ill
- 2 borderline ill
- 3 mildly ill
- 4 moderately ill
- 5 markedly ill
- 6 severely ill
- 7 extremely ill

The **Clinical Global Impression – Improvement** scale (CGI-I) is a 7 point scale that requires the Investigator to assess how much the subject's illness has improved or worsened *relative to a Baseline state* at the beginning of the intervention and rated as:

- 1 very much improved
- 2 much improved
- 3 minimally improved
- 4 no change
- 5 minimally worse
- 6 much worse
- 7 very much worse

12. EQ-5D-5L

EQ-5D-5L (http://www.euroqol.org/home.html) is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The EQ-5D-5L is designed for self-completion by subjects or caregivers (Euroqol 1990) of subjects aged ≥ 12 years.

EQ-5D-5L will be administered according to the schedule of assessments (Appendix A: Schedule of Assessments).

13. NEUROPSYCHOLOGICAL TESTING

13.1. Child Behavior Checklist (CBCL)

CBCL is a questionnaire by which parents rate a child's problem behaviors and competencies. This instrument can either be self-administered or administered through an interview.

There are two versions of the checklist. The preschool checklist (CBCL/1½-5) is intended for use with children aged 18 months to 5 years. The school-age version (CBCL/6-18) is for children aged 6 to 18 years. It is an important measure for children's emotional, behavioral and social aspects of life and is used as a diagnostic tool for a variety of behavioral and emotional problems.

Validated CBCL questionnaires are available in English, Czech, French, Flemish, German, Italian, and Spanish. They will be administered only for subjects whose parents/caregivers readily understand one of these languages.

13.2. Adult Behavior Checklist (ABCL) and Adult Self-Report (ASR)

The ABCL is a questionnaire used to obtain information about the individual's adaptive functioning and problems. It is completed by an observer who knows the individual well, such as a spouse, partner, family member, or friend. It is intended for use with adults aged 19 to 59 years. Alternatively, the ASR is a similar questionnaire that may be completed by those subjects able to self-complete the form.

Validated ABCL/and ASR questionnaires are available in US English. They will be administered only for subjects and caregivers who readily understand English.

The ABCL and ASR, like the CBCL, is used as a diagnostic tool for a variety of behavioral and emotional problems.

During administration of the CBCL and ABCL/ASR, a trained professional will explain the questionnaires to the subject and family and answer any questions they may have. The CBCL and ABCL/ASR will be administered according to the schedule of assessments (Appendix A: Schedule of Assessments).

14. PK AND OTHER ASSESSMENTS

Samples for assessment of RAVICTI (glycerol phenylbutyrate) Oral Liquid and NaPBA metabolites will be collected at the EITP visit. The specific PK parameters to be analyzed will be as follows:

For all subjects:

- Plasma levels of PBA, PAA and PAGN
- Urinary excretion of PAGN

The time of sample collection, last meal prior to each sample collection, and all study medications doses should be recorded.

The blood volume required for PK is 0.5 mL at each time point.

For this protocol, Hour 0 samples should be collected just before the first main meal and dose after an overnight fasting or after 4 hours without high calorie and protein intake. Water or low calorie juice is allowed before Hour 0. However, for subjects who are unable to fast, the PK samples should still be collected with Hour 0 occurring just before the first dose and meal of the day.

Single samples of blood and urine should also be collected upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity.

14.1. Handling of Blood Samples for PK Analysis

At each designated time point, the requisite amount of blood will be drawn, processed, frozen, and prepared for shipment to the designated central laboratory

- Hour 0 (just before the first main meal and dose after an overnight fasting or after 4 hours without high calorie and protein intake: i.e., 08:00 [8:00 am])
- Hour 4 (prior to lunch and second dose: i.e., 12:00 [12:00 pm] prior to dosing)
- Hour 8 (approximately 2-4 hours after lunch or the after second main meal: i.e. approximately 16:00 [4:00 pm] prior to dosing)
- Upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity

Detailed instructions regarding PK blood sample timing and handling are provided in the Laboratory Manual.

14.2. Handling of Urine Samples for PK Analysis

Urine will be collected for the time intervals designated in the schedule of assessments (Appendix A: Schedule of Assessments) including upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity. The urine samples will be handled in accordance with the instructions provided in the Laboratory Manual.

The 8 hour spot urine collections are intended to capture metabolites excreted over 8 hours from the full daily dose of the study drug.

- Hour 0 (just before the first main meal and dose after an overnight fasting or after 4 hours without high calorie and protein intake: i.e., 08:00 [8:00 am])
- Hour 8 (approximately 2-4 hours after lunch or after the second main meal: i.e., approximately 16:00 [4:00 pm] prior to dosing)

Spot urine is defined as a single aliquot of urine from a void at a particular time point. The timing of spot urine samples for each collection must be recorded in the eCRF.

15. STATISTICS

15.1. Sample Size and Power

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 patients was chosen considering the number of patients 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 will complete the study. The rate of treatment success will be presented for each treatment arm with appropriate statistical tests performed. Descriptive statistics for all endpoints will be presented. Further details of statistical analysis will be provided in the Statistical Analysis Plan (SAP).

15.2. Interim Analysis

No formal interim analysis is planned for this study.

15.3. Endpoints and Analyses

15.3.1. Efficacy

15.3.1.1. Initial Treatment Period Endpoints (RAVICTI vs NaPBA)

The efficacy endpoints that will be evaluated during the Initial Treatment Period are:

- Rate of Treatment Success (Primary)
- Drug discontinuation due to any reason

15.3.1.2. Transition, Maintenance, and Safety Extension Periods (RAVICTI)

The efficacy endpoints that will be evaluated during the Transition, Maintenance, and Safety Extension Periods are:

- Control of plasma ammonia
- Annualized rate of HAC

15.3.2. Safety and Tolerability Endpoints

The endpoints that will be evaluated for safety and tolerability are:

- Assessment of AEs
- Standard clinical laboratory tests
- Amino acid panel
- Rate of drug discontinuation due to AEs

15.3.3. Clinical Outcome Assessments

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

15.4. Methods of Analysis

Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables, and frequency and percentages for categorical variables. Statistical hypothesis testing will be performed for selected endpoints. Significance levels (p-values) and confidence intervals (CIs) will be calculated using appropriate statistical methods.

Data will also be summarized by age group for the primary endpoint, treatment success.

The primary endpoint will also be stratified by NaBz, provided that there are least 2 non-NaBz subjects in each treatment group.

A formal SAP that will provide details of all analyses and presentation of study data will be prepared prior to database lock.

15.4.1. Significance Level and Adjustment for Multiplicity

Analyses will be performed at the two-sided 0.05 level. There will be no adjustment for multiplicity. Details will be provided in the SAP.

15.4.2. Analysis Populations

The following populations will be considered in the analysis of data for this study. Assignment or exclusion of subjects from the analysis populations will be performed:

- 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 safety analyses performed for this study. Subjects will be included based on medication received.
- Modified intention-to-treat (mITT) population: The mITT population will include all subjects from either treatment group with 1) no major eligibility violations, 2) who have received at least one dose of study drug and 3) have a data point post randomisation. Subjects will be included in the mITT based on the treatment subjects are randomised to. This will be the primary population for efficacy.
- 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

15.4.3. Baseline Demographic Variables

Demographic data including age, race, and gender will be summarized using descriptive statistics. Baseline variables including medical history, vital signs, laboratory data, and other Baseline disease characteristics will be summarized using descriptive statistics. Summaries will be provided for the safety population. If the analysis populations differ, selected variables will also be summarized separately for each of the analysis populations (safety, mITT). Listings will include all randomised subjects.

15.4.4. Subject Disposition

The number and percentage of subjects who discontinued the study prematurely will be summarized. The reasons for early study termination will also be presented.

15.4.5. Efficacy Variables

The primary efficacy endpoint is the rate of Treatment Success, as defined in Section 6.3. Additionally, 8-hour AUC, the peak (C_{max}) and mean levels of venous ammonia will be summarized by treatment. Plasma ammonia levels will be summarized using descriptive statistics at each time point on Day 1, and at the end of the Initial Treatment Period, and by treatment.

Since ammonia data will be collected through local laboratories that may have different normal ranges, all ammonia analyses will be performed using ammonia results standardized to a common unit (µmol/L) and normalized to a common ULN per age group. Details will be provided in the SAP.

During the Transition, Maintenance and Safety Extension Periods, descriptive statistics of blood ammonia at each scheduled onsite visit will be presented.

Frequency of HACs during the Maintenance and Safety Extension Periods will be presented along with the year prior to enrollment period.

Plasma PBA, PAA, and PAGN and urinary excretion of PAGN (the terminal metabolite of PBA) will also be analyzed. Data will be summarized for the EITP visit by time point using descriptive statistics.

15.4.6. Safety Variables

Safety will be evaluated in the safety population via AEs, vital signs, and clinical laboratory measurements.

All summaries of AEs will include treatment-emergent AEs (TEAEs), defined as events with an onset date on or after the first dose of study medication. Events will be summarized by treatment received according to the most recent dose of study drug received prior to the onset of the event. The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to study treatment will also be provided. Serious AEs and AEs leading to discontinuation of study treatment will be presented by system organ class and preferred term.

Liver function tests and additional selected laboratory tests will be summarized by study treatment and study visit. Laboratory tests will be classified relative to the normal reference range (normal, low, or high) and will be summarized by study treatment and visit.

Vital signs, including blood pressure, respiratory rate, temperature, and pulse, will be summarized by study treatment and visit.

Concomitant medications will be summarized and/or included in the data listings.

Neuropsychological testing results (CBCL and ABCL/ASR) will be summarized and/or listed.

Data for the Initial Treatment Period will be presented separately from data for the Transition, Maintenance, and Safety Extension Periods.

15.4.6.1. Statistical Analysis of Safety Variables

Safety data will be presented descriptively. No formal analyses will be conducted.

15.4.7. Statistical Analysis of Efficacy Variables

Where appropriate, Fisher's exact test will be used for analysis of rates, and t-tests and non-parametric tests (Wilcoxon) for analysis of continuous endpoints. Data will be log transformed as appropriate (e.g., AUCs). If appropriate analyses will also be performed based on whether subjects were receiving NaBz at baseline. Details will be included in the SAP.

15.4.7.1. Analysis of Treatment Success and Ammonia$_{8\text{-hour AUC}}$ at the End of Initial Treatment Period Visit

The primary endpoint is the rate of treatment success by treatment at the end of the Initial Treatment Period of the study. The two treatment groups will also be compared using the two-sample t-test and the nonparametric Wilcoxon rank-sum test. Further details will be provided in the SAP.

The mITT population will be used for the primary analysis of the primary efficacy endpoint.

Evaluable subjects are defined as those subjects with calculable ammonia AUC at the End of the Initial Treatment Period visit. If subjects have missing data at the 4 hour timepoint for calculation of the ammonia 8 hour AUC but have values available at the 0 and 8 hour timepoints, then AUC will be calculated using the available values, which is equivalent to linear interpolation of the missing value. If the subjects are missing ammonia measurement for either 0 hour or the 8 hour timepoint or both timepoints (0 hour and 8 hour) then the AUC will not be calculated and the subjects will not be used in the analysis of the AUC.

15.4.7.2. Other Efficacy Analyses During the Initial Treatment Period

Plasma ammonia levels and changes from Baseline will be summarized by sampling time point with descriptive statistics. Treatments will be compared using two-sample t-tests and Wilcoxon rank-sum tests.

15.4.7.3. Analysis of PK Parameters During the Initial Treatment Period

Descriptive statistics for all plasma metabolites (PBA, PAA and PAGN) and urinary metabolites (PAGN) from all spot urine samples during the 8-hour period including minimum and maximum concentrations and at various time points will be presented. There will be no PK parameters calculated. Further information will be provided in the SAP.

15.4.7.4. Analysis During the Transition, Maintenance, and Safety Extension Periods

The number and percentage of abnormal ammonia values and ammonia values ≥2 times the ULN will be summarized by visit. The average plasma ammonia levels and change from Baseline values during the Transition, Maintenance, and Safety Extension Periods will also be summarized.

The frequency of HAC episodes will be summarized and compared with the frequency of HAC episodes during the 1 year pre-enrollment period.

Descriptive statistics for CBCL/ABCL/ASR and EQ-5D-5L assessment instruments during the Maintenance and Safety Extension Periods by time point will be presented.

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

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Required information will be entered into the appropriate eCRFs, which are to be maintained in order and current so they reflect the latest information in the subject's source records. All records are to be kept in conformance with applicable guidelines and standard operating procedures (SOPs). When the study is completed, the Investigator must retain the essential documents for as long as needed to comply with regulatory and sponsor requirements. The Investigator will notify the sponsor prior to moving or destroying any of the study documents.

16.1. Study Monitoring

The sponsor representative is responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities, and upon request, inspecting the various records of the trial. The sponsor's clinical monitor is responsible for inspecting the eCRFs throughout the study to verify: selected data against source records; adherence to the protocol; completeness, accuracy, and consistency of data; and to monitor adherence to GCPs. The monitor must have access to subject medical records and other study-related records needed to verify entries on the eCRFs. In addition, the sponsor representative may contact the site via email, phone, teleconference, or web conference or online meeting to review study progress.

The Investigator agrees to cooperate with the monitor.

16.2. Audits and Inspections

The sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities, and upon request, inspecting the various records of the trial. This study may be selected for audit by representatives of the sponsor's Clinical Quality Assurance department or designee. Inspection of the site facilities (i.e., participant areas, drug storage areas, record storage areas, etc.) and review of study-related records may occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

16.3. Institutional Review Board/Independent Ethics Committee

The protocol, informed consent form, assent form, recruiting advertisements (if any), and subject instructions will be reviewed and approved by a properly constituted IRB/IEC that is in compliance with the requirements of ICH GCP and local and country requirements and is responsible for reviewing clinical studies. A copy of the letter indicating approval will be provided to the sponsor prior to study initiation.

No amendments to this protocol will be permitted without approval from the study sponsor. These communications will be documented in writing.

The Investigator and appropriate representatives from the sponsor will sign the protocol to document their willingness to adhere to this protocol and to conduct the study in accordance with GCPs.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Data will be entered into a password-protected EDC database in accordance with the Study Reference Manual and/or eCRF Completion Guidelines.

When the database is declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by written notice, as approved by the sponsor.

The Investigator will be responsible for ensuring the accuracy, completeness, legibility (of the source records), and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with source documents or the discrepancies should be explained.

Corrections to the eCRFs will be made in accordance with the Study Reference Manual and/or eCRF Completion Guidelines .

To ensure the quality of the clinical data across all participants and sites, a clinical data-management review will be performed. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to protocol and GCPs. To resolve any questions arising from the clinical data-review process, data queries will be directed to the site for completion.

The Principal Investigator will sign and date the indicated places on the eCRF. This signature will indicate that the Principal Investigator inspected or reviewed the data on the eCRF and the data queries, and that the Investigator agreed with the content.

18. ETHICS

18.1. Ethics Review

The protocol, informed consent form, assent form, recruiting advertisements (if any), and subject instructions will be reviewed and approved by a properly constituted IRB/IEC before any subject is enrolled at each study site.

18.2. Ethical Conduct of the Study

This study will be performed with adherence to the principles of GCP as required by applicable country and local regulations and by the ICH E6 Guidance for Industry: GCP Consolidated Guidance, April 1996, and in accordance with the ethical principles of the Declaration of Helsinki and its amendments.

18.3. Written Informed Consent

In accordance with ICH GCPs, written informed consent by the subject or the subject's parent/legal guardian for those under 18 years of age or the local age of consent must be obtained prior to a subject's participation in the study.

19. DATA HANDLING AND RECORD KEEPING

The Investigator must ensure that all participants' confidentiality will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents that are submitted to the sponsor, participants should be identified by an identification code and not by their names.

19.1. Inspection of Records

All records are to be kept in conformance with applicable guidelines and SOPs.

19.2. Retention of Records

When the study is completed, the Investigator must retain the essential documents for as long as needed to comply with regulatory and sponsor requirements. The Investigator will notify the sponsor prior to moving or destroying any of the study documents.

20. REFERENCES

In-text Reference	Reference List
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21. APPENDICES

A. Schedule of Assessments

B. Hedonic Scale to Assess Palatability

C. Clinical Global Impression (CGI)

D. Assessment of Drug Preference

APPENDIX A.SCHEDULE OF ASSESSMENTS

	Screen	Baseline (Days-3 thru -1)	Initial Treatment Period		End Treatment/ Start Next Period	Transition Period (7 days)	Maintenance Period[11]			End Maintenance/ Start Safety	Safety Extension[11, 14]		Added Visits	Post Study
Visit			**Day 1**	**ITP 1, 2, & 3** (Weekly)	**EITP** (ITP Wk 4 -End of Initial Treatment Period)[4, 22]	**ETPD 7** (Transit Day 7)	**MP1**[11] (Maint Wk 2) **Phone/ email**	**MP2** (Maint Wk 4)	**MP3** (Maint Wk 6) **Phone/ email**	**MP4** (Maint Wk 8)	**SE1-2** (Safety Wks 4 & 8)	**EOS** (Safety Wk 12 or Early Termination)	**Unsched Visit** [11, 15]	**30 Days Post EOS** **Phone/email**
Visit Windows				**± 2 days**[17]	**± 2 days**[17]	**± 2 days**	**± 4 days**	**± 7 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**NA**	**+ 7 days**
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Physical/Neurological Exam		X		X	X			X		X		X		
Medical and UCD History		X												
Randomisation[21]			X											
Vital Signs		X	X	X	X	X		X		X	X	X		
Height[1], Weight and Head Circumference (Birth to 10 years old)		X			X			X		X	X	X		
Chemistry /Haematology		X		X	X	X		X		X	X	X		

	Screen	Baseline (Days -3 thru -1)	Initial Treatment Period		End Treatment/ Start Next Period	Transition Period (7 days)	Maintenance Period[11]			End Maintenance/ Start Safety	Safety Extension[11, 14]		Added Visits	Post Study
Visit			**Day 1**	**ITP 1, 2, & 3** (Weekly)	**EITP** (ITP Wk 4 -End of Initial Treatment Period)[4, 22]	**ETPD 7** (Transit Day 7)	**MP1**[11] (Maint Wk 2) **Phone/ email**	**MP2** (Maint Wk 4)	**MP3** (Maint Wk 6) **Phone/ email**	**MP4** (Maint Wk 8)	**SE1-2** (Safety Wks 4 & 8)	**EOS** (Safety Wk 12 or Early Termination)	**Unsched Visit**[11, 15]	**30 Days Post EOS** **Phone/email**
Visit Windows				**± 2 days**[17]	**± 2 days**[17]	**± 2 days**	**± 4 days**	**± 7 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**NA**	**+ 7 days**
8-Hour Amino Acid Panel [2]					X									
Fasting Amino Acid Panel [3, 15]			X	X		X		X		X	X	X	X	
8-Hour Ammonia [2]					X									
8-Hour PK [2, 10]					X									
Spot Blood PK													X[19]	
AST, ALT, Total Bilirubin													X[20]	
Fasting Ammonia [3, 15]			X	X		X		X		X	X	X	X	
8-Hour Spot Urine [2, 12]					X									
Spot Urine PK[12]													X[19]	
Urine Pregnancy Test		X			X			X		X	X	X		

	Screen	Baseline (Days -3 thru -1)	Initial Treatment Period		End Treatment/ Start Next Period	Transition Period (7 days)	Maintenance Period[11]			End Maintenance/ Start Safety	Safety Extension[11, 14]		Added Visits	Post Study
Visit			**Day 1**	**ITP 1, 2, & 3** (Weekly)	**EITP** (ITP Wk 4 -End of Initial Treatment Period)[4, 22]	**ETPD 7** (Transit Day 7)	**MP1**[11] (Maint Wk 2) **Phone/ email**	**MP2** (Maint Wk 4)	**MP3** (Maint Wk 6) **Phone/ email**	**MP4** (Maint Wk 8)	**SE1-2** (Safety Wks 4 & 8)	**EOS** (Safety Wk 12 or Early Termination)	**Unsched Visit**[11, 15]	**30 Days Post EOS** **Phone/email**
Visit Windows				**± 2 days**[17]	**± 2 days**[17]	**± 2 days**	**± 4 days**	**± 7 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**NA**	**+ 7 days**
Diet Prescription by Investigator or Dietician			X	X	X	X		X		X	X	X		
Assess Compliance with Diet Prescription			X	X	X	X	X	X	X	X	X	X	X	
Actual Protein and Calorie Intake (in-clinic)					X									
Assess G or NG tube use[9]		X		X	X	X		X		X	X	X		
Drug Preference Assessment						X[8]								
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (AEs)		X	X	X	X	X	X	X	X	X	X	X	X	

	Screen	Baseline (Days -3 thru -1)	Initial Treatment Period		End Treatment/ Start Next Period	Transition Period (7 days)	Maintenance Period[11]			End Maintenance/ Start Safety	Safety Extension[11, 14]		Added Visits	Post Study
Visit			**Day 1**	**ITP 1, 2, & 3** (Weekly)	**EITP** (ITP Wk 4 -End of Initial Treatment Period)[4, 22]	**ETPD 7** (Transit Day 7)	**MP1[11]** (Maint Wk 2) **Phone/ email**	**MP2** (Maint Wk 4)	**MP3** (Maint Wk 6) **Phone/ email**	**MP4** (Maint Wk 8)	**SE1-2** (Safety Wks 4 & 8)	**EOS** (Safety Wk 12 or Early Termination)	**Unsched Visit [11, 15]**	**30 Days Post EOS** **Phone/email**
Visit Windows				**± 2 days[17]**	**± 2 days[17]**	**± 2 days**	**± 4 days**	**± 7 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**NA**	**+ 7 days**
Dispense/ Collect Study Drug (Compliance check)			X	X	X	X	X[16]	X	X[16]	X	X	X		
Initial Dose and Observation[5]			X		X[13]									
CBCL or ABCL/ASR[6]		X								X		X		
CGI-Severity[7]		X								X		X		
CGI-Improvement[7]										X		X		
EQ-5D-5L		X			X					X		X		
Hedonic Scale					X	X[8]								
Date and Time Last Dose												X		
Reason for Termination												X		

	Screen	Baseline (Days -3 thru -1)	Initial Treatment Period		End Treatment/ Start Next Period	Transition Period (7 days)	Maintenance Period[11]			End Maintenance/ Start Safety	Safety Extension[11, 14]		Added Visits	Post Study
Visit			**Day 1**	**ITP 1, 2, & 3** (Weekly)	**EITP** (ITP Wk 4 -End of Initial Treatment Period)[4, 22]	**ETPD 7** (Transit Day 7)	**MP1**[11] (Maint Wk 2) **Phone/ email**	**MP2** (Maint Wk 4)	**MP3** (Maint Wk 6) **Phone/ email**	**MP4** (Maint Wk 8)	**SE1-2** (Safety Wks 4 & 8)	**EOS** (Safety Wk 12 or Early Termination)	**Unsched Visit**[11, 15]	**30 Days Post EOS** **Phone/email**
Visit Windows				**± 2 days**[17]	**± 2 days**[17]	**± 2 days**	**± 4 days**	**± 7 days**	**± 4 days**	**± 7 days**	**± 7 days**	**± 7 days**	**NA**	**+ 7 days**
SAE / Pregnancy Post EOS														X[18]

1. Height will be measured at Baseline for all subjects. At the EITP visit, and throughout the Maintenance and Safety Extension Period, height will be measured only for those subjects with BSA < 1.3 m^2. Height measurement should be made with the use of a stadiometer.
2. For the 8-hour amino acid (Hour 0 and Hour 8 only), blood and spot urine (Hour 0 and Hour 8 only) and ammonia and PK assessments samples will be collected relative to the first morning dose as follows:
   - Hour 0 (just before the first main meal and dose after an overnight fast or 4-6 hours without high calorie and protein intake; i.e., 08:00 [8:00 am] for those who can tolerate fasting)
   - Hour 4 (just before lunch and prior to dosing; i.e., 12:00 [12:00 pm])
   - Hour 8 (~2–4 hours after lunch or the second main meal; i.e., approximately16:00 [4:00 pm] prior to dosing)
3. Collect single sample prior to morning dose (just before the first main meal and dose after an overnight fast or 4-6 hours without high calorie and protein intake; i.e., 08:00 [8:00 am] for those who can tolerate fasting)
4. An optional overnight stay may be utilized for subject convenience or Investigator discretion, based on dosing requirements of the subject and/or the subject's travel requirements to the site.
5. Subjects will be observed for at least 1 hour following the first dose in the Initial Treatment Period, and subjects in treatment Arm 2 also at the EITP visit after the first dose of RAVICTI.
6. CBCL is administered to subjects 18 months to 18 years of age, while the ABCL/ASR is administered to subjects 19 to 59 years of age. For subjects on NaBz at baseline, they should remain on NaBz for their baseline assessments.
7. CGI Scoring: See Appendix C of the protocol

8. Arm 2 only
9. Assessment of G or NG tube use only for subjects with G or NG tubes
10. Plasma PK analysis for PBA, PAA, and PAGN.
11. Biochemical markers (plasma ammonia and if indicated blood amino acid panel) should be drawn and considered for any dose adjustments at least every 7 days until stable during the Initial Treatment Period . During Transition, Maintenance, and Safety Periods, biochemical markers should be assessed after dose and diet changes at appropriate intervals (see Dose Adjustment Algorithm in section 3.8) not > 7 days after each dose/diet adjustment. This can occur at unscheduled visits throughout the study as needed.
12. Urine PK analysis for PAGN
13. For subjects in Treatment Arm 2, the first dose of RAVICTI will be taken on the evening of the EITP visit after 8-hour ammonia, amino acid panel, PK, and spot urine samples have been collected (i.e., approximately 16:00 [4:00 pm]).
14. During the Safety Extension Period, additional visits and assessments may be scheduled at the discretion of the Investigator.
15. Blood sample(s) can be non-fasting, for subjects who cannot fast and in situations where fasting cannot be accomplished, such as HAC and neurological AE grade >2 and at the Investigators discretion. For every ammonia and amino acid panel, the fasting status (fasting/non-fasting) of the subject at the time of the blood collection will be recorded.
16. Compliance check only.
17. As counted from the prior scheduled visit.
18. The 30 day post end of study check for SAEs and pregnancy may be done via remote contact (phone, email, etc.) or visit if it coincides with standard of care.
19. To be collected upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of HAC or PAA toxicity.
20. To be collected on any day that a PK sample is collected and upon presentation at the study center (and as feasible at other health care facilities) with signs and symptoms of hyperammonemia, HAC or PAA toxicity.
21. Randomisation to be completed following baseline assessments and confirmation of eligibility, up to and including Initial Treatment Period Day 1.For subjects in Treatment Arm 1, where Ammonia or Amino Acid panel (glutamine, threonine, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, valine) results are not available on the day of EITP visit; the investigator will contact the subject (phone/email) within 2 days of the visit, to adjust the dose of RAVICTI if necessary, and to confirm whether the subject should proceed to the Transition Period or Maintenance Period 1.

APPENDIX B. HEDONIC SCALE TO ASSESS PALATABILITY

Hedonic scale is a validated scale developed to test palatability of food (Peryam 1957, Chen 1996) and has been extensively used to assess palatability of flavored medications (Matsui 2007). Subjects (or parents or caregivers) are asked to rate the palatability of RAVICTI (glycerol phenylbutyrate) Oral Liquid and NaPBA based on the subject's reactions to each drug using the following hedonic scale during the study periods indicated below.

Likes very much	Likes moderately	Neither likes or dislikes	Dislikes moderately	Dislikes very much

Hedonic scale is performed at the following time points during the Initial Treatment and Transition Periods:

Initial Treatment Period

1. EITP visit for all subjects

Transition Period

2. Transition Day 7 visit for Treatment Arm 2 subjects only

APPENDIX C. CLINICAL GLOBAL IMPRESSION (CGI)

The **Clinical Global Impression – Severity** scale (CGI–S) is a 7–point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy 1976, Guy 2000). Considering total clinical experience, a patient is assessed on severity of illness at the time of rating relative to Baseline.

- 1 normal, not at all ill
- 2 borderline ill
- 3 mildly ill
- 4 moderately ill
- 5 markedly ill
- 6 severely ill
- 7 extremely ill

The **Clinical Global Impression – Improvement** scale (CGI–I) is a 7 point scale that requires the Investigator to assess how much the subject's illness has improved or worsened *relative to a Baseline state* at the beginning of the intervention and rated as:

- 1 very much improved
- 2 much improved
- 3 minimally improved
- 4 no change
- 5 minimally worse
- 6 much worse
- 7 very much worse

APPENDIX D. ASSESSMENT OF DRUG PREFERENCE

Assessment of Drug Preference:

1. Which drug do you prefer?* (Circle one)	AMMONAPS® or BUPHENYL® (sodium phenylbutyrate)	RAVICTI® (glycerol phenylbutyrate) Oral Liquid

2. Why do you prefer this drug*? Mark all that apply.

- [ ] taste
- [ ] volume (amount of drug that must be given)
- [ ] side effect profile (please specify)

- [ ] ease of administration (please describe what is easier about your choice)

- [ ] other (please specify)

*Subject should be queried directly. However for young children, the parent/legal guardian can report on behalf of the child if more appropriate.