Study: HPN-100-014

NCT#: 01948427

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

Date of Document:
PROTOCOL: **11 February 2013**

CLINICAL STUDY PROTOCOL FOR RAVICTI®

Administrative Change 1 to Protocol Number: HPN-100-014

Long-Term Registry of Patients with Urea Cycle Disorders (UCDs)

Short title: THRIVE

Version 2.0, incorporating Amendment 1
Date: 11 February 2013

Sponsor:
Horizon Therapeutics, Inc.
520 Lake Cook Road
Suite 520
Deerfield Illinois 60015

PROTOCOL

1. TITLE PAGE

Study Title: Long-Term Registry of Patients with Urea Cycle Disorders (UCDs)

Protocol Number: Administrative Change 1 to HPN-100-014

Title Page
currently reads:

Study No:	HPN-100-014
Study Title:	Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)
Clinical Phase:	4
Study Sponsor:	Hyperion Therapeutics, Inc. [redacted]
Study Medical Monitor:	[redacted] Vice President Clinical Development and Medical Affairs Hyperion Therapeutics, Inc. [redacted]
Date of Protocol:	11 February 2013 (Amendment 1)
Ethics Statement:	This study will be conducted in compliance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.
Confidentiality:	Hyperion Therapeutics, Inc. This protocol is the property of Hyperion Therapeutics, Inc. and may not—in full or in part—be transferred, reproduced, published, or otherwise used without the express permission of Hyperion Therapeutics, Inc.

Title Page
changed to:

Study No:	HPN-100-014
Study Title:	Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)
Clinical Phase:	4
Study Sponsor:	Horizon Therapeutics, Inc. 520 Lake Cook Road Suite 520 Deerfield, Il 60015
Study Medical Monitor:	[redacted] Senior Medical Director Horizon Pharma, Inc. [redacted]
Date of Protocol:	11 February 2013 (Amendment 1)
Ethics Statement:	This study will be conducted in compliance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.
Confidentiality:	Horizon Therapeutics, Inc. This protocol is the property of Horizon Therapeutics, Inc. and may not—in full or in part—be transferred, reproduced, published, or otherwise used without the express permission of Horizon Therapeutics, Inc.

The Study sponsor has changed from Hyperion Therapeutics, Inc. to Horizon Therapeutics, Inc., an affiliate of Horizon Pharma, due to the acquisition of Hyperion Therapeutics, Inc. by Horizon Pharma Ireland Limited. The following sections within the protocol are changed from "Hyperion" to "Horizon".

Protocol Synopsis, Retrospective Data Collected at Study Enrollment Currently reads:	Patients who have participated in other Hyperion studies may be enrolled in this registry, and the data available from those studies may be used.
Protocol Synopsis, Retrospective Data Collected at Study Enrollment Changed to:	Patients who have participated in other Horizon studies may be enrolled in this registry, and the data available from those studies may be used.
Section 5.2.1 Retrospective Data Collected at Study Enrollment Currently reads:	Patients participating in other Hyperion studies and already receiving glycerol phenylbutyrate may be enrolled in this registry, and the data available from those studies may be used.
Section 5.2.1 Retrospective Data Collected at Study Enrollment Changed to:	Patients participating in other Horizon studies and already receiving glycerol phenylbutyrate may be enrolled in this registry, and the data available from those studies may be used.
Section 6.2.2 Serious Adverse Events Currently reads:	Hyperion will assess any hospitalization or death that is unexpected and deemed to be related to Glycerol phenylbutyrate or any other Hyperion product, by the Investigator, and will file a report of the event to the FDA.
Section 6.2.2 Serious Adverse Events Changed to:	Horizon will assess any hospitalization or death that is unexpected and deemed to be related to Glycerol phenylbutyrate or any other Horizon product, by the Investigator, and will file a report of the event to the FDA.

Section 10.1 Sample Size Currently reads:	Up to 500 patients of whom at least 100 patients are being treated with RAVICTI. According to Wolters Kluwer data received by Hyperion in September 2010, there were an estimated 406 patients on NaPBA during the time period of 01 April 2009 through 31 March 2010.
Section 10.1 Sample Size Changed to:	Up to 500 patients of whom at least 100 patients are being treated with RAVICTI. According to Wolters Kluwer data received by Horizon in September 2010, there were an estimated 406 patients on NaPBA during the time period of 01 April 2009 through 31 March 2010.
Section 11.5 Monitoring of the Study Currently reads:	The Study Sponsor, Hyperion Therapeutics, and its representatives will monitor the study at the clinical site according to the Monitoring Plan.
Section 11.5 Monitoring of the Study Changed to:	The Study Sponsor, Horizon Therapeutics, and its representatives will monitor the study at the clinical site according to the Monitoring Plan.

UCD Registry Protocol

Study No:	HPN-100-014
Study Title:	Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)
Clinical Phase:	4
Study Sponsor:	Hyperion Therapeutics, Inc. [redacted]
Study Medical Monitor:	[redacted] Vice President Clinical Development and Medical Affairs Hyperion Therapeutics, Inc. [redacted]
Date of Protocol:	11 February 2013 (Amendment 1)
Ethics Statement:	This study will be conducted in compliance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.
Confidentiality:	

PROTOCOL SIGNATURE PAGE

Protocol Number: HPN-100-014

Protocol Title: Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)

Hyperion Therapeutics, Inc.

[redacted]

Vice President Clinical Development and Medical Affairs

2/11/2013

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Number: HPN-100-014

Protocol Title: Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)

Hyperion Therapeutics, Inc.

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

PROTOCOL SYNOPSIS

Title	Long-Term Registry of Patients With Urea Cycle Disorders (UCDs)
Protocol Number	HPN-100-014
Phase	4
Objectives	To characterize the demographics and clinical course of the patient population diagnosed with UCD To track growth and neurocognitive outcomes for patients with UCDs. To generate comparative effectiveness data in UCD patients.
Study Design	This is a multi-center, prospective, non-interventional study designed to collect data on safety and outcomes in patients with UCDs. It is designed to permit all interested healthcare providers to participate as Investigators, and all interested patients to participate. No controls are planned. Patients enrolled in this registry will be required to provide a select set of data at baseline and to undergo regular office visits and data collection, as indicated in Appendix A.
Rationale	UCDs disproportionately affect children and females: depending on the severity of the defect, a UCD can manifest shortly after birth or later in life. This study will track long-term outcomes in UCD patients and effects of ammonia-scavenging agents on neuropsychological functions of UCD patients. The main goal of medical management of UCD patients is to prevent chronic or acute hyperammonemic states leading to central nervous damage. This requires restriction in dietary protein intake and the use of nitrogen scavenging agents if diet alone does not adequately control patients. Glycerol phenylbutyrate, sodium phenylbutyrate and sodium benzoate are major nitrogen scavenging agents used in these patients. RAVICTI™ (glycerol phenylbutyrate) Liquid, a prodrug of phenylbutyrate (PBA) and a pre-prodrug of the active compound phenylacetate (PAA), has been recently approved for chronic treatment of patients with UCDs.[12] Previously, NaPBA was the only approved drug in the U.S. for the chronic treatment of the most prevalent UCDs. Although both drugs share a similar mechanism of action, unlike NaPBA, which is a salt, glycerol phenylbutyrate is a triglyceride consisting of 3 molecules of PBA joined via ester linkage to glycerol. The chemical form of glycerol phenylbutyrate helps mitigate the taste, odor, sodium content, and pill burden associated with NaPBA and confers different pharmacokinetic (PK) characteristics. PBA enters the circulation more slowly when delivered as glycerol phenylbutyrate compared with NaPBA, because glycerol phenylbutyrate requires digestion via pancreatic lipases[12] Although not approved for UCD, sodium benzoate has also been traditionally used as another nitrogen scavenging agent either alone or in combination with NaPBA RAVICTI™ has been studied in 5 clinical trials, involving approximately 114 adult and pediatric UCD patients ages 2 months and above.[14,15] A study in UCD patients <6 years of age[16] (HPN-100-012) and a continued access protocol for participants in UCD clinical trials[17] (HPN-100-011) are ongoing. Results to date suggest satisfactory safety and ammonia-lowering activity that is at least as good as that afforded by an equivalent dose of NaPBA.[12,14,15]

Duration of Study	10 years
Patient Population and Key Selection Criteria	• Patients with a confirmed or suspected diagnosis of UCD. • Signed informed consent/HIPAA Authorization and medical records release by the patient or a legally acceptable representative.
Number of Patients	Up to 500 UCD patients of whom at least 100 will be receiving RAVICTI™ (glycerol phenylbutyrate) Liquid
Outcome Variables and Assessments	**Control of blood ammonia levels:** • Mean and maximum blood ammonia levels, retrospectively and during the study • Frequency of hyperammonemic crises, retrospectively and during the study **Serious adverse events (SAEs):** • Frequency of SAEs
	Procedure Training (job specific) • Neuropsychological test scores: **Adaptive Behavior Assessment System, second edition (ABAS-II)**[18] The ABAS-II measures adaptive skills for individuals from birth to 89 years. Age-specific rating forms will be used for evaluation of infants and children by parents or caregivers, and self-evaluation by adults. The ABAS-II provides an estimate of IQ and has a strong correlation with Wechsler IQ scales. The ABAS-II will be completed annually for patients of all ages. **The Behavior Rating Inventory of Executive Function (BRIEF)** [19] The BRIEF is a set of clinical scales for executive function, including behavior, cognition, and the Global Executive Composite. Parent response forms will be used for preschool and school-aged children, and a self-report form will be used for adults. The BRIEF will be completed annually for patients 4 years and older. **Growth and development assessments (pediatric patients):** • Z scores derived from height, weight, body surface area (BSA), and body mass index (BMI) compared to standardized values • Occurrence of developmental disabilities and delays **UCD medication discontinuation or change in medication:** • Reasons for discontinuation of, or change in, ammonia-scavenging medications **Additional Data Points (when available)** • For patients on sodium phenylbutyrate or glycerol phenylbutyrate, available plasma and urine PK data • Actual dietary protein intake (up to 3 consecutive days) • Information regarding the common side effects patients have been experiencing with their UCD medications If these data points are available in electronic format, it may be possible to transfer the data to the EDC.

Study Procedures	Eligible patients will be enrolled in the study and followed for up to 10 years, (Schedule of Assessments, Appendix A). At the time of enrollment, retrospective and baseline data will be collected. During the study, patients will be asked to report episodes of hyperammonemic crisis, available ammonia levels, and other information. Age-appropriate neuropsychological testing will be performed. SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual. Patients who become pregnant during this study will be invited to participate in the UCD pregnancy registry (Protocol HPN-100-018).
Data Collection Procedures	Data concerning patient treatment and clinical condition will be collected at the indicated time points (retrospective, baseline, and prospective) and entered into the Registry EDC system by the site personnel.
Retrospective Data Collected at Study Enrollment:	The following data, for the 12 months preceding enrollment, will be obtained through abstraction of medical records and family interview. For patients already receiving RAVICTI, the 12 months immediately before commencement of RAVICTI will also be obtained. Patients who have participated in other Hyperion studies may be enrolled in this registry, and the data available from those studies may be used. • All hyperammonemic crises, including admission and peak ammonia detected during the crisis and documented cause, if available and the type of UCD medication patients were on at the time • All available outpatient ammonia values. For patients with more than 2 ammonia values in a given month, only the highest and lowest ammonia values to will be reported. • All available outpatient glutamine values. For patients with more than 2 values in a given month, only the highest and lowest ammonia values to will be reported • Duration, dose, frequency, and route of administration of all ammonia-scavenging agents such as NaPBA, glycerol phenylbutyrate, or sodium phenylacetate / sodium benzoate, and reasons for discontinuation, if applicable • Available weight and height values • Available age-appropriate neuropsychological test results
Baseline Data Collected at Study Enrollment:	• Demographic data • Age at first presentation of symptoms • Age at diagnosis • Presentation: newborn screening vs. clinical symptoms • UCD subtype • Ammonia-scavenging medication(s), including dose, frequency, and route of administration • Other medications of interest, including: arginine, citrulline and amino acid supplements • Height and weight • Developmental status, disabilities and delays (Appendix D) • Neuropsychological tests • Prescribed total daily protein and caloric intake • Last available ammonia values

	• Last available glutamine and branched-chain amino acid (BCAA) values including leucine, isoleucine and valine • Data points of interest (Appendix B)
Prospective Data Collection After Enrollment:	• For patients who begin or alter their UCD treatment close to the time of enrollment, ammonia and glutamine values are recommended to be obtained within 7 to 30 days after enrollment and if judged necessary by the treating healthcare provider • Fasting ammonia and amino acid panel, at least annually after the first 30 days • For patients on restricted diet: prescribed diet, including total daily protein and caloric intake • Hyperammonemic crises, including admission and peak ammonia detected during the crisis, and documented cause, if available and the type of UCD medication patients were on at the time • Ammonia-scavenging medication(s), including dose, frequency, and route of administration • Reasons for discontinuation of, or changes in, ammonia-scavenging medication. • Other medications of interest, including: arginine, citrulline, amino acid supplements • Height and weight • Developmental status, disabilities and delays (Appendix D) • Neuropsychological tests • Data points of interest (Appendix B) • SAEs are to be reported as described in Section 6.2.2.3 and the Registry Reference Manual. • Available plasma and urine PK data • Actual dietary protein intake when available
Statistical Methods	A formal statistical analysis plan (SAP) that will provide details of all analyses and presentation of study data will be approved prior to data analysis. Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and n and percent for categorical variables.
Sample size:	Up to 500 patients of whom at least 100 patients are being treated with RAVICTI™
Analysis Population:	Data will be presented for all patients enrolled in the study. Additional subgroups also may be examined, as deemed appropriate (pediatric versus adult, UCD type, etc.).
Disposition, Demographic, and Prospective Data:	Disposition data will be summarized by UCD medication with descriptive statistics and presented in listings. Demographic and clinical data will be summarized by UCD medication with descriptive statistics and presented in listings.
Outcome Data:	Post-baseline values and/or change from baseline in the outcome variables will be summarized by UCD medication with descriptive statistics, and, where appropriate, graphical presentations, and presented in listings.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

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

1. INTRODUCTION

1.1. Background

A urea cycle disorder (UCD) is an inborn error 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.[1] these are rare diseases, with an overall estimated incidence in the US of 1 in 30,000 live births.[2]

Table 1: Urea Cycle Disorders

Deficiency	Abbreviation	Inheritance Pattern	Estimated Prevalence in US
Ornithine transcarbamylase	OTC	X-linked	1:14,000
Argininosuccinate synthetase	ASS	Autosomal recessive	1:57,000
Carbamyl phosphate synthetase	CPS	Autosomal recessive	1:62,000
Argininosuccinate lyase	ASL	Autosomal recessive	1:70,000
Arginase	ARG	Autosomal recessive	1:350,000
N-acetylglutamate synthetase	NAGS	Autosomal recessive	(unknown/very rare)
Ornithine translocase	HHH	Autosomal recessive	(unknown/very rare)
Aspartate glutamate transporter	CITRIN	Autosomal recessive	(unknown/very rare)

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.[2] Acute hyperammonemic episodes at any age carry the risk of encephalopathy and resulting neurologic damage, sometimes fatal; but even chronic, sub-critical hyperammonemia can result in impaired cognition.[3] UCDs are therefore associated with significant incidence of neurological abnormalities and intellectual and developmental disabilities over all ages.[4,5] UCD patients with neonatal-onset disease are especially likely to suffer cognitive impairment[5] and death[6] compared with patients who present later in life.

Management of acute hyperammonemic crises may require hemodialysis and/or intravenous (IV) administration of sodium phenylacetate and sodium benzoate (marketed in the US as AMMONUL®).[7] 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 includes restriction of dietary protein; arginine and citrulline supplementation, which can enhance waste nitrogen excretion for certain UCDs; and oral, ammonia-scavenging drug therapy that provides an alternate path for waste nitrogen removal. Until the approval of RAVICTI™ (glycerol phenylbutyrate) Liquid, sodium

phenylbutyrate (NaPBA; marketed in the US as BUPHENYL®)[8] was the only ammonia-scavenging agent available in the US for maintenance treatment of the most prevalent UCDs. NaPBA has been demonstrated to improve long-term survival in UCD patients, by reducing the incidence of deaths due to hyperammonemic encephalopathy, when administered at the recommended dose levels.[8]

Despite dietary and pharmacologic management, UCD patients still experience episodes of hyperammonemia, with the risk of hyperammonemic encephalopathy requiring aggressive medical intervention[2] and chronic hyperammonemia, with cumulative neurocognitive impairment.[5] Furthermore, compliance with NaPBA treatment is difficult, especially for pediatric patients, due to the high pill burden (up to 40 pills or 40 mL of dissolved powder daily for patients taking 20 g of NaPBA), foul taste, unpleasant odor, and high sodium content (~2300 mg/day for patients taking 20 g). Because NaPBA is rapidly absorbed, and because of the short plasma half-life of the active metabolite phenylacetate (PAA), the BUPHENYL label recommends dosing 3 to 6 times/day.[8] Some pediatric patients with severe deficiency states may require nasogastric or gastrostomy tubes to ensure adequate nutrition and compliance with this treatment regimen.[9,10,11]

1.2. Study Rationale

UCDs disproportionately affect children and females: depending on the severity of the defect, a UCD can manifest shortly after birth or later in life. This study will track long-term outcomes in UCD patients and effects of ammonia-scavenging agents on neuropsychological functions of UCD patients.

The main goal of medical management of UCD patients is to prevent chronic or acute hyperammonemic states leading to irreversible central nervous damage. This requires restriction in dietary protein intake and the use of nitrogen scavenging agents if diet alone does not adequately control patients. Glycerol phenylbutyrate, sodium phenylbutyrate and sodium benzoate are major nitrogen scavenging agents used in these patients.

Glycerol phenylbutyrate, a prodrug of PBA and a pre-prodrug of the active compound PAA, recently has been approved for chronic treatment of patients with UCDs.[12] Although glycerol phenylbutyrate and NaPBA share a similar mechanism of action, unlike NaPBA, which is a salt, glycerol phenylbutyrate is a triglyceride consisting of 3 molecules of PBA joined via ester linkage to glycerol. The chemical form of glycerol phenylbutyrate helps to mitigate the taste, odor, sodium content, and pill burden associated with NaPBA, and confers more favorable pharmacokinetic (PK) characteristics. PBA enters the circulation more slowly when delivered as glycerol phenylbutyrate, compared with NaPBA, because glycerol phenylbutyrate requires digestion via pancreatic lipases.[12] Although not approved for UCD, sodium benzoate has also been traditionally used as another nitrogen scavenging agent either alone or in combination with NaPBA

Glycerol phenylbutyrate has been studied in 5 clinical trials, involving approximately 114 adult and pediatric UCD patients ages 2 months and above.[14,15] A study in UCD patients <6 years of age[16] (HPN-100-012) and an continued access protocol for participants in UCD clinical trials [17] (HPN-100-011) are ongoing. Results to date suggest satisfactory safety and ammonia-lowering activity that is at least as good as that afforded by an equivalent dose of NaPBA.[12,14,15]

2. OBJECTIVES AND OUTCOME VARIABLES

2.1. Objectives

The objectives of this study are:

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

2.2. Outcome Variables

- Control of blood ammonia levels:
  - Mean and maximum blood ammonia levels, retrospectively and during the study
  - Frequency of hyperammonemic crises, retrospectively and during the study
- Frequency of serious adverse events (SAEs)
- Neurocognitive outcomes, evaluated by changes in neuropsychological test scores:
  - Adaptive Behavior Assessment System, second edition (ABAS-II)
  - The Behavior Rating Inventory of Executive Function (BRIEF)
- Growth and development (pediatric patients):
  - Z scores derived from height, weight, body surface area (BSA), and body mass index (BMI) compared to standardized values
  - Occurrence of developmental disabilities and delays
- UCD medication discontinuation or change in medication:
  - Reasons for discontinuation of, or change in, ammonia-scavenging medication
- Additional Data Points (when available)
  - Actual dietary protein intake at predefined intervals
  - For patients on sodium phenylbutyrate or glycerol phenylbutyrate: plasma and urine PK

3. STUDY CONDUCT

3.1. Overall Design of the Study

This is a non-interventional, multi-center registry to be conducted in patients with UCDs. Investigators will prescribe treatments based on usual clinical practice, and there will be no restrictions on the use of commercially available medications. As an observational study, this study will not change the patient/ healthcare provider relationship, nor influence the healthcare provider's drug prescription or the therapeutic management of the patient.

Study visits, procedures, and evaluations are summarized in the Schedule of Assessments (Appendix A) and described in detail in Sections 5.2.

Patients with UCDs will be recruited and invited to attend a Baseline visit. After eligible patients are enrolled, retrospective and baseline data will be collected.

Patients will be followed for up to 10 years, during which time they will be assessed by their healthcare provider. Patients and healthcare provider will be asked to report episodes of hyperammonemic crisis, available ammonia values, and other information. Assessments of follow-up information, data points of interest (Appendix B), and age-appropriate neuropsychological testing (Appendix C) will be performed annually. SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual.

Patients who become pregnant during this registry will be invited to participate in the UCD pregnancy registry (Protocol HPN-100-018)

3.2. Patient Discontinuation and Study Site or Study Termination

3.2.1. Withdrawal of Individual Patients Prior to Study Completion

Patient may decide to discontinue participation (by notifying their Investigator verbally and in writing) at any time without penalty and without affecting future medical care A patient may be withdrawn from the study prior to completion for any of the following reasons:

- Withdrawal of patient consent;
- Any other reason, such that continuation of the patient's participation is thought by the Investigator to be inappropriate.

If a patient withdraws or is withdrawn, the reason should be documented in the electronic case report form (eCRF).

3.2.2. Study or Study Site Termination

The Sponsor reserves the right, at any time, to discontinue enrollment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons.

3.3. Bias and Limitations of the Study

3.3.1. Selection Bias

All UCD patients, regardless of treatment they receive, are eligible to enroll in this registry. In order to minimize bias in the selection of patients, the Investigators are encouraged to consecutively enroll all patients who consent and meet the selection criteria, regardless of treatment, health status, or other considerations.

3.3.2. Patients Lost to Follow-Up

It is expected that some patients will transfer their medical care to a new healthcare provider over the course of their participation in the study. If this occurs, contact information for the new healthcare provider will be requested, and the new healthcare provider may be invited to participate in the study. If the new healthcare provider is not willing to participate in the study, the patient will be asked to sign a medical records release form requesting and permitting the new healthcare provider to provide copies of the patient's medical records (per the data collection time points, Appendix A) for abstraction of study data.

A central investigator will be identified to take responsibilities for data collection and data entry for patients who may not have access to a participating investigator. The following are examples of such cases:

- If a participating investigator decides to end his/her participation in the study, enrolled patients will be asked to transfer to the central investigator.
- If a patient lives in a geographical area where there is no participating investigator or their healthcare provide declines to participate in this registry, the central investigator may enroll that patient and assume responsibility for data collection and data entry for that patient

The central investigator will not be involved in direct management of patients but only collection of study specific data points. The details of processes involved in these cases will be outlined in the Registry Reference Manual.

3.4. Registry Reports

The Sponsor and/or designee will prepare, at a minimum, an annual summary report to the appropriate regulatory authorities where needed. Confidential site-specific and aggregate national reports will be provided on a periodic basis. Annual reports will be de-identified and include accrual rates; summary demographic, clinical, and safety data; and total person-years of follow-up. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

The Sponsor and/or designee will submit a final registry report to the appropriate regulatory authority after all enrolled patients have completed 10 years of follow-up, or have been lost to follow-up; or after the registry has been terminated by the Sponsor.

4. STUDY POPULATION

4.1. Inclusion Criteria

A patient must meet **all** of the following criteria to be eligible for participation in the study.

1. Confirmed or suspected diagnosis of UCD.
2. Signed informed consent and HIPAA Authorization, by the patient or a legally acceptable representative, obtained before any study-related activities are undertaken. Assent should be obtained from pediatric patients according to local regulations.
3. Signed medical records release form, by the patient or a legally acceptable representative, permitting abstraction of the patient's medical records at Baseline and during participation in the study.

4.2. Exclusion Criteria

A patient who meets **any** of the following criteria is not eligible for participation in the study.

1. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

5. STUDY PROCEDURES

5.1. Site Enrollment and Training

The Sponsor or designee will invite Investigators with sufficient resources (time, personnel, and facilities) to participate in the study. Investigators will be required to obtain approval from the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and will be responsible for maintaining all related documents, before enrollment of any patient into the study. The study is designed to minimize the burden of participation.

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure collection of high-quality data for this registry. All sites will be trained on the protocol, registry logistics, and the electronic data capture (EDC) system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting SAEs, deaths, changes in treatments due to AEs, and other information.

5.2. Baseline Visit Procedures and Evaluations

An initial Baseline Visit will be scheduled for patients who are considered for study participation at the discretion of the investigator. After written informed consent is obtained, each patient will be entered into the registry database and assigned a unique study ID number. Study eligibility will be determined by review of the inclusion/exclusion criteria. Patients who are enrolled in the study will then have the following information abstracted from their medical records and undergo the baseline assessments. For patients who may be enrolled by the central investigator the data required for the Baseline Visit may be obtained from their treating physicians after signing appropriate medical records release forms.

5.2.1. Retrospective Data Collected at Study Enrollment

The following retrospective data, for the 12 months preceding enrollment into the study, will be abstracted from the patient's medical record and obtained from family interviews. Patients participating in other Hyperion studies and already receiving glycerol phenylbutyrate may be enrolled in this registry, and the data available from those studies may be used. Available data for all patients may be transferred electronically from other databases to the registry data base.

- All available outpatient ammonia values.
- All available glutamine values.
- Duration, dose, frequency, and route of administration of all ammonia-scavenging agents such as NaPBA, glycerol phenylbutyrate, or sodium phenylacetate / sodium benzoate, or carglumic acid, and reasons for discontinuation, if applicable.
- All hyperammonemic crises, including admission, peak and discharge ammonia detected during the crisis and documented cause, if available.
- Available weight and height.
- Available age-appropriate neuropsychological test results.

5.2.2. Baseline Data Collected at Study Enrollment

The following data will be recorded at the time of enrollment into the study.

- Demographic information (Section 6.1).
- Age at first presentation of symptoms.
- Age at diagnosis.
- Presentation: newborn screening vs. clinical symptoms.
- UCD subtype.
- Ammonia-scavenging medication(s), including dose, frequency, and route of administration.
- Other medications of interest, including dose: arginine, citrulline, and amino acid supplements.
- Height and weight.
- Developmental status and disabilities and delays (Appendix D) .
- Neuropsychological testing (may be performed ≤2 months after enrollment). If neuropsychological testing was performed within 6 months preceding enrollment, the data may be used as baseline values for this study.
- Prescribed total daily protein and caloric intake.
- Most recent available ammonia values.
- Most recent available glutamine and branched-chain amino acid (BCAA) values including leucine, isoleucine and valine.
- Data points of interest (Appendix B).
- Plasma and urine PK for patients on sodium phenylbutyrate or glycerol phenylbutyrate
- Actual dietary protein intake at predefined intervals
- Liver function tests and hematology parameters when available

5.3. Initial Study/Treatment Period/New UCD Treatment, First 30 Days

In patients who start a new nitrogen scavenging agent or switch to a new UCD treatment a visit is typically performed within 30 days to assess the effects of the drug. Therefore, it is recommended that data from such visits be recorded.

The following data, when available, will be recorded, within 30 days of starting a new UCD treatment or switching treatments.

- Ammonia and glutamine values, as judged necessary by the Investigator.
- Ammonia-scavenging medication, including dose, frequency, and route of administration.

- Reasons for discontinuation of, or changes in, ammonia-scavenging medication.
- Hyperammonemic crises if any since last visit, including admission, peak and discharge ammonia detected during the crisis, and documented cause, if available.
- SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual.
- Plasma and urine PK for patients on sodium phenylbutyrate or glycerol phenylbutyrate.
- Liver function tests and hematology parameters

5.4. Annual Visits, Years 1 to 10

The following data will be recorded, at least annually:

- Ammonia and amino acid panel. Collection of fasting ammonia is highly recommended.
- Prescribed total daily protein and caloric intake.
- Hyperammonemic crises since the last recorded visit, including admission, peak and discharge ammonia detected during the crisis, and documented cause, if available.
- Ammonia-scavenging medication(s), including dose, frequency, and route of administration.
- Reasons for discontinuation of, or changes in, ammonia-scavenging medication since the last recorded visit.
- Other medications of interest, including dose: arginine, citrulline, and amino acid supplements.
- Height and weight.
- Developmental status, disabilities and delays (Appendix D).
- Neuropsychological testing, annually.
- Data points of interest (Appendix B).
- SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual.
- Plasma and urine PK for patients on sodium phenylbutyrate or glycerol phenylbutyrate
- Actual dietary protein intake at predefined intervals
- Liver function tests and hematology parameters when available

5.5. Standard Visits

Additional visits as part of standard of care may occur between annual study visits. If such visits occur, any available data from the list below will be collected (All visits will be recorded as sequential study visits in the database):

- Ammonia and amino acid panel. Collection of fasting ammonia is highly recommended.
- Prescribed total daily protein and caloric intake.
- Hyperammonemic crises if any since last visit, including admission, peak and discharge ammonia detected during the crisis, and documented cause, if available.
- Ammonia-scavenging medication(s), including dose, frequency, and route of administration.
- Reasons for discontinuation of, or changes in, ammonia-scavenging medication since the last recorded visit.
- Other medications of interest, including dose: arginine, citrulline and amino acid supplements
- Height and weight.
- Developmental status, disabilities and delays (Appendix D).
- Neuropsychological testing.
- Data points of interest (Appendix B).
- SAEs will be reported as described in Section 6.2.2.3 and the Registry Reference Manual.
- Plasma and urine PK for patients on sodium phenylbutyrate or glycerol phenylbutyrate
- Actual dietary protein intake at predefined intervals.
- Liver function tests and hematology parameters

5.6. Home Study Visits

The option of utilizing a home health care nurse will be provided to investigators and patients. The home health care nurse will not be involved in direct management of patients or obtaining any blood samples but only oversight of collection of certain data points that are typically collected through completing questionnaires or forms such as BRIEF, ABAS-II, and data points of interest. The details of processes involved in these cases will be outlined in the Registry Reference Manual. Home health care nurses involved in this study will be properly trained on the protocol and necessary procedures.

6. STUDY ASSESSMENTS

6.1. Demographic and Clinical Assessments

Demography:

- Age
- Sex
- Race
- Ethnic origin

Urea Cycle Disorder History:

- Age at first presentation of symptoms
- Presentation: newborn screening vs. clinical symptoms
- Age at diagnosis
- UCD subtype
- G tube placement

Past and Current Treatments:

- Ammonia-scavenging medication(s), including dose, frequency, and route of administration
- Prescribed total daily protein and caloric intake
- Other medications of interest, including dose: arginine, citrulline, and amino acid supplements

Patient Clinical Status:

- Height and weight
- Ammonia values, including time of blood draw in relation to last meal and last ammonia-scavenging drug administration
- Fasting glutamine and BCAA values including leucine, isoleucine and valine
- Data points of interest (Appendix B)

Additional Data Points (when available)

- Patients on sodium phenylbutyrate or glycerol phenylbutyrate: plasma and urine PK samples
- Actual dietary protein intake

If these data points are available in electronic format, it may be possible to transfer the data to the EDC.

6.2. Outcome Measures

6.2.1. Ammonia-Scavenging Medication and Ammonia Control

The following data will be used to evaluate control of blood ammonia levels:

- Mean and maximum blood ammonia levels
- Frequency of hyperammonemic crises

The EDC will include CRF pages to capture all the hyperammonemic crises. The captured data points may include ammonia values at admission, maximum and at discharge, medication used to treat the crisis and any known precipitating factors.

Reasons for any change in ammonia-scavenging medication, or discontinuation of medication, will be recorded.

6.2.2. Serious Adverse Events

Since this registry is observational in nature, recording of adverse events by investigational sites will not be mandated. However, occurrence of hospitalizations and deaths will be collected as part of the observation in all patients.

Hyperion will assess any hospitalization or death that is unexpected and deemed to be related to Glycerol phenylbutyrate or any other Hyperion product, by the Investigator, and will file a report of the event to the FDA.

6.2.2.1. Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

6.2.2.2. Definition of Serious Adverse Events

A serious AE (SAE) is an AE that has any of the following outcomes:

- Is fatal
- Is fatal or life-threatening, i.e., in the view of the Investigator, places the patient at immediate risk of death from the reaction as it occurred. A life-threatening SAE would not be an AE that, had it occurred in a more serious form or was left untreated, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis can be fatal.
- Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongation of an existing hospitalization. Hospitalization will not itself be considered an AE. 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 after the signing of the informed consent will not be considered an AE.

- Is a congenital anomaly/birth defect.
- Any other important medical event that may not result in death, be life-threatening or require hospitalization, but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2.2.3. Documentation of Serious Adverse Events

SAE data will be recorded in the patient eCRF, including start and end dates, Investigator-specified severity and relationship, action taken, and outcome.

6.2.2.4. Reporting of Serious Adverse Events

SAE reporting will commence after a patient has provided informed consent. In the event of an SAE, the Investigator will notify the Sponsor or designee, as instructed in the Registry Reference Manual, within 5 business days of the investigator becoming aware of the event. The sponsor or designee must be notified of any fatal or life-threatening SAEs within 24 hours of the Investigator becoming aware of the event. A written report, including the investigator's assessment of causality, must be recorded in the eCRF. The event must also be documented in source documentation. See the Registry Reference Manual for complete instructions.

After receipt of the initial report, the information will be reviewed, and the Investigator will be contacted to request additional information or for data clarification. If required, a follow-up report including all new information obtained on the event must be prepared and sent to designated contact for SAE reporting. Follow-up reports will be filed as necessary until the event has resolved or attained a stable outcome.

The Sponsor assumes responsibility for appropriate reporting of SAEs assessed as related to sponsor specific products to regulatory authorities. The Investigator will report SAEs to the IRB/IEC that approved the registry protocol per institutional requirements, unless otherwise required by local regulations and documented by the IRB/IEC.

6.2.3. Growth and Development Outcomes (pediatric patients)

- Z scores derived from height, weight, BSA, and BMI comparison to standardized values
- Occurrence of developmental disabilities and delays (Appendix D)

6.2.4. Neurocognitive Outcomes

Neurocognitive outcomes will be evaluated by neuropsychological test scores at baseline and during the study (see also Appendix C). Since these tests are primarily self-reported or parent-reported questionnaires the completion of these tests may be done during an office visit or at home. See the Registry Reference Manual for complete instructions.

- Adaptive Behavior Assessment System, second edition (ABAS-II)[18]

The ABAS-II measures adaptive skills for individuals from birth to 89 years. Age-specific rating forms will be used for evaluation of infants and children by parents or caregivers, and self-

evaluation by adults. The ABAS-II provides an estimate of IQ and has a strong correlation with Wechsler IQ scales.

The ABAS-II will be completed annually for patients of all ages.

- The Behavior Rating Inventory of Executive Function (BRIEF)[19]

The BRIEF is a set of clinical scales for executive function, including behavior, cognition, and the Global Executive Composite. Parent response forms will be used for preschool and school-aged children, and a self-report form will be used for adults.

The BRIEF will be completed annually for patients 4 years and older.

7. PRIOR AND CONCOMITANT MEDICATIONS

Dose, frequency, and route of administration will be recorded for medications of interest, including: arginine, citrulline, and amino acid supplements within 12 months prior to enrollment and during the study.

8. DISEASE TREATMENTS

Treatment for UCDs will be prescribed by the Investigator according to usual clinical practice. No attempt will be made to regulate the use of UCD drugs.

Duration, dose, frequency, and route of administration of all ammonia-scavenging agents, such as BUPHENYL® (NaPBA) , Carbaglu (carglumic acid), other forms of NaPBA, glycerol phenylbutyrate, sodium benzoate, or sodium phenylacetate / sodium benzoate (AMMUNOL®), will be recorded.

9. DATA MANAGEMENT

All data collected in the context of this study will be stored and evaluated in accordance with regulatory requirements and applicable guidance for electronic records.

9.1. Medical Record Abstraction

Electronic case report forms (eCRFs) will be used. Data will be extracted from the patient's medical record and entered into the EDC system according to the schedule presented in Appendix A. Patients will be identified by use of the ID number assigned to them when they enroll in the registry.

Before the first patient's medical record is abstracted, the Sponsor and/or designee will meet with the Investigator and the study center's personnel to train them on recording the data on the eCRFs using the EDC system.

9.2. Electronic Case Report Forms and Data Capture System

Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with instructions from the Sponsor and/or designee. Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

On-line logic checks will be built into the system, so that illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study site and answered electronically by that study site's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on the data, will be collected.

The Investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

10. STATISTICAL METHODS

A formal statistical analysis plan (SAP) that will provide details of all analyses and presentation of study data will be approved prior to data analysis. To adapt to the evolving research needs of the UCD community, the analysis plans may be modified for new objectives identified during the course of the study, and minor modifications to the case report form may be made to address new treatments and diagnostics if needed.

10.1. Sample Size

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

10.2. Study Populations and Analyses

- Disposition data will be presented for all patients who attended a Baseline visit.
- All other analyses will be based on all patients who enrolled in the study.
- Additional subgroups also may be examined, as deemed appropriate (pediatric versus adult, UCD type, presentation, type of UCD treatment, etc.).

Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and frequency (n and percent) for categorical variables.

10.2.1. Disposition, Demographic, and Clinical Analyses

Disposition, demographic and clinical data (data points of interest, Appendix B) will be summarized descriptively by UCD medication and presented in listings.

10.2.2. Outcome Measures

Post-baseline values and/or change from baseline in the outcome variables will be summarized by UCD medication with descriptive statistics, and where appropriate, graphical presentations, and in listings. A complete statistical analysis plan will be developed.

SAEs will be coded using MedDRA Version 13.1 or later. Incidence of SAEs will be summarized descriptively by UCD medication, system organ class, and preferred term. All SAEs will be presented in listings.

Incidence of key outcome variables will be presented in listings.

11. ETHICAL AND ADMINISTRATIVE ISSUES

11.1. Informed Consent

Patients considered for enrollment will be given a package containing details about the Registry study, informed consent for participation in the Registry, and Health Insurance Portability and Accountability Act (HIPAA) authorization to access patient's protected health information. Before any protocol-specified procedures are carried out, the Investigator or designee will explain details of the protocol and study procedures, as well as the risks involved, to patients (and if applicable, their legally acceptable representative). Patients will be informed that they are free to withdraw from the study at any time.

Each patient, or a legally acceptable representative, must sign an informed consent form (ICF), approved by the IRB/IEC, indicating their consent to participate. Assent should be obtained from pediatric patients according to individual IRB/IEC requirements. ICFs and assent forms will conform to the requirements of 21 CFR 50.20-27 and International Conference on Harmonisation (ICH) E6 4.8, Principles of Good Clinical Practices (GCP). The original signed ICFs must remain in the patient's file at the study site. Each patient will receive a copy of the signed ICF. During the registry, patients reaching the age of 18 years, or the legal age of majority according to local regulations, must provide written informed consent to continue participation in the registry.

Each patient enrolled in the study, or a legally acceptable representative, also must sign a medical records release form permitting abstraction of medical data from other healthcare providers for entry in the study EDC system. Individual patient data included in the study database will be treated in compliance with all applicable laws and regulations regarding privacy protection.

11.2. Institutional Review Board / Independent Ethics Committee Approval

The protocol and the ICF must be reviewed and approved by the study site's IRB/IEC before the study is initiated. The Investigator is then responsible for informing the IRB/IEC of the completion of the study and should provide any required study status and/or safety report(s).

11.3. Adherence to the Protocol

The study must be conducted as described in the approved protocol.

11.4. Protocol Amendment

Any amendment to the protocol will be created by the Study Sponsor, and subsequently submitted by the site to the IRB/IEC and appropriate regulatory authority as appropriate. If the protocol amendment substantially alters the study design or increases the potential risk or discomfort to the patients, written consent for continued participation in the study must be obtained.

11.5. Monitoring of the Study

The Study Sponsor, Hyperion Therapeutics, and its representatives will monitor the study at the clinical site according to the Monitoring Plan. At the monitoring visits, the progress of the study and any procedural or data issues will be discussed with the Investigator and/or designee. Patient source documents should be available for review; the Investigator will permit the Sponsor, representatives of the Sponsor, the IRB/IEC, or regulatory authorities to inspect facilities and original records relevant to this study.

11.6. Retention of Patient Records

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

11.7. Confidentiality and Publication

The information in this and related documents from the Study Sponsor includes information that is confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IRB/IEC, or local regulatory agency.

An investigator-led steering committee will be established and chartered to guide the scientific discourse and publications related to this study. None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of the steering committee.

11.7.1. Publication Policy

As this is a multicenter study, it is the intent of the Sponsor to publish or present the study results as agreed with the Steering Committee. The Steering Committee, in conjunction with the Sponsor, will establish a uniform procedure for the publication and dissemination of results from this study. For manuscripts based on multi-center study results which are subsequent to the primary publications on such results, the investigational site shall furnish the Sponsor with a copy of any proposed publication at least thirty (30) days in advance of the proposed submission date. Within this thirty-day period, the Sponsor shall review the proposed publication for technical content, including patentable inventions, and for the disclosure of Confidential Information. Not later than the end of the thirty-day period, the Sponsor shall inform the investigational site or Investigator in writing of any objection to inclusion of specific content in the proposed publication. Any Sponsor objection shall be limited to, and specify, the location and content of each item of Confidential Information contained in the proposed publication, publication of which is deemed objectionable by the Sponsor, and of each potentially patentable

invention which is disclosed in the proposed publication. Upon receiving the written objection from the Sponsor, the Investigator shall edit the proposed publication to remove the objectionable Confidential Information before submission. In addition, the Investigator shall either delete disclosure of all potentially patentable inventions or delay submission of the proposed publication for up to ninety (90) days so that any appropriate patent application(s) can be filed. In addition, the Steering Committee must approve any publication that involves results not solely based on site-specific study results prior to submission or disclosure to a third party. For manuscripts solely based on site-specific study results, the Sponsor requests a thirty-day review process from the investigational site as described above, with the right to request removal of Confidential Information and delay for filing patent application(s). However, manuscripts solely based on site-specific study results do not require approval of the Sponsor or the Steering Committee, and neither the Sponsor nor the Steering Committee has the right to require removal of the investigational site's site-specific study results or to approve the manuscript.

The detailed of the publication and additional information will be further defined in the Charter for Steering Committee.

11.8. Steering Committee

The Steering Committee is comprised of thought leaders in the areas of Urea Cycle Disorders. The Committee will have the following responsibilities:

- Provide advice and guidance on the Registry study design and protocol;
- Provide advice and guidance on the variables to be captured on the Case Report Form for the Registry;
- Provide guidance on site selection into the Registry;
- Review data results and provide insights on the interpretation of the data on a semi-annual basis;
- Provide input on the planning and organization of abstracts and manuscripts;
- Draft and review abstracts and manuscripts;
- Review abstracts and papers for submission to scientific journals and conferences;
- Present data at scientific conferences.

Details of roles and responsibilities of the Steering Committee will be defined in the Charter for Steering Committee.

11.9. Coordination

The Sponsor has the right to terminate the Registry at any time. All tangible property provided to Registry patients, Investigators, and their organizations in connection with this Registry shall be and remain the exclusive property of the Sponsor. All data, reports, or other information generated under this Registry (and any other results of such data, reports, or other information) shall be and remain the exclusive property of the Sponsor or its successors in interest. In the event that the Sponsor or any successors in interest terminates its financial support of this Registry the Sponsor would work to, following the guidance of the Steering Committee, entrust the data from the Registry to a non-profit organization (such as the National Urea Cycle

Foundation). Registry data will be maintained over the lifetime of the Registry, but not greater than ten years. At the end of the Study, a de-identified dataset will be transferred to the Sponsor.

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13. APPENDIXES

APPENDIX A. SCHEDULE OF ASSESSMENTS

Schedule for the UCD Registry:

	Baseline/ Enrollment	Day 7 to 30	Annual Visits Years 1 to 10)	Standard Visits
Informed consent	X			
Demography	X			
UCD medical history	X			
UCD status and treatment:				
Ammonia-scavenging medications	X	X	X	X
Prescribed protein and calories[a]	X		X	X
Ammonia levels[b]	X	X	X	X
Amino acid panel	X	X	X	X
Hyperammonemic crises	X	X	X	X
Reasons for change in, or discontinuation of, ammonia-scavenging medications		X	X	X
Data points of interest[c]	X		X	X
Concomitant medications of interest[d]	X		X	X
Height	X		X	X
Weight	X		X	X
Development assessment[e]	X		X	
Neuropsychological tests:[f]				
ABAS-II: All ages	X		X	
BRIEF: Age 4 and older	X		X	
Serious adverse events (SAEs)		X[g]	X[g]	X
Additional data points when available				
Plasma and urine PK	X	X	X	X
Actual dietary protein intake at predefined intervals	X	X	X	X

Note: Standard visits are visits that occur between annual visits as part of standard care of the patients. These visits will be recorded as unscheduled visits, and indicated data will be collected, if available.

a: Prescribed dietary protein and calorie intake will be recorded at the Baseline visit and thereafter, if there is a change in prescribed diet.

b: The time of the last dose and meal must be recorded whenever single blood samples for ammonia are drawn.

c: Data points of interest are defined in Appendix B and refer to select data points collected for the 12 months preceding enrollment and during the study.

d: Concomitant medications of interest include arginine, citrulline, and amino acid supplements.

e: Please see Appendix D. For pediatric patients only; may be performed ≤1 month before or after enrollment

f: Please see Appendix C. May be performed ≤6 months before, or ≤2 months after enrollment.

g: SAEs are to be reported as described in Section 6.2.2.3 and the Registry Reference Manual.

APPENDIX B. DATA POINTS OF INTEREST

The data points of interest attempt to capture signs and symptoms that are commonly associated with uncontrolled UCD or have been reported as common side effects of UCD medication.

Assessed by Investigator			
	Yes	**No**	**NA**
Attention-deficit / hyperactivity disorder (ADHD)			
Learning disability			
Cerebral palsy			
Mental retardation			
Hypertension			
G-tube or nasogastric tube			
Menstrual cycle disorder (specify below)			
Other developmental disabilities (specify below)			
Cancer diagnosis (specify below)			
Type of cancer:_____ Date of diagnosis: _____ Is there a family history of similar cancer? If yes, please specify. _____			

Nitrogen scavenging agents patient is receiving at the time of assessment (please check):

☐ None ☐ BUPHENYL ☐ RAVICTI ☐ AMMUNOL ☐ Carbaglu ☐ Other (specify): _____

Assessed by Investigator and/or Reported by Caregiver/Parents	**No**	**Rarely** Once a month	**Sometimes** Almost Once a week	**Frequently** 2-3 times a week	**Always** Almost daily	**NA**
Body odor						
GASTROINTESTINAL						
Nausea upon or after taking nitrogen scavenging agent						
Vomiting upon or after taking nitrogen scavenging agent						
Refusal to eat due to taste or smell of nitrogen scavenging agent						
Decreased appetite						
Recurrent abdominal pain						
Burning sensation in mouth or throat						
Irritability/agitation/excessive crying						
Heartburn						

NEUROLOGICAL						
Lethargy or sleepiness						
Chronic or recurrent headache						
For Patients with Gastrostomy or Nasogastric Tubes						
Does the patient use his/her gastrostomy or nasogastric tube for nitrogen scavenging agent administration?						
Does the patient use his/her gastrostomy or nasogastric tube for food administration?						
Does the patient use his/her gastrostomy or nasogastric tube for administration of dietary supplements (e.g. arginine, citrulline, amino acids)?						

NA: Unable to assess

APPENDIX C. NEUROPSYCHOLOGICAL TESTS

Adaptive Behavior Assessment System-Second Edition (ABAS-II)[18]

The ABAS-II will be completed annually for all ages, using the appropriate form for each age category. No teacher forms will be used. The forms may be completed during office visits or at home. See the Registry Reference Manual for complete instructions.

The ABAS-II measures adaptive skills for individuals ages birth to 89 years. There are 5 rating forms, for evaluation of various age ranges by parents, teachers, informants and the individual himself or herself. The forms include the Parent/Primary Caregiver Form (ages 0-5 years); Parent Form (ages 5-21 years); Teacher/Daycare Provider Form (Ages 2-5 years); Teacher Form (ages 5-21 years) and the Adult Form (ages16-89, which can be completed by the adult or an informant). The number of items ranges from 193 to 241 items, and the form can be completed in approximately 20 minutes.

The following Skill Areas are assessed in the Parent Form: Communication, Community Use, Functional Academics, Home Living, Health and Safety, Leisure, Self-Care, Self-Direction, Social and Work. A scaled score of 10 + 3 represents the mean. The following four Composite Scores are derived from the sum of the scaled scores: General Adaptive Composite (GAC), Conceptual, Social and Practical. These Composite Scores have a mean of 100 and a standard deviation of 15.

The ABAS-II standardization samples included 1350 respondents for the infant-preschool Parent/Primary Caregiver Form, 1670 respondents for the Parent Form, and 900 respondents for the Adult Self-Report Form. Reliability coefficients were generally .90 for all scales and all forms. Test-retest reliability coefficients were also about .90. Inter-rater correlations were extremely high (generally above .80 for each scale on each form). In terms of validity, correlations between the ABAS-II and the Vineland Adaptive Behavior Scales (VABS) were moderate to high, with a correlation of .70 between the ABAS-II GAC and the Vineland Adaptive Behavior Composite. The correlation between the ABAS-II GAC and the BASC Adaptive Skills Composite is .80.

The ABAS also provides an estimate of IQ. The correlation is .61 between the ABAS-II (Parent Form) GAC and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III), and .41 between the ABAS-II (Parent Form) GAC and the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). For individuals aged 7-21 years, the correlation between the ABAS (Parent Form) GAC and IQ on the Wechsler Abbreviated Scale of Intelligence (WASI) is .42.

The Behavior Rating Inventory of Executive Function (BRIEF)[19]

The BRIEF will be completed annually for ages 4 and above, using the appropriate form for each age category.

The BRIEF provides theoretically and empirically derived clinical scales that measure aspects of executive function. The clinical scales form broader indices of behavior and cognition and an overall score, the Global Executive Composite. Two additional scales (Inconsistency and Negativity) provide a measure of validity of responses. Parent response forms are available for

Preschool and School-Aged Children. A self-report form and an informant response form are available for adults, permitting a uniform measure across all ages. All forms were standardized on normative samples representing a broad variety of race/ethnicity, age and geographical population density.

Rater responses are scored on a 1-3 scale, with 1 corresponding to Never (N), 2 corresponding to Sometimes (S) and 3 corresponding to Often (O). The sum of the raw score for each scale is converted to a T score. Percentile scores and Confidence Intervals are provided in age specific tables. A T score of 50 +/- 10 represents the mean of the T-score distribution, and a score of 65 represents 1.5 standard deviations above the mean, which is the recommended threshold for an "abnormally elevated" score and is considered "clinically significant". The questionnaire is completed within 10-15 minutes.

The Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) is designed for children aged 2 years, 0 months through 5 years 11 months. To be completed by parents (guardians) or teachers, this questionnaire contains 63 items within five scales: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organization. The clinical scales form broad indexes of Inhibitory Self-Control (ISCI), Flexibility (FI) and Emergent Metacognition (EMI) and an overall composite score, the Global Executive Composite (GEC).

The BRIEF-P was standardized on a normative sample of 460 children. The test was determined to have adequate internal consistency, with alpha =.95 for the Global Executive Composite score and > 90 for each of the clinical scales and indexes. Test-retest stability was .90 for the GEC over an average interval of 4.5 weeks. In terms of validity, the BRIEF-P Working Memory scale and the Plan/Organize scale were highly correlated with an ADHD questionnaire ($r = .88, .86$, $p<.001$). Greater than 70% of children with diagnoses of ADHD and autism spectrum disorder received "clinically significant" T Scores (>65), while less than 7% of children in the control group received scores in this range. A score of <8 on the Inconsistency Scale and a score of <4 on the Negativity Scale indicate validity of responses.

The Behavior Rating Inventory of Executive Function (BRIEF) for school-age children (ages 5-18 years) contains 86 items within 8 scales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor. These scales form two indexes, Behavioral Regulation and Metacognition and the overall General Executive Composite. The BRIEF was standardized on a normative sample of 1,419 children.

A score of >6 on the Inconsistency Scale and a score of >5 on the Negativity Scale possibly invalidate the responses (or indicate severe executive function deficits, as might occur in severe traumatic brain injury or autism).

Internal consistency was between .80 and .98 on all scales and indexes. Test-retest reliability was above .80 over a two-week period for the Behavioral Regulation Index, the Metacognition Index, and the overall General Executive Composite. In terms of validity, the Behavioral Regulation index correlated .70 with the ADHD Rating Scale (Hyperactivity/Impulsivity). Scale scores on the BRIEF correlated significantly with other measures of general behavioral functioning but were generally unrelated to scores on tests of emotional functioning.

The Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) Self-Report and Informant Report are designed for adults, ages 18 to 90 years, with a minimum fifth-grade reading level. The BRIEF-A has 75 items comprising 9 clinical scales: Inhibit, Shift, Emotional

Control, Self-Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, Organization of Materials. Three validity scales are used: Negativity, Infrequency and Inconsistency. The clinical scales form two indexes: Behavioral Regulation and Metacognition. In addition, an overall summary score, the Global Executive Composite (GEC) is calculated.

Scores > 6 on the Negativity Scale, >3 on the Infrequency Scale and >8 on the Inconsistency Scale are considered elevated and indicate a need to determine if the responses are valid.

The BRIEF-A was standardized on a normative sample obtained throughout the US via Internet sampling methodology. A total of 1196 adults completed the self-report form, and 1215 adults completed the informant form. Gender accounted for less than 2% of the variance in any scale. Age-related differences were found on all self-report form scales except for the Self-Monitor Scale, with younger adults reporting greater difficulties. Therefore, separate norms are provided for 8 age categories.

Alpha coefficients for internal consistency were above .80 on all scales, with somewhat higher scores of the Informant Report than for the Self-Report forms. Test-retest stability over an average of 4 weeks was adequate for all scales, and correlations with neuropsychological tests of executive functioning were as high as .87 for the Informant Form; all were above .50 for the General Executive Composite.

APPENDIX D. DEVELOPMENTAL MILESTONES

Age	Developmentally Delayed?	
2 Months	□ Yes	□ No
3 Months	□ Yes	□ No
4 Months	□ Yes	□ No
6 Months	□ Yes	□ No
7 Months	□ Yes	□ No
9 Months	□ Yes	□ No
12 Months	□ Yes	□ No
18 Months	□ Yes	□ No
2 Years	□ Yes	□ No
3 Years	□ Yes	□ No
4 Years	□ Yes	□ No
5 Years	□ Yes	□ No

The following list is proposed as general guidelines for assessment of developmental milestones. The data will be captured if available. **Generally age-appropriate milestones for reference only**

Age	Normal Developmental Behavior
2 Months	Smiles at the sound of your voice and follows you with their eyes as you move around a room
3 Months	Raises head and chest when lying on stomach Grasps objects Smiles at other people
4 Months	Babbles, laughs, and tries to imitate sounds; holds head steady
6 Months	Rolls from back to stomach and stomach to back Moves objects from hand to hand
7 Months	Responds to own name Finds partially hidden objects
9 Months	Sits without support, crawls, babbles "mama" and "dada"
12 Months	Walks with or without support Says at least one word Enjoys imitating people
18 Months	Walks independently, drinks from a cup, says at least 15 words, points to body parts
2 Years	Runs and jumps Speaks in two-word sentences Follows simple instructions Begins make-believe play
3 Years	Climbs well Speaks in multiword sentences Sorts objects by shape and color

4 Years	Gets along with people outside the family Draws circles and squares Rides a tricycle
5 Years	Tells name and address Jumps, hops, and skips Gets dressed Counts 10 or more objects

Source : http://children.webmd.com/features/is-your-baby-on-track