



## Observational Study Protocol

**Study No:** HPN-100-018

**Product:** RAVICTI™ (glycerol phenylbutyrate) Liquid

**Study Title:** Pregnancy Exposure Registry of Patients With Urea Cycle Disorders (UCDs) Treated with sodium phenylbutyrate and/or glycerol phenylbutyrate

**Clinical Phase:** 4

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**Date of Protocol:** 11 February 2013 Final

**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.

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**PROTOCOL SIGNATURE PAGE**

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**Hyperion Therapeutics, Inc.**



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Masoud Mokhtarani, MD



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Date

Vice President Clinical Development and Medical Affairs

## PROTOCOL SYNOPSIS

<b>Title</b>	Pregnancy Exposure Registry of Patients With Urea Cycle Disorders (UCDs) Treated with sodium phenylbutyrate and/or glycerol phenylbutyrate
<b>Protocol Number</b>	HPN-100-018
<b>Phase</b>	4
<b>Objectives</b>	To evaluate the outcomes of pregnancy in women with UCDs who were exposed to sodium phenylbutyrate (NaPBA) and/or glycerol phenylbutyrate (GPB) at any time within 90 days prior to first day of Last Menstrual Period (LMP) or during pregnancy. The outcomes of primary interest are major congenital anomalies.
<b>Study Design</b>	This is an observational study designed to collect data on pregnancy outcomes in patients with UCDs who have been treated with NaPBA and/or GPB. Data will be collected directly from patients, prescribers, genetic counselors, gynecologists, pediatricians and other Health Care Professionals (collectively referred to as HCPs) who may be caring for the patient during the pregnancy or caring for the child. Patients enrolled in this registry will be required to provide a select set of data at enrollment and periodically during pregnancy. HCPs will be contacted during the pregnancy, within 4 weeks after the estimated delivery date (EDD), and for pediatric follow-up up to 12 weeks of age.
<b>Background and Rationale</b>	<p>The main goal of medical management of patients with UCD 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 (GPB), sodium phenylbutyrate (NaPBA) and sodium benzoate (NaBZ) are nitrogen scavenging agents used in these patients. Little is known about the potential impact of these products on birth outcomes.</p> <p>UCDs disproportionately affect children and females: depending on the severity of the defect, a UCD can manifest shortly after birth or later in life. The focus of this study will be pregnancy outcomes in patients with UCDs who were administered NaPBA and/or GPB during their pregnancy. The primary objective is to determine the rate of major congenital anomalies. Additional outcome data for the child such as metabolic status, possible diagnosis of UCD, and the presence or absence of hyperammonemia up to 12 weeks post-birth will also be collected and summarized.</p> <p>The United States Food and Drug Administration (FDA) has classified NaPBA and glycerol phenylbutyrate (GPB) as Pregnancy Category C. There are no adequate and well-controlled studies of either NaPBA or GPB in pregnant women. In rabbits given GPB at doses up to 2.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined area under the curve [AUCs] for PBA and PAA) during the period of organogenesis, maternal toxicity, but no effects on embryo-fetal development, was observed. In rats given glycerol phenylbutyrate at 1.9 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined AUCs for PBA and PAA), no adverse embryo-fetal effects were observed. Maternal toxicity, reduced fetal weights, and variations in skeletal development were observed in rats at doses greater than or equal to 5.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined AUCs for PBA and PAA). RAVICTI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p>
<b>Duration of Study</b>	The registry will continue until the target number of 50 prospectively collected pregnancies is reached. The study's progress will be monitored through annual study reports including re-evaluation of progress toward the targeted number of pregnancies.

<p><b>Patient Population and Key Selection Criteria</b></p>	<ul style="list-style-type: none"> <li>• Female patients of reproductive potential with a confirmed or suspected diagnosis of a UCD.</li> <li>• Exposure to NaPBA and/or GPB at any time within 90 days prior to first day of Last Menstrual Period (LMP) or during pregnancy.</li> <li>• Signed informed consent and medical records release by the patient or a legally acceptable representative.</li> </ul>
<p><b>Number of Patients</b></p>	<p>Up to 50 phenylbutyrate derivative-exposed prospectively collected pregnancies. The registry will also include retrospective reports of exposed pregnancies.</p>
<p><b>Outcome Variables and Assessments</b></p>	<p><b>Reproductive History</b></p> <ul style="list-style-type: none"> <li>• Parity, Gravity, Outcomes</li> </ul> <p><b>Genetic findings in prenatal testing:</b></p> <ul style="list-style-type: none"> <li>• Findings relative to UCD status such as family history of UCD (affected parents, siblings) and prenatal testing for UCD screening</li> </ul> <p><b>Medication use prior to and during pregnancy (including timing and exposure details)</b></p> <ul style="list-style-type: none"> <li>• UCD medications</li> <li>• Other medications</li> </ul> <p><b>Pregnancy Outcomes:</b></p> <ul style="list-style-type: none"> <li>• Live birth, Spontaneous abortion/miscarriage, elective/therapeutic abortion, fetal death/stillbirth</li> <li>• Neonatal characteristics:             <ul style="list-style-type: none"> <li>o Status at birth (alive, stillborn)</li> <li>o Apgar Score (1 to 10)</li> <li>o Mental status (alert, lethargic, comatose)</li> <li>o Respiratory status (normal, tachypneic, intubation/ventilation)</li> <li>o Congenital anomalies (yes/no; if yes, type and whether major or minor)</li> <li>o Disposition (discharged to home, hospitalized [if hospitalized, length of hospitalization], transferred to neonatal intensive care unit [NICU], transferred to other institution)</li> <li>o Metabolic status (normal, acidosis, alkalosis)</li> <li>o Ammonia level if any taken</li> <li>o UCD status if known</li> <li>o Hyperammonemia requiring therapy (yes/no; If therapy required, type of treatment [protein restriction, intravenous [IV] nitrogen scavengers, IV arginine, enteral nitrogen scavengers, enteral arginine, enteral citrulline, hemodialysis, other])</li> </ul> </li> <li>• Pediatric Follow-up             <ul style="list-style-type: none"> <li>o Diagnosis of UCD if one is made</li> <li>o UCD management (medication, dietary restriction, and dietary supplements), if applicable</li> <li>o Feeding behavior and weight</li> <li>o Developmental milestones</li> <li>o Evidence of any abnormality, if applicable</li> </ul> </li> </ul>
	<p><b>Serious adverse events (SAEs) for mothers and babies</b></p> <ul style="list-style-type: none"> <li>• Frequency of SAEs</li> </ul> <p><b>Additional Data Points</b></p>

	<ul style="list-style-type: none"> <li>• Available maternal plasma and urine PK data</li> </ul>
<b>Study Procedures</b>	Eligible patients will be enrolled in the study through the United BioSource Corporation (UBC) Call Center (CC) and followed through pregnancy outcomes and the final assessment such as evaluation of infant if a live birth (Appendix A).
<b>Data Collection Procedures</b>	Data concerning patient history, pregnancy outcomes, and infant assessment will be collected at the indicated time points (enrollment, per trimester, pregnancy outcome, and infant follow-up –up to 12 weeks) and entered into the Registry Electronic Data Capture (EDC) system by UBC CC personnel.
<b>Statistical Methods</b>	<p>A formal statistical analysis plan (SAP) that will provide details of all analyses and presentation of registry data will be approved prior to data analysis.</p> <p>Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and and percent for categorical variables.</p>
<b>Sample size:</b>	Up to 50 prospectively (outcome is not known at time of report).collected pregnancies will be targeted. Data will also be included on any pregnancies reported retrospectively (i.e., pregnancy outcome is known at the time of report receipt).
<b>Analysis Population:</b>	Data will be presented for all patients enrolled in the registry. A separate analysis will be done for retrospective reports.
<b>Outcome Data:</b>	The primary outcome is major congenital abnormalities.

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## 1. LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
AUC	area under the curve
CC	Coordinating Center
CDC	Centers for Disease Control and Prevention
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
GPB	Glycerol Phenylbutyrate
HCP	Health Care Professional
IRB	Institutional Review Board
IV	Intravenous
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
NaPBA	Sodium Phenylbutyrate
NOAEL	no-observed-adverse-effect level
PAA	Phenylacetate
PAGN	Phenylacetylglutamine
PBA	Phenylbutyrate
PK	Pharmacokinetic
UBC	United BioSource Corporation
UCDs	Urea Cycle Disorders
US	United States



## 2. BACKGROUND INFORMATION

### 2.1 Disease Under Treatment

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.<sup>2</sup>

### 3. 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.<sup>2</sup> 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.<sup>3</sup> UCDs are therefore associated with significant incidence of neurological abnormalities and intellectual and developmental disabilities over all ages.<sup>4,5</sup> UCD patients with neonatal-onset disease are especially likely to suffer cognitive impairment<sup>5</sup> and death<sup>5</sup> compared with patients who present later in life.

UCDs disproportionately affect children and females: depending on the severity of the defect, a UCD can manifest shortly after birth or later in life. The main goal of medical management of UCD patients is to prevent chronic or acute hyperammonemic states leading to central nervous system damage. This requires restriction in dietary protein intake and the use of nitrogen scavenging agents if diet alone does not adequately control patients. GPB, NaPBA and sodium benzoate are major nitrogen scavenging agents used in these patients.

This pregnancy exposure registry (PER) will track pregnancy outcomes of female UCD patients who have been treated with NaPBA and/or GPB s during their pregnancy. This PER protocol

has been developed following principles provided in the FDA Guidance for Industry: Establishing Pregnancy Exposure Registries.<sup>6</sup>

### 3.1 Products Under Study

NaPBA and GPB are metabolized similarly. After cleavage from sodium or glycerol backbone respectively, they are absorbed as PBA and converted to PAA which is conjugated with glutamine to form phenylacetylglutamine (PAGN) excreted in urine. In non-clinical and clinical studies intact GPB has not been detected in plasma.

#### 3.1.1 Glycerol phenylbutyrate

Glycerol phenylbutyrate, a prodrug of PBA and a pre-prodrug of the active compound PAA, has been recently approved for chronic treatment of patients with UCDs. 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, GPB is a triglyceride consisting of 3 molecules of PBA joined via ester linkage to glycerol. The chemical form of GPB 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 GPB compared with NaPBA, because GPB requires digestion via pancreatic lipases. 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 is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients  $\geq 2$  years of age with urea cycle disorders (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 (eg, essential amino acids, arginine, citrulline, protein-free calorie supplements).<sup>9</sup>

#### Limitations of Use:

- RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
- The safety and efficacy of RAVICTI for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established.
- The use of RAVICTI in patients  $< 2$  months of age is contraindicated.

#### 3.1.1.1 Safety

#### 3.1.1.2 Reproductive and Developmental Toxicity Studies

In rabbits given glycerol phenylbutyrate at doses up to 2.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined area under the curve [AUCs] for PBA and PAA) during the period of organogenesis, maternal toxicity, but no effects on embryo-fetal development, was observed. In rats given glycerol phenylbutyrate at 1.9 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined AUCs for PBA and PAA), no adverse embryo-fetal effects were observed. Maternal toxicity, reduced fetal weights, and variations in skeletal development were

observed in rats at doses greater than or equal to 5.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients (based on combined AUCs for PBA and PAA). RAVICTI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of glycerol phenylbutyrate during the period of organogenesis up to 350 mg/kg/day in rabbits produced maternal toxicity, but no effects on embryo-fetal development. The dose of 350 mg/kg/day in rabbits is approximately 2.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients, based on combined AUCs for PBA and PAA. In rats, at an oral dose of 300 mg/kg/day of glycerol phenylbutyrate (1.9 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients, based on combined AUCs for PBA and PAA) during the period of organogenesis, no effects on embryo-fetal development were observed. Doses  $\geq$ 650 mg/kg/day produced maternal toxicity and adverse effects on embryo-fetal development including reduced fetal weights and cervical ribs at the 7th cervical vertebra. The dose of 650 mg/kg/day in rats is approximately 5.7 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients, based on combined AUCs for PBA and PAA. No developmental abnormalities, effects on growth, or effects on learning and memory were observed in rats through day 92 postpartum following oral administration in pregnant rats with up to 900 mg/kg/day of glycerol phenylbutyrate (8.5 times the dose of 6.87 mL/m<sup>2</sup>/day in adult patients, based on combined AUCs for PBA and PAA) during organogenesis and lactation.

### 3.1.1.3 Clinical Pregnancy Data

As of 04 Oct 2012, there have been four pregnancies reported in the Hyperion Therapeutics UCD clinical trials, as follows:

The partner of subject 05-7611 became pregnant while the subject was participating in HPN-100-007. The pregnancy was reported to the investigator by the subject on 20 May 2010. The subject later reported that his partner gave birth to a full-term, healthy female infant on 20 Dec 2010. No information was obtained regarding the partner. Subject 05-7611 was a 26 year old Hispanic/Latino male whose medical history was significant for ornithine transcarbamylase deficiency, mild retardation (diagnosed 1984), asthma (diagnosed 2001), sinus bradycardia (diagnosed Jul 2008), abdominal pain (since May 2003), mild icterus (since Feb 2003), poor appetite (since Aug 2002), and fatigue (since 2003).

Subject 01-7622, a 25 year old Caucasian female, experienced a Grade 1 spontaneous abortion while enrolled in study HPN-100-007. The subject also participated in study HPN-100-006. The subject's medical history was significant for argininosuccinate synthetase deficiency, a breast abscess due to a fungal infection (Jul 2007), and morbid obesity. The subject had a regular study visit on 03 May 2011, and had the protocol-specified urine pregnancy test done by the hospital laboratory, which was negative. On 24 May 2011 the subject had another regular study visit and had the required urine pregnancy test done by the hospital laboratory, which came back positive. This was approximately three weeks after her last menstrual period. The site then performed an over-the-counter urine pregnancy test, which was also positive. The subject reported that she planned to carry the pregnancy to term. The subject was terminated from the study, all study drug was collected, and she was started on BUPHENYL<sup>®</sup> (sodium phenylbutyrate [NaPBA]). On 31 May 2011 the subject informed the site that she had gotten her menstrual period. The subject had another urine pregnancy test at a clinic near her home on 06 Jun 2011, which was

negative. Because the subject was on BUPHENYL<sup>®</sup> for a week prior to getting her menstrual period, it was considered a co-suspect medication in this event.

Subject 03-117633, a 20 year old Caucasian female, experienced Grade 1 hyperammonemia while hospitalized after giving birth to a healthy infant during study HPN-100-011. The subject also participated in studies HPN-100-006 and HPN-100-007. The subject's medical history was significant for ornithine transcarbamylase deficiency, irregular periods (since Mar 2010), abnormal Papanicolaou smear of the cervix, and human papilloma virus infection (diagnosed Sep 1993). The subject had a previous hospitalization for hyperammonemia on study. On 19 Dec 2011, the subject reported that she had become pregnant. She had been on Depo-Provera injection for birth control throughout her study participation, but had switched to oral contraceptives two months prior. As permitted per protocol, the investigator elected to keep the subject on study. She was admitted to the hospital for induction of labor on 20 Aug 2012. Since she was on "nothing by mouth" status for labor, dosing with HPN-100 was delayed, but no doses were missed. A peripherally inserted central catheter was placed and total parenteral nutrition was started. Intravenous (IV) arginine was also started. She had a normal full-term vaginal delivery on 21 Aug 2012 at 00:20, and the infant was healthy. At 01:30 her ammonia level was 66 umol/L (normal range: 11-51 umol/L). At 05:40 it was 122 umol/L. She did not have altered consciousness or any other clinical symptoms of elevated ammonia. She did experience some edema. She was treated with IV Ammonul. At 12:30 on 21 Aug 2012, her ammonia level had decreased to 34 umol/L, and it never went above normal again during the hospitalization. IV Ammonul and arginine were discontinued on 22 Aug 2012. The subject was discharged from the hospital in stable condition on 24 Aug 2012, at which time this event was considered resolved.

Subject 05-117625, a 19 year old African-American female, reported on 18 Oct 2011 that she had become pregnant while participating in study HPN-100-011. Her sister (subject 05-117626) subsequently reported that subject 05-117625 gave birth to a healthy infant in Apr 2012. According to the sister, subject 05-117625 had stopped taking HPN-100 while pregnant. Subject 05-117625 did not respond to repeated requests for additional information, so no direct verification was obtained. The subject was terminated from the study as lost to follow-up. The subject's medical history was significant for ornithine transcarbamylase deficiency and persistent juvenile pattern T wave inversion (diagnosed Jun 2010). The subject also participated in studies HPN-100-006 and HPN-100-007.

### **3.1.2 Sodium phenylbutyrate – (NaPBA)**

NaPBA is marketed in the United States (US) indicated as an adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life).

Per the BUPHENYL Prescribing Information<sup>8</sup> "BUPHENYL is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients

with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.

NaPBA is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine via acetylation to form PAGN. PAGN then is excreted by the kidneys. On a molar basis, it is comparable to urea (each containing two moles of nitrogen). Therefore, PAGN provides an alternate vehicle for waste nitrogen excretion.

NaPBA is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. NaPBA must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.

#### **3.1.2.1 Safety**

*Pregnancy Category C.*

Animal reproduction studies have not been conducted with BUPHENYL®. It is also not known whether NaPBA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NaPBA should be given to a pregnant woman only if clearly needed.

## **4. PRIMARY OBJECTIVE**

The primary objective of the PER is to evaluate the outcomes of pregnancy in women with UCDs who were exposed to NaPBA and/or GPB at any time within 90 days prior to first day of LMP or during pregnancy. The outcomes of primary interest are major congenital anomalies.

## **5. REGISTRY DESIGN**

This registry is an observational longitudinal cohort study of women with UCDs who were exposed to NaPBA and/or GPB at any time within 90 days prior to the first day of the LMP or during pregnancy. The outcomes of primary interest are major congenital anomalies. Study visits are as per usual care. Hyperion or its designee has developed and is conducting the PER. Coordinating Center (CC) personnel will collect and record data in an EDC system. Data sources include patients, healthcare practitioners (genetic counsellors, gynecologists, obstetricians, pediatricians and primary care practitioners). Data are entered at patient enrollment, each trimester, within 4 weeks after the estimated date of delivery (EDD), and when the infant is 8 to 12 weeks of age.

## 6. STUDY POPULATION

### 6.1 Number of Subjects

UCD is an ultraorphan disease; see [Section 9.2](#) of this protocol for further discussion of the available potential subjects.

A sample size of 50 prospectively (i.e., pregnancy outcome is unknown at the time of the report) collected pregnancies will be targeted. In addition, all reports received retrospectively (i.e., the pregnancy outcome is known at the time of the report) will be collected and analyzed separately.

### 6.2 Inclusion Criteria for Study Patients

The Registry is designed for open enrollment of all patients meeting the following criteria:

- Female patients of reproductive potential with a confirmed or suspected diagnosis of UCD.
- Pregnancy exposure to NaPBA and/or GPB at any time within 90 days prior to first day of LMP or during pregnancy.
- Oral or written informed consent and medical records release by the patient or a legally acceptable representative. A patient will provide oral consent over the phone and be sent hardcopy informed consent and medical records release forms for signature to be returned to the CC. Following receipt of the signed forms, data collection will proceed.
- Able and willing to provide healthcare professional and secondary contact information.

### 6.3 Case Definition of Prospectively vs. Retrospectively Enrolled Pregnant Patients

In order to reduce the bias that may occur when outcome information is known prior to enrollment, women are advised to enroll in the Registry as soon as their pregnancy is known, preferably in the first trimester before the condition of the fetus has been assessed through prenatal testing. In order to determine the impact of such a bias, pregnancy reports and outcomes will be classified as either prospective or retrospective and will be analyzed separately.

The criteria for **prospective case enrollment** is:

- Prospective cases will include patients enrolled after exposure to NaPBA and/or GPB but before the outcome of the pregnancy is known. An exception will be made that women who have undergone prenatal testing that could provide knowledge of the outcome of pregnancy will be considered as a prospective report if the outcome of the testing is normal. Note: Because early prenatal testing is so prevalent, it may be difficult to achieve adequate numbers of prospectively identified patients if all pregnancies with prior prenatal testing are excluded from the prospective analysis. Therefore, the primary analysis includes pregnancies enrolled prior to outcome but after a prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risks of birth defects. To examine this potential source of bias, the analysis will also be conducted excluding the subgroup of women who reported prenatal testing at the time of enrollment.

All other patients will be counted as retrospective enrollment.

The retrospective and prospective **cases will be collected** in a similar fashion, but treated separately as part of any analyses or reports.

## **7. REGISTRY PROCEDURES**

### **7.1 Registry Awareness**

Active outreach will occur to solicit reports of women exposed to NaPBA and/or GPB during pregnancy. The CC will use some or all of the following options to make health care professionals and patients aware of the PER:

- Discussion with female patients of reproductive potential by physicians who have patients participating in the UCD registry (HPN-100-014)
- Reminder to physicians participating in HPN-100-014 to invite all their patients who become pregnant (including those not enrolled in HPN-100-014) to join the PER
- Reminder to all physicians participating in other clinical trials to invite all their patients who become pregnant to join the PER
- Notification of all prescribers of NaPBA and/or GPB
- Notification of UCD education and support groups
- UCD Pregnancy Registry website
- Hyperion website
- FDA pregnancy registry website
- Toll-free telephone number printed on patient materials
- Toll-free registry number and registry website printed on the Prescribing Information for the NaPBA and/or GPB products marketed by Hyperion

### **7.2 Registration Procedures**

Reporting of pregnancy exposures to phenylbutyrate derivatives is voluntary. Pregnancies should be reported as early as possible, before prenatal testing has been performed.

The CC will maintain toll-free telephone lines and toll-free faxes to facilitate subject enrollment, data collection, and data queries.

The Registry will accept reports of NaPBA and/or GPB -exposed pregnancies from the following sources:

- Patient self-referral through telephone contact with the CC
- Prescriber or other HCP referrals
- Pregnancies reported to Hyperion directly

The CC will explain the purpose and scope of the Registry, obtain verbal consent for participation and send the patient a Release of Medical Information form and a Registry Brochure. In some cases, the CC may send information to the patient's HCP as an intermediary.

### **7.3 Registry Contact Schedule**

During the course of the pregnancy, the CC will contact the patient once per trimester. The patient's HCPs will be contacted at 6 to 7 months of gestation for the Prenatal Follow-Up and within 4 weeks after the EDD for Pregnancy Outcome Follow-Up. The infant's HCP will be contacted when the infant is 8 to 12 weeks of age for pediatric follow-up.



### 7.3.1 Registry Activities

#### Patient and Health Care Professional (HCP) Outreach

Data Collection	Registration/ Enrollment <sup>2</sup>	CC Contact With the Patient at Each Trimester	CC Contact With The Patient's HCP(s) at the Prenatal Follow-up, 6 to 7 Months of Gestation	CC Contact with the HCP(s) at the Pregnancy Outcome Follow- up <sup>3</sup> Within 4 Weeks After the EDD	CC Contact with the Infant's HCP at the Pediatric Follow-up, 8 to 12 Weeks Old <sup>4</sup>
Consent <sup>1</sup>	X				
Patient Demographics and Pregnancy History	X				
Contact Information	X	X	X		
Concomitant Medications	X				
Medical History	X				
Pregnancy Status/ Outcome		X	X		
Pediatric History and Examinations				X	
Serious Adverse Events (Pregnancy Related)		X	X	X	X

1. The CC obtains verbal informed consent. The CC then mails the patient an Informed Consent form and Release of Medical Information form to sign and return. If the patient is a minor, verbal consent must be obtained from the parent or legal guardian and verbal assent must be obtained from the patient.

2. The patient will self-enroll and additional contact will be made with the practitioner to obtain medical information.

3. The CC will contact the patients HCP earlier in the pregnancy for outcome data if the patient reports an adverse pregnancy outcome or a therapeutic abortion.

4. The CC will contact the infant's HCP, designated either at registration/enrollment or during one of the previous collection time periods.

### 7.3.2 Information Collected at Enrollment

The following information will be collected at enrollment. This information will be collected from the reporter and/or the patient, and may be supplemented by information from the patient's practitioner.

#### Reporter

- Contact information
- Medical specialty, if HCP

#### Patient information provided by the Reporter or the Patient

- Patient demographic and contact information
  - Contact information for parent or legal guardian if patient is a minor
- Birth date, race and ethnic origin
- Complete name and address, telephone numbers, and e-mail address
- Name, address, and telephone number of a secondary contact outside of the patient's household in the case that the patient is unable to be contacted
- Pregnancy history
- Previous pregnancies – parity, gravity, outcomes
- Complications in previous pregnancies
- Maternal medical history
- Maternal surgical history
- Date of last menstrual period
- Estimated delivery date
- Method of pregnancy confirmation
- Prenatal testing
- Outcome (if reported retrospectively)
- Current medication use
  - Details on UCD treatments
- Possible risk factors
  - Smoking
  - Caffeine
  - Alcohol use
  - Recreational drugs
- Relevant disease history:
  - UCD history (including UCD therapies)
  - Treatment with NaPBA and/or GPB
  - Product name(s)
  - Duration of treatment
  - Dose of products to which exposed during pregnancy

### 7.3.3 Information Collected at the Pregnancy Outcome Follow-up

#### Information Collected at Each Trimester

- Changes in maternal contact information
- Changes in secondary contact information

- Changes in current pregnancy status

#### Information Collected for the Prenatal Follow-up

The following information will be collected from the patient's practitioner at approximately 6 to 7 months for the Prenatal Follow-up:

- Changes in maternal contact information
- Pregnancy status, including prenatal testing, risk factors, and changes in medical condition and medications

### **7.3.4 Information Collected at the Pregnancy Outcome Follow-up**

#### **7.3.4.1 Neonate**

- Outcome of pregnancy: Live birth, Spontaneous abortion/miscarriage, elective/therapeutic abortion, fetal death/ stillbirth
- Apgar score (1 to 10)
- Mental status (alert, lethargic, comatose)
- Respiratory status (normal, tachypneic, intubation and ventilation)
- Congenital anomalies (yes/no, if yes, type)
- Disposition (discharged to home, hospitalized, [if hospitalized, length of hospitalization], transferred to neonatal intensive care unit [NICE], transferred to other institution)
- Metabolic status (normal, acidosis, alkalosis)
- Hyperammonemia requiring therapy (yes/no; If therapy required, type of treatment [protein restriction, intravenous [IV] nitrogen scavengers, IV arginine, enteral nitrogen scavengers, enteral arginine, enteral citrulline, hemodialysis, other])

### **7.3.5 Information Collected at the Pediatric Follow-Up (8 to 12 weeks after delivery)**

- Feeding behavior and weight
- Developmental milestones
- Evidence of any abnormality, if applicable

## **7.4 Study Discontinuation**

### **7.4.1 Losses to Follow-up**

Reports of pregnancy exposure for patients enrolled in the Registry will be collected as per Hyperion's pharmacovigilance process. Thus, at least 3 attempts to obtain information about the outcome of pregnancy will be made within 3 months following EDD before the case is considered lost to follow-up. The CC will contact the healthcare professional using multiple follow-up mechanisms (i.e., mail, fax, telephone, or e-mail) based on prior success and/or healthcare professional preference to minimize the occurrence of missing data. If the CC is unable to solicit the outcome of the pregnancy from the HCP, the patient may be contacted for outcome information. In areas where it is possible to match against birth and death records, a final check will be made for comparison against vital statistics records.

## **7.4.2 Withdrawal of Consent**

Every patient or her legal representative has the right to withdraw consent from the PER.

## **7.5 Classification of Outcomes**

### **7.5.1 Pregnancy Outcomes**

Pregnancy outcomes will be classified into one of the following mutually exclusive categories: spontaneous abortion/miscarriage, elective abortion, fetal death/stillbirth, and live birth. Other Registry outcomes of interest are: ectopic pregnancy, maternal death, and neonatal death. The Registry will attempt to assess all outcomes for the presence of birth defects.

#### **7.5.1.1 Spontaneous Abortion/Miscarriage**

The Registry defines any loss of a fetus due to natural causes at less than 22 weeks gestation as spontaneous abortion. If available, data from gross or pathological examination of the abortus or fetus will be evaluated for structural or chromosomal defects.

#### **7.5.1.2 Elective or Therapeutic Abortion**

The Registry defines an elective or therapeutic abortion as any induced or voluntary fetal loss during pregnancy. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects.

#### **7.5.1.3 Fetal Death/Stillbirth**

Fetal death or stillbirth refers to fetuses born dead at  $\geq 22$  weeks gestation or weighing  $\geq 500$  grams. Fetal death occurring at  $\geq 22$  weeks, but  $< 28$  weeks gestation is considered an early fetal loss. Fetal death occurring at  $\geq 28$  weeks is considered a late fetal loss. If available, data from gross or pathologic examination of the abortus or fetus will be evaluated for structural or chromosomal defects. The Registry will make the final classification between fetal death/stillbirth and spontaneous abortion based on gestational age and weight. If these parameters are not available, the Registry will accept the classification indicated by health care professional.

#### **7.5.1.4 Live Birth**

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate breathing or showing any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached.

#### **7.5.1.5 Ectopic Pregnancies**

Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome including induced termination, maternal death, live birth, or spontaneous pregnancy loss. The Registry adopts definitions outlined in the Center for Disease Control (CDC) National Center for Health Statistics (NCHS) surveillance system.<sup>11</sup>

### **7.5.2 Maternal Death**

The Registry defines a maternal death as a death in a pregnant woman during pregnancy, labor, or delivery.

### **7.5.3 Neonatal Death**

The Registry defines a neonatal death as any death occurring in a neonate prior to 28 days of life. Any structural or congenital defect detected in the gross or pathologic examination of the deceased neonate will be evaluated.

### **7.5.4 Birth Defects**

The Registry adopts the term “birth defect” for an abnormality usually referred to as “congenital abnormality.” A detailed description of birth defects is located in Appendix I.

#### **7.5.4.1 Major Defects**

Criteria for major defects will be those used in the Metropolitan Atlanta Congenital Defects Program (MACDP).<sup>10</sup> The MACDP defines a case as one having at least 1 major structural birth defect or syndrome. It uses a defect collection and coding system known commonly as “BPA” codes that was established by the British Pediatric Association (BPA), World Health Organization, and modified by the CDC (National Center for Birth Defects and Developmental Disabilities, 2004). The system is divided into “codable” and “conditional” defects. Codable defects are usually significant structural malformations or genetic syndromes. UCDs are excluded from this analysis.

## **8. SAFETY DEFINITIONS AND REPORTING**

Only serious adverse events (SAEs) related to pregnancy and pregnancy outcome are required to be recorded under this protocol using the appropriate SAE Report Form. Any non-pregnancy related SAEs reported to the CC will be considered spontaneous reports and are to be forwarded directly to Hyperion.

If the patient or their HCP reports a pregnancy-related SAE, a field in the database will trigger Hyperion’s designed Safety Reporting Vendor to collect the SAE information and initiate follow-up in accordance with the FDA regulations.

The reporting physician must assess the relationship of the pregnancy-related SAE to the phenylbutyrate derivate and record the assessment on an SAE Report Form. The definitions for relationships can be found in the following table.

An SAE is any event that:

- results in death
- is an immediate threat to life
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly or birth defect, or
- any other event which requires intervention to prevent death or hospitalization.

SAEs will be reported to the CC and follow-up will be obtained as needed.

## **9. STATISTICAL CONSIDERATIONS**

### **9.1 General Discussion of the Analysis and Control Groups**

Complete analytical specifications, including tables and listings, will be included in the Statistical Analysis Plan (SAP), which will be prepared separately. All statistical analyses will be coordinated by Hyperion or designee.

Data will be presented using descriptive statistics using number and percent for categorical endpoints, n, mean, standard deviation (SD, ), standard error (SE) of Mean, median, minimum (min, ), maximum (max) for continuous endpoints. The primary analyses will also present 95% confidence intervals (CI).

Depending on the quantity of available data, a logistic regression model may be used to assess the relationship of the dependent binomial variable (had/did not have a major congenital defect) to medication use and other characteristics such as maternal age, race, birthweight and gestational age with the prospective Registry dataset. This model will also produce odds ratios with 95% confidence intervals indicating the likelihood and range of possibility of each independent variable to produce a birth defect.

### **9.2 Sample Size**

UCD is an ultraorphan disease and the majority of undiagnosed or untreated patients either die or are severely developmentally delayed. The Ornithine Transcarbamylase (OTC) Deficiency is the most prevalent UCD and the only x-linked UCD with an incidence of 1 in 14,000 live births. Homozygote females are severely affected and may be developmentally delayed. Heterozygote OTC females may be either carriers or have some residual urea cycle capacity that will manifest as hyperammonemia later in life or during a crisis such as pregnancy. Therefore the number of UCD female patients who may get pregnant while on therapy is expected to be very small.

Every attempt will be made to recruit eligible participant to this pregnancy registry using methods found to be effective in like pregnancy exposure registries. However, the number of women who will be candidates for inclusion with an eligible pregnancy cannot be accurately estimated. Given the relatively small volume of use of these products, the target enrollment for this registry is 50 prospectively enrolled pregnancies.

Any pregnancies reported in previous clinical studies with phenylbutyrate derivatives or spontaneous reports of pregnancies with known outcomes will be considered retrospective reports and will be included in the Registry and analyzed separately.

### 9.3 Potential Biases

As reporting of pregnancies will be totally voluntary, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies may be more likely to be reported.

The calculation of risk of birth defects will exclude fetal losses (spontaneous abortions, induced abortions, or fetal deaths) for which no birth defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The PER will attempt to obtain information on birth defects detected at the time of fetal loss. However, the reporting health care professional may not know the defect status of the aborted fetus. Evaluating spontaneous pregnancy losses is problematic for a number of reasons. First, the number of pregnancy losses in the general population is not well established. Early losses generally occur frequently and losses decrease as pregnancy progresses. Collecting information on pregnancy losses is difficult in this voluntary PER when enrollment time or initial contact with manufacturer cannot always be regulated. Spontaneous losses are likely to occur before the pregnancy is recognized. Even if the pregnancy is recognized, it may not be reported to the PER if the spontaneous loss occurred prior to PER enrollment.

Enrolled pregnancies for which outcome information is unobtainable will be considered lost to follow-up. It is possible that outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases of the loss to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each group will be conducted in an attempt to address this potential source of bias.

### 9.4 Estimates of Prevalence of Birth Defects

For the primary analysis, the prevalence of birth defects reported to the PER is calculated by dividing the number of birth defects by the total number of live births. Pregnancy losses with reported birth defects at  $\geq 22$  gestation weeks are included in the numerator to increase sensitivity and to allow comparison with the national population-based birth defect surveillance systems (CDC MACDP) that uses this convention.

A secondary analysis, including pregnancy losses with reported birth defects occurring at  $< 22$  gestation weeks in the calculation of risk, will be conducted. The analysis of birth defects outcomes will be stratified by earliest trimester of exposure, maternal age, and other maternal risk factors, as appropriate. Statistical analysis will consider maternal age as it influences the rate of chromosomal abnormalities.

Ninety-five percent confidence intervals for birth defect rates will be calculated to assess the degrees of confidence. The prevalence in exposed cases will be compared with the prevalence observed in the population-based birth defect data sources. The strength of evidence for lack of elevated levels of major birth defects in pregnancy exposures to NaPBA and/or GPB will be assessed by comparing the observed proportion of birth defects in the PER with rates from the external birth defect data sources, using a chi-square test.

## **10. ETHICAL, REGULATORY, AND ADMINISTRATIVE REQUIREMENTS**

An independent Ethics Committee will review and approve this PER protocol. The PER will collect information routinely documented in the patient and infant medical record, with no PER-required interventions or procedures to be conducted.

Patients will be asked to participate in the PER, and to provide Authorization for Release of Medical Information. Patients are free to withdraw participation in the PER at any time.

Data provided by the patient and her HCP(s) will be kept strictly confidential. Patient data will be tracked in the PER using identification numbers and patient initials. Complete patient identifying information required for mail and telephone follow-up will be stored in a separate database, with access restricted to key CC personnel.

### **10.1 Registry Steering Committee**

Hyperion or designee will convene an external Registry Steering Committee as suggested in the FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries <sup>(1)</sup>.

All birth defects reported will be reviewed by the Registry Steering Committee or designee to determine whether additional follow-up with the reporting physician is required in order to classify the event, and will review the coded datasets overall for accuracy and internal consistency. Additional external medical consultants may be utilized periodically as needed to evaluate reported defects. The Steering Committee Charter will further define the roles and responsibilities of the Steering Committee.

### **10.2 Informed Consent**

Prior to any information being collected under this protocol, verbal informed consent and signed Informed Consent and Release of Medical Information forms (mailed to the patient by CC) must be obtained from the patient. If the patient is a minor, verbal and written consent must be obtained from the parent or legal guardian and verbal and written assent must be obtained from the patient.

### **10.3 Changes to Final PER Protocol**

The Ethics Committee and appropriate regulatory authorities will be contacted, as applicable, about changes to the protocol.

### **10.4 Record Retention**

Hyperion and UBC will follow their applicable SOPs regarding retention of records.

### **10.5 PER Completion**

The Registry Steering Committee will be notified of completion or termination of this PER.



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## 12. APPENDIX I

### DEFINITION OF BIRTH DEFECTS

The Pregnancy PER has adopted the term “birth defect” for an abnormality usually referred to as a “congenital abnormality” and defines birth defect according to the following criteria:

1. Any major structural or chromosomal defect diagnosed with signs/symptoms, using the Centers for Disease Control and Prevention (CDC) MACDP classification of birth defects (CDC MACDP, 1998; British Pediatric Association [BPA], 1979).
2. On a case-by-case basis, through evaluator review and agreement from external advisors (if required), clusters of 2 or more minor abnormalities that might in combination constitute a birth defect, even if the outcome of each event alone would not constitute a birth defect according to the CDC MACDP classification (CDC MACDP, 1998; BPA, 1979).
3. On a case-by-case basis, through evaluator review and agreement from external advisors (if required), any structural or chromosomal defect (that satisfy criterion 1 or 2) detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant will be included, if available, to increase the sensitivity of Pregnancy PER monitoring. To maintain as much consistency with the CDC birth defect surveillance system as possible without missing a potential signal, only cases meeting the CDC MACDP criteria and those with 2 or more minor defects will be included for analysis. The CDC guidelines disqualify the following as birth defects:
  - those findings that are present in infants with outcomes at <36 weeks gestational age or if gestational age is unavailable, weighing <2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias.
  - infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized birth defect.
  - birth defects identified in outcomes with a gestational age of <20 weeks.