IND NUMBER: 73,480
STUDY NUMBER: HPN-100-011
INVESTIGATIONAL DRUG: HPN-100
STUDY TITLE: Long Term Use of HPN-100 in Urea Cycle Disorders
SPONSOR: Horizon Therapeutics, Inc.
520 Lake Cook Road, Suite 520
Deerfield, IL 60015
Version: 4.0 (Canada), Amendment 03, Administrative Change 1
Date: October 21, 2015

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PROTOCOL SIGNATURE PAGE

Protocol Number: HPN-100-011
Version 4.0 (Canada), Amendment 03, Administrative Change 1
Protocol Title: Long-Term Use of HPN-100 in Urea Cycle Disorders

Horizon Therapeutics, Inc.

Chief Medical Officer & Executive Vice President, Research and Development

Date

Senior Medical Director, Clinical Development

Date

Date

Executive Director, Biostatistics, Premier Research
PROTOCOL SIGNATURE PAGE

Protocol Number: HPN-100-011
Version 4.0 (Canada), Amendment 03, Administrative Change 1
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Horizon Therapeutics, Inc.

______________________________
[Redacted]
Chief Medical Officer & Executive Vice President, Research and Development

______________________________
[Redacted]
Senior Medical Director, Clinical Development

______________________________
Executive Director, Biostatistics, Premier Research

[Redacted]
Date

21 Oct 2015
Date
INVESTIGATOR SIGNATURE PAGE

Protocol Number: HPN-100-011
Version 4, Amendment 03, Administrative Change 1

Protocol Title: Long-Term Use of HPN-100 in Urea Cycle Disorders

Horizon 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
### STUDY PERSONNEL CONTACT INFORMATION

<table>
<thead>
<tr>
<th>Name</th>
<th>Senior Medical Director, Clinical Development</th>
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<td>Horizon Pharma</td>
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<tr>
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# SUMMARY TABLE OF CHANGES

Protocol Version 4.0 (Canada), Amendment 3 (12 February 2013) to Protocol Version 4.0 (Canada), Amendment 3, Administrative Change 1 (21 October 2015)

In addition to the changes highlighted in the table below, this amendment incorporates the following changes to the previous protocol:

- Corrects minor typographical and grammatical errors

<table>
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<th>Amended Text Version 4.0, Amendment 3, Administrative Change 1 21 October 2015</th>
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<td>Page 32, Procedures for Reporting Adverse Events:</td>
<td>Page 36, Procedures for Reporting Adverse Events:</td>
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<td>Addition of Text</td>
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## SYNOPSIS

<table>
<thead>
<tr>
<th>Title of Study</th>
<th>Long-Term Use of HPN-100 in Urea Cycle Disorders</th>
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<tbody>
<tr>
<td>Protocol No.</td>
<td>HPN-100-011</td>
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<tr>
<td>Objective</td>
<td>To evaluate the safety of long-term use of HPN-100 in the management of urea cycle disorders (UCDs)</td>
</tr>
<tr>
<td>Study Drug</td>
<td>HPN-100 [(glyceryl tri-(4-phenylbutyrate)] (investigational product)</td>
</tr>
<tr>
<td>Treatment Arms</td>
<td>All subjects will receive open-label HPN-100.</td>
</tr>
<tr>
<td>Study Population</td>
<td>Subjects with a diagnosis of UCD who completed Study HPN-100-005, HPN-100-007, or HPN-100-012 may be eligible to enroll.</td>
</tr>
<tr>
<td>Study Design</td>
<td>This is a long-term safety study of HPN-100 in UCD subjects. Subjects will be assessed regularly for safety and control of their venous ammonia. Hyperammonemic crisis events will be characterized with respect to contributing factors such as intercurrent illness, diet, and noncompliance with medication.</td>
</tr>
<tr>
<td>Safety Assessments</td>
<td>Assessments will include safety laboratory tests, amino acid panel, and venous ammonia. Adverse events (AEs) will be recorded on an ongoing basis.</td>
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<tr>
<td>Primary Endpoint</td>
<td>Rate of adverse events</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>• Venous ammonia levels • Number and causes of hyperammonemic crises • Neuropsychological testing</td>
</tr>
<tr>
<td>Sample Size and Statistical Considerations</td>
<td>No formal statistical hypothesis testing will be performed.</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>• Male or female subjects who completed protocol HPN-100-005, HPN-100-007, or HPN-100-012 • Signed informed consent by subject and/or subject’s legally authorized representative • Negative pregnancy test for all females of childbearing potential</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>• Any clinical or laboratory abnormality or medical condition that, at the discretion of the investigator, may put the subject at increased risk by participating in this study • Known hypersensitivity to phenylacetate (PAA) or phenylbutyrate (PBA) • Liver transplant, including hepatocellular transplant • Pregnant, breastfeeding or lactating females</td>
</tr>
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</table>
| **Investigational Product, Dosage and Mode of Administration** | HPN-100 [glyceryl tri-(4-phenylbutyrate)] will be administered orally three times daily (TID) with meals.

Subjects who have completed Study HPN-100-005, HPN-100-007, or HPN-100-012 will continue to receive open-label HPN-100, initially at the same dose which they were receiving at the time they completed study HPN-100-005, HPN-100-007, or HPN-100-012.

The investigator may subsequently adjust the dose for any subject if judged clinically appropriate [the dose should not exceed the equivalent of 20 grams (g) of NaPBA (~17.4 milliliters (mL) total daily dose of HPN-100)]. |
| **Duration of Study** | Until HPN-100 is available through the Health Canada Special Access Program |
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<th>Explanation</th>
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<tr>
<td>A&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Amount excreted over 24 hours</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ARG</td>
<td>Arginase</td>
</tr>
<tr>
<td>ASL</td>
<td>Argininosuccinate lyase</td>
</tr>
<tr>
<td>ASS</td>
<td>Argininosuccinate synthetase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;</td>
<td>Area under the concentration from time 0 (pre-dose) to 24 hours</td>
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<td>BRIEF</td>
<td>Behavior rating inventory of executive function</td>
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<td>BUN</td>
<td>Blood urea nitrogen</td>
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<tr>
<td>CBC</td>
<td>Complete blood count</td>
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<tr>
<td>CBCL</td>
<td>Child behavior checklist</td>
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<td>Cmax&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>Maximum plasma concentration at steady state</td>
</tr>
<tr>
<td>Cmin&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>Minimum plasma concentration at steady state</td>
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<tr>
<td>CPS</td>
<td>Carbamyl phosphate synthetase 1</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
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<tr>
<td>CV</td>
<td>Coefficient of variation</td>
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<td>CVLTL</td>
<td>California verbal learning test</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>Case report form</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>HPN-100</td>
<td>Glyceryl tri-(4-phenylbutyrate), GT4P</td>
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<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>INR</td>
<td>International normalized ratio</td>
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<td>Magnetic resonance imaging</td>
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<td>NAGS</td>
<td>N-acetylglutamate synthetase</td>
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<td>NaPBA</td>
<td>Sodium phenylbutyrate</td>
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<td>Explanation</td>
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<td>---------------------------------</td>
<td>-------------------------------------------------</td>
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<td>OTC</td>
<td>Ornithine transcarbamylase</td>
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<tr>
<td>PAA</td>
<td>Phenylacetate</td>
</tr>
<tr>
<td>PAGN</td>
<td>Phenylacetylglutamine</td>
</tr>
<tr>
<td>PBA</td>
<td>Phenylbutyrate</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<td>PP</td>
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<td>Serious adverse event</td>
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<td>Standard operating procedure</td>
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<td>TID</td>
<td>Three times daily</td>
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<tr>
<td>TNAUC</td>
<td>Time-normalized area under the curve</td>
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<td>UCD</td>
<td>Urea cycle disorder</td>
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<td>ULN</td>
<td>Upper limit of normal</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WASI</td>
<td>Wechsler abbreviated scale of intelligence</td>
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1. **BACKGROUND INFORMATION**

1.1. **Medical Introduction and Background**

Urea cycle disorders (UCDs) are inborn errors of metabolism that can result from decreased or absent activity of any of the following enzymes: carbamyl phosphate synthetase (CPS), N-acetylglutamate synthetase (NAGS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), or arginase (ARG). These disorders prevent the conversion of waste nitrogen into urea and result in the accumulation of toxic levels of ammonia in the blood and brain of affected patients (Brusilow 1996).

The age of onset of UCDs is typically in the neonatal period, but onset can occur at any age, depending on the severity of the disorder. Patients with severe enzyme deficiencies, resulting in complete inactivity of one of the urea cycle enzymes, typically develop symptoms within the first week of life, while patients with mild to moderate enzyme deficiencies may become symptomatic as children, and those with mild deficiencies may become symptomatic as adults.

The urea cycle is the major route for metabolism of waste nitrogen in the body. The urea cycle is normally very efficient, and waste nitrogen, in the form of ammonia and other metabolites, does not accumulate in the absence of urea cycle dysfunction or general hepatic dysfunction. Ammonia is a normal metabolic product of amino acid catabolism, which occurs in both the liver and the brain. In the urea cycle, which is completed in the liver, ammonia is converted to urea, eliminating 2 moles of waste nitrogen from ammonia per mole of urea generated.

Therapeutic strategies for patients with UCDs are aimed at both reducing the requirement for ureagenesis and exploiting pathways for the synthesis and excretion of other waste nitrogen products that may serve as substitutes for urea. Approaches include dietary protein restriction, arginine or citrulline supplementation, which can enhance waste nitrogen excretion for certain UCDs, and administration of nitrogen-scavenging drugs. Nitrogen-scavenging drugs for UCDs include sodium phenylbutyrate (NaPBA) tablets or powder for the chronic management of UCDs, and intravenous sodium phenylacetate together with sodium benzoate (10%/10%) (marketed in the United States [US] as AMMONUL®), which is an acute parenterally administered treatment for hyperammonemia in patients with UCDs.

Patients with UCDs who experience hyperammonemia despite dietary nitrogen restriction plus dietary supplementation with arginine or citrulline typically require administration of the ammonia-scavenging agent NaPBA. Patients with UCDs who are treated with NaPBA may still experience episodes of hyperammonemic encephalopathy requiring hospitalization and immediate aggressive medical intervention. Orthotopic liver transplantation may also be considered for patients with severe disease that manifests itself in the neonatal period.

NaPBA tablets and powder have been approved for marketing in the US since 1996 (Trade name: BUPHENYL®) and in the European Union (EU) since 1999 (Trade name: AMMONAPS®) as adjunctive therapy in the long-term management of patients with UCDs involving deficiencies of CPS, OTC, or ASS. Some patients with UCDs are still treated with oral sodium benzoate (Gorker 2005); however, sodium benzoate is not approved by the US Food and
Drug Administration (FDA), nor the European Medicines Agency (EMA), and is thought to be less effective than NaPBA, because each mole of the active metabolite of NaPBA, phenylacetate (PAA), scavenges 2 moles of ammonia (same nitrogen-scavenging capacity as urea), while one mole of benzoate scavenges only one mole of ammonia. This reflects the fact that glutamine, which conjugates with PAA to form PAGN, contains two nitrogens, whereas glycine, which conjugates with benzoate to form hippuric acid, contains only one nitrogen.

Figure 1 illustrates how phenylbutyrate (PBA) (via PAA) and benzoate provide an alternative pathway for nitrogen disposal in patients without a fully functioning urea cycle. Following oral administration, PBA undergoes β-oxidation to the active metabolite PAA, which is then conjugated with glutamine in the liver and kidney and excreted as phenylacetylglutamine (PAGN) (in higher primates and humans) (James 1972). Two moles of nitrogen are removed per mole of PAA when it combines with glutamine to form PAGN, which is then excreted by both renal glomerular filtration and tubular secretion. The nitrogen content of PAGN per mole is identical to that of urea (both contain 2 moles of nitrogen).

Figure 1: Alternative-Pathway Therapy for Nitrogen Disposal


1.2. Summary of Potential Risks and Benefits

HPN-100, a prodrug of PBA and a pre-prodrug of the active compound PAA, is under development as an alternative therapy to NaPBA in patients with UCDs. HPN-100 is expected to provide similar or superior nitrogen-scavenging ability, while eliminating the current issues of bad taste, odor, sodium content, and pill burden.

Three clinical studies have been completed to date: UP 1204-001 in healthy subjects, UP 1204-002 in healthy volunteers and in subjects with liver impairment, and UP 1204-003 in adult subjects with UCDs.
UP 1204-001 was a phase 1, randomized, cross-over, open-label study of HPN-100 in 24 healthy male subjects administered oral NaPBA and oral HPN-100 (equivalent to 3 g/m² of PBA per dose for both study drugs). There were no deaths or serious adverse events (SAEs). More adverse events (AEs) occurred with NaPBA (21 AEs in 10 subjects) than with HPN-100 (6 AEs in 2 subjects). Adverse events reported with NaPBA treatment included gastrointestinal (nausea, vomiting, dysgeusia, epigastric discomfort, and flatulence) and neurological AEs (dizziness, headache, euphoric mood, and visual acuity reduced). None of the AEs reported after HPN-100 treatment (upper abdominal pain, nausea, vomiting, increased blood creatinine kinase, and contusion) were considered related to HPN-100. There were no clinically significant changes or apparent trends with treatment in laboratory values, vital signs, electrocardiogram (ECG) results, or physical examination findings.

UP 1204-002 was a phase 1, open-label study of HPN-100 in subjects with hepatic impairment with cirrhosis (n=24) and in age- and gender-matched control subjects with normal hepatic function (n=8). Overall, AEs were reported in 26/32 subjects. There were no SAEs, no severe AEs, and no AEs leading to withdrawal. The most frequent individual AEs were increased body temperature, which was reported in 10 subjects, and decreased platelet count, which was reported in 5 subjects. Upper abdominal pain, nausea, and dyspepsia were all reported in 3 or more subjects, and headache was reported in 7 subjects. The majority of AEs were mild in severity, and there were no severe AEs. Adverse events observed in cirrhotic subjects were generally consistent with liver disease. In healthy volunteers (n=8), reported AEs included epigastric discomfort and headache in 2 subjects each, and diarrhea, blood glucose increased, alanine aminotransferase (ALT) increased, alkaline phosphatase increased, C-reactive protein increased, eosinophil count increased, and platelet count decreased in 1 subject each. The principal findings of protocols UP 1204-001 and UP 1204-002 have been published (McGuire 2010).

UP 1204-003 was a phase 2, open-label, fixed sequence, switch-over study of the safety, tolerability, and pharmacokinetics (PK) of HPN-100 compared to NaPBA in adult subjects with UCDs (Lee 2010). The study was conducted at 4 US centers and enrolled 14 adult UCD patients, 10 of whom completed the study. All subjects who received at least one dose of HPN-100 completed the study. Upon enrollment, subjects received NaPBA for 7 days and were then admitted to a study unit for overnight observation and 24-hour PK, venous ammonia measurements, amino acids, and urine collections. Subjects were then converted to the PBA equimolar dose of HPN-100, either in a single step or in multiple steps depending on the total dose of NaPBA (9 out of 10 subjects converted in a single step). Subjects stayed on the 100% HPN-100 dose for 7 days and were then re-admitted to the study unit for repeated 24-hour PK, venous ammonia, amino acids, and urine collections.

The results of UP 1204-003 demonstrate that, when administered at doses which are the PBA molar equivalent of NaPBA, HPN-100 is well tolerated and exhibits a similar safety profile to NaPBA. A total of 48 AEs were reported in 9 of the 10 subjects. The overall safety profile was similar for the two drugs; 21 AEs were reported in 7 subjects during 100% NaPBA treatment, and 15 AEs were reported in 5 subjects during 100% HPN-100 treatment. There were two SAEs related to hyperammonemia (Subjects 03-001 and 05-001); both occurred during 100% NaPBA treatment (one SAE was prior to 100% HPN-100 treatment, and one was after the subject completed 100% HPN-100 treatment and switched back to NaPBA). No SAEs occurred during
100% HPN-100 treatment. The hyperammonemic event in Subject 03-001 led to withdrawal from the study prior to initiating HPN-100 treatment; however, this subject entered the study at a later date once stable and was assigned a new subject number, 03-004. The hyperammonemic event in this subject (03-001/03-004) was attributed to noncompliance. Subject 05-001 experienced hyperammonemia 21 days after switching from 100% HPN-100 to 100% NaPBA, which was attributed to noncompliance.

HPN-100-005 is a phase 2, open-label, fixed sequence, switch-over study of the safety, tolerability, and PK of HPN-100 compared to NaPBA in pediatric subjects with UCDs; subjects completing the switchover are offered treatment with HPN-100 as part of the 12 month open label safety extension. The Switch Over part of the study was conducted at 5 US centers and enrolled 11 pediatric UCD patients aged 6-17, all of whom completed the study and enrolled in the safety extension. Upon enrollment into the Switch Over part, subjects received NaPBA for 7 days and were then admitted to a study unit for overnight observation and 24-hour blood-sampling for PK, ammonia and amino acids as well as urine collections. Subjects were then converted to the PBA equimolar dose of HPN-100 and received HPN-100 for 7 days before being re-admitted to the study unit for repeated 24-hour blood-sampling for PK, ammonia and amino acids and urine collections.

During the Switch Over part of study HPN-100-005, a total of 8 AEs were reported in 5 of the 11 pediatric subjects enrolled. A total of 3 AEs were reported in 2 subjects during NaPBA treatment and 6 AEs in 4 subjects during 100% HPN-100 treatment. There were no SAEs, and no hyperammonemic events during the switch-over period of study HPN-100-005.

Figure 2 presents a comparison of the ammonia values from adult (Study UP 1204-003) and pediatric (HPN-100-005) UCD subjects. The 24 hour ammonia pattern with feeding and fasting as well as the effect of HPN-100 on lowering ammonia were very similar for adults (TNAUC ~32% lower on HPN-100 as compared with NaPBA) and pediatric (TNAUC ~27% lower on HPN-100 as compared with NaPBA) subjects.

**Figure 2:** Comparison of Adult and Pediatric Ammonia Values (TNAUC) For Individual Subjects Following Seven Days of Dosing with Either NaPBA or HPN-100

![Time Normalized AUC 24hr in Adults UCD UP 1204-003](image1)

![Time Normalized AUC 24hr in Pediatrics UCD HPN-100-005](image2)

Area under the curve for serial venous ammonia values obtained after 7 days of treatment with NaPBA (BUP/BUPHENYL) and HPN-100 (HPN/HPN-100).
The mean peak venous ammonia value during HPN-100 treatment was 29% lower than that observed with NaPBA (56.3 vs. 79.1 µmol/L in adults and 47.77 vs. 55.66 µmol/L in paediatric subjects; not statistically significant). The overall mean TNAUC for venous ammonia was above the upper limit of normal during NaPBA treatment (38.4 µmol/L in adults and 33.1 µmol/L in pediatrics), but was within the normal range after switching to HPN-100 (26.1 µmol/L in adults and 25.0 µmol/L in pediatric subjects). While these differences in venous ammonia between HPN-100 and NaPBA did not achieve statistical significance, these results collectively suggest that HPN-100 may offer more effective ammonia control than NaPBA.

Table 1 summarizes the PK parameters obtained from the adult (UP 1204-003) and pediatric (HPN-100-005) studies. The PK results for HPN-100 are reasonably similar for adults and children after treatment with HPN-100. The ‘outlier’ in the pediatric data set is PBA-AUC following treatment with NaPBA (739 vs. 236 µg∙h/mL in adults and pediatric patients, respectively), which is both more highly variable and lower than PBA following HPN-100 in pediatric subjects. By contrast, PBA levels following treatment with HPN-100 were similar (540 vs. 631 µg∙h/mL in adults and pediatric patients, respectively), as were blood levels of PAA and PAGN.

**Table 1:** Comparison of Pharmacokinetic Parameters at Steady State – NaPBA vs. HPN-100 in UCD Subjects

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Arithmetic Mean (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaPBA Adults UP 1204-003 (N=10)</td>
</tr>
<tr>
<td>PBA in Plasma</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-24}$ (µg∙h/mL)</td>
<td>739 (49.1)</td>
</tr>
<tr>
<td>C$_{max,ss}$ (µg/mL)</td>
<td>141 (44.3)</td>
</tr>
<tr>
<td>C$_{min,ss}$ (µg/mL)</td>
<td>0.588 (255)</td>
</tr>
<tr>
<td>PAA in Plasma</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-24}$ (µg∙h/mL)</td>
<td>595.6 (123.9)</td>
</tr>
<tr>
<td>C$_{max,ss}$ (µg/mL)</td>
<td>53.0 (94.7)</td>
</tr>
<tr>
<td>C$_{min,ss}$ (µg/mL)</td>
<td>3.56 (194.4)</td>
</tr>
<tr>
<td>PAGN in Plasma</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-24}$ (µg∙h/mL)</td>
<td>1133 (31.1)</td>
</tr>
<tr>
<td>C$_{max,ss}$ (µg/mL)</td>
<td>83.3 (25.8)</td>
</tr>
<tr>
<td>C$_{min,ss}$ (µg/mL)</td>
<td>16.8 (86.1)</td>
</tr>
<tr>
<td>PAGN in Urine</td>
<td></td>
</tr>
<tr>
<td>U-PAGN$_{24-hour Excretion}$ (µg)</td>
<td>12 153 473 (48.2)</td>
</tr>
<tr>
<td>Fe$_{0.24}$ (%)</td>
<td>56.2 (13.5)</td>
</tr>
</tbody>
</table>
1.3. Study Rationale

There is extensive clinical experience with NaPBA, which has been shown to be safe and effective in improving long-term survival in patients with UCDs (i.e., reducing the incidence of deaths due to hyperammonemic encephalopathy) when administered at the recommended dose levels.

Compliance with NaPBA is difficult due to a 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 half life of the active metabolite PAA, the BUPHENYL package insert recommends 3–6 times/day dosing. Some pediatric patients with severe deficiency states require nasogastric or gastrostomy tubes to ensure adequate compliance with the complex treatment regimens (Maestri 1999, McBride 2004, Singh 2007). All of these factors render NaPBA very difficult to take, and compliance is suboptimal even for UCD patients with the most severe deficiency states, whose alternative is life-threatening hyperammonemia.

HPN-100 [glyceryl tri-(4-phenylbutyrate)], is a nitrogen-scavenging agent with improved PK characteristics and palatability that is expected to improve the ease of administration and provide a significant quality-of-life benefit to UCD patients. In contrast to NaPBA which is a salt, HPN-100 is a triglyceride, which delivers 3 moles of PBA per each mole of HPN-100 and is a nearly odorless and tasteless, colorless to pale yellow organic oil. HPN-100 contains no sodium, is expected to improve the ease and comfort of administration of medication, and provides a substantially reduced pill burden due to the concentrated nature of the drug. These advantages would represent a significant advance in the management of UCD patients and may result in improved compliance and outcomes.

The findings from UP 1204-003 were largely corroborated by the findings from Protocol HPN-100-005 in pediatric subjects. Twenty-four hour ammonia profiles were very similar, including the directionally lower values on HPN-100 as compared with NaPBA. HPN-100 safety was satisfactory in both adult and pediatrics subjects, and the PK profiles of HPN-100 were similar.

The present protocol is a treatment protocol to allow continued use of HPN-100 for the treatment of UCD subjects who complete 12 months of treatment in Study HPN-100-005, HPN-100-007, or HPN-100-012. Under this protocol, long-term safety will continue to be assessed.

1.4. Conduct of Trial and Compliance with GCP

This study will be conducted in compliance with the protocol, in accordance with the Guidance for Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) E6, and in accordance with applicable regulatory requirements.
1.5. Study Population
Subjects with a diagnosis of UCD who completed Study HPN-100-005, HPN-100-007, or HPN-100-012 may be eligible to enroll.
2. TRIAL OBJECTIVES AND ENDPOINTS

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

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

2.1. Primary Endpoint

The primary endpoint is the rate of adverse events.

2.2. Secondary Endpoints

The secondary endpoints are the following:

- Venous ammonia levels
- Number and causes of hyperammonemic crises
- Neuropsychological testing
3. **OVERALL STUDY DESIGN AND PLAN**

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

Please refer to Section 4.3 for subject withdrawal criteria.

3.2. **Dose Selection**
As in Study HPN-100-005, HPN-100-007, and HPN-100-012 the dose of NaPBA and thus HPN-100 is chosen based on the severity of the enzyme deficiency, on the content of the subject’s diet, and on the intake of amino acids or other supplements, and thus will vary among subjects.

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

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

Dose adjustments will be calculated by the investigator based on a clinical assessment of the subject’s ammonia-scavenging needs (e.g., severity of the UCD defect, dietary protein intake, and urinary PAGN excretion).

3.3. **Duration of the Study**
Subjects will stay on this study until HPN-100 is available through the Health Canada Special Access Program.

3.4. **Management of Episodes of Hyperammonemia**
Throughout this Treatment Protocol, occurrence of hyperammonemic crises will be captured. The following must be captured at a minimum on the appropriate case report forms (CRFs):

- Precipitating factors (e.g., infection, intercurrent illness, stress, change in diet, noncompliance with HPN-100, noncompliance with other UCD medication)
- If due to noncompliance, reasons for noncompliance
- Ammonia level at hospital admission
- Signs and symptoms suggestive of hyperammonemia
3.4.1. Hyperammonemic Crisis

Hyperammonemic crisis is defined as follows:

- Clinical symptoms associated with ammonia of ≥ 100 µmol/L

Symptoms suggestive of an acute hyperammonemic crisis may include the following:

- Vomiting
- Nausea
- Headache
- Protein intolerance

3.4.1.1. Management of Hyperammonemic Crisis and Withdrawal of Subjects

Intercurrent episodes of hyperammonemia may be treated with rescue medication, with or without hemodialysis, at the investigator’s discretion. Any hospitalization for hyperammonemia should be considered an SAE. If sodium phenylacetate/sodium benzoate injection 10%/10% (AMMONUL®) is used as rescue medication for intercurrent hyperammonemia and if study medication is suspended during such treatment, study medication should be reintroduced as soon as practical. The sodium phenylacetate/sodium benzoate 10%/10% infusion should be continued for a minimum of 2 hours after reintroducing HPN-100.

3.4.2. Symptoms Suggestive of Chronic Hyperammonemia

Presence of at least two of the following clinical criteria would constitute evidence of chronic hyperammonemia:

- Recurrent vomiting
- Protein intolerance (becoming physically ill with high protein intake on multiple occasions leading to a self-imposed low-protein diet)
- Episodic lethargy
- Psychosis (episodic)
- Abnormal neurological examination (hypotonia, spasticity, hyperreflexia, and/or clonus)
- Brain edema (evidence on magnetic resonance imaging [MRI] or computed tomography [CT] scan)
- Chronic migraine headaches

New or worsening manifestations of chronic hyperammonemia, as compared with baseline, may be treated with an HPN-100 dose adjustment or the use of rescue medications such as AMMONUL®.
4. **SELECTION AND WITHDRAWAL OF SUBJECTS**

4.1. **Subject Inclusion Criteria**

- Male and female subjects who completed HPN-100-005, HPN-100-007, or HPN-100-012
- Signed informed consent by subject and/or subject’s legally authorized representative
- Negative pregnancy test for all females of childbearing potential

4.2. **Subject Exclusion Criteria**

- Any clinical or laboratory abnormality or medical condition that, at the discretion of the investigator, may put the subject at increased risk when participating
- Known hypersensitivity to PAA or PBA
- Liver transplant, including hepatocellular transplant
- Pregnant, breastfeeding or lactating females

4.3. **Subject Withdrawal Criteria**

Subjects may be withdrawn for any of the following reasons:

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

Please refer to Section 6.2 for procedures in case of early termination.
5. TREATMENT OF SUBJECTS

5.1. Description of Study Drug

HPN-100 [glyceryl tri-(4-phenylbutyrate)] is a precursor of PBA. PBA is released from HPN-100 in the gastrointestinal tract and acts as a nitrogen-scavenging agent in the body. PBA is a precursor of the active agent PAA, which combines with glutamine and ammonia to form PAGN, which is excreted in urine.

The chemical name for HPN-100 is glyceryl tri-(4-phenylbutyrate). The empirical formula is C\textsubscript{33}H\textsubscript{38}O\textsubscript{6} and the molecular weight is 530.67.

It is a colorless to pale yellow, nearly odorless and tasteless oil that is administered neat (undiluted) orally or via gastrostomy tube. The density is 1.1033 g/L.

HPN-100 contains no inactive ingredients.

Each mL of HPN-100 delivers 1.02 g of PBA.

5.2. Study Drug Dosage and Administration

5.2.1. Preparation

No special preparation is needed for HPN-100, which is administered neat (undiluted). Each mL of HPN-100 equals 1.1 g glyceryl tri-(4-phenylbutyrate) and delivers 1.02 g of PBA.

Food grade flavors (lemon, lime, orange and tangerine oil) may be mixed in accordance with the pharmacy manual by the Pharmacist.

5.2.2. Dose and Administration

HPN-100 will be administered orally three times daily (TID) with meals. Please refer to section 3.2 for complete information on dose selection and adjustment.

The maximum recommended dose of HPN-100 in subjects weighing less than 20 kg is 0.53 mL/kg/day (equivalent to 600 mg/kg/day of NaPBA), and is 11.48 mL/m\textsuperscript{2}/day in heavier subjects (equivalent to 13g/m\textsuperscript{2}/day of NaPBA). The maximum HPN-100 dose should be 17.4 mL/day, which is equivalent to 20 g/day of NaPBA.

5.3. Study Drug Materials and Management

5.3.1. Study Drug Packaging and Labeling

HPN-100 will be supplied in glass bottles with teflon screw-caps, and labeled with study identification information. Disposable oral syringes and Adapta Caps™ will be provided for measuring and administering HPN-100.

Food grade flavors may also be provided for use by the Pharmacist, if requested by a subject.
5.3.2. **Study Drug Storage**
HPN-100 is capped with nitrogen and stored at room temperature (15 to 30°C [59 to 86°F]). After opening, keep the bottle tightly closed after each use. Please reference the Pharmacy Manual for detailed information on study drug packaging, labeling and storage.

5.3.3. **Study Drug Dispensing and Disposal**
HPN-100 will be supplied by the Sponsor or designee.

HPN-100 will be either dispensed to the subject through the Investigator or designee at each site or by a centralized pharmacy per Investigator order. The maximum supply of HPN-100 for a single shipment will be a 3 to 6-month supply.

Subjects are NOT allowed to dispose of empty containers.

See Pharmacy Manual for complete instructions.

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

5.4.1. **Prohibited Medications**
The following prohibited medications may not be used during the study:

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

If, in the opinion of the treating physician, any of these medications are needed for treatment of a study participant, the investigator, in conjunction with the medical monitor, should discuss the feasibility of early termination.

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

5.5. **Randomization and Blinding**
This is a non-randomized, open-label study.
6. **STUDY PROCEDURES**

The study Schedule of Study Assessments is provided in Appendix A. All Study Visits should occur in the morning and, if possible, fasted (before breakfast).

### 6.1. Study Visits

#### 6.1.1. Baseline Visit (Month 0)

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

- Obtain informed consent from subject
- Physical and neurological Exam
- Record medical history
- Record concomitant medications
- Measure height and weight
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect blood for safety laboratory assessments (see Section 8.2 for a list of tests)
- Perform urine pregnancy test
- Collect single blood sample for venous ammonia level assessment. Record time of blood sample and last dose
- Collect blood for amino acid panel
- Administer neuropsychological battery (Appendix B)
- Assess conformance to inclusion/exclusion criteria
- Record AEs
- Dispense HPN-100
6.1.2. **Routine Clinic Visits (Every 6 Months)**

Subjects should visit the clinic as prescribed by the Investigator, but at a minimum a visit must occur every 6 months until the HPN-100 is available to the subject through the Health Canada Special Access Program or the subject terminates HPN-100 for other reasons. At each clinic visit the following will be recorded:

- Inquiry about a hyperammonemic crisis since the last visit. Record necessary information per Study Manual
- Record concomitant medications (including any HPN-100 dose adjustment. If dose adjustment is made, record reason)
- Physical and neurological Exam
- Measure height and weight
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect single blood sample for venous ammonia level assessment.
- Collect blood for safety laboratory assessments and amino acid panel (see Section 8.2)
  - Note: if labs were drawn within 30 days of study visit (e.g., as part of another study or standard of care), only the research labs not drawn need to be administered.
- Perform urine pregnancy test
  - Note: Animal reproductive studies are in progress. It is not known whether HPN-100 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Should a subject become pregnant while taking HPN-100, continued administration should be at the discretion of the Investigator in consultation with the study subject, taking into account the risk/benefit of continued administration, and with prior approval from the Sponsor.
- Record prescribed protein and calories
- Record AEs
- Dispense HPN-100

6.1.3. **Unscheduled Visits**

Should a subject have an unscheduled visit (e.g., unscheduled clinic visit, emergency room visit, or hospitalization) the following will be recorded:

- Record Reason for the visit (e.g., hyperammonemic crisis, vomiting, lethargy, seizure, fever, diarrhea, dehydration, anorexia, or other)
  - If the visit meets the definition of a SAE, complete a SAE report form, see Section 8).
– If the visit is due to a hyperammonemic crisis, complete the hyperammonemic event CRF.

- Record concomitant medications (including any HPN-100 dose adjustment. If dose adjustment is made, record reason)
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect single blood sample for venous ammonia level assessment
- Collect blood for safety laboratory assessments and amino acid panel
- Perform urine pregnancy test

- Note: Animal reproductive studies are in progress. It is not known whether HPN-100 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Should a subject become pregnant while taking HPN-100, continued administration should be at the discretion of the Investigator in consultation with the study subject, taking into account the risk/benefit of continued administration, and with prior approval from the Sponsor.

- Record prescribed protein and calories
- Record AEs

6.1.4. Annual (12 Month) / End of Study Visit

Subjects will visit the clinic a minimum of every 6 months until HPN-100 is available through the Health Canada Special Access Program. Assessments for every 12 months or the final visit are the same as the 6 month visit, with the exception of performing the neuropsychological battery, as follows:

- Inquiry about a hyperammonemic crisis since the last visit. Record necessary information per Study (Reference) Manual
- Record concomitant medications (including any HPN-100 dose adjustment. If dose adjustment is made, record reason)
- Physical and neurological exam
- Measure height and weight
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect single blood sample for venous ammonia level assessment
- Collect blood for safety laboratory assessments and amino acid panel (see Section 8.2)
  - Note: if labs were drawn within 30 days of study visit (e.g., as part of another study or standard of care), only the research labs not drawn need to be administered.
- Perform urine pregnancy test
− Note: Animal reproductive studies are in progress. It is not known whether HPN-100 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Should a subject become pregnant while taking HPN-100, continued administration should be at the discretion of the Investigator in consultation with the study subject, taking into account the risk/benefit of continued administration, and with prior approval from the Sponsor.

- Administer neuropsychological battery (Appendix B)
- Record prescribed protein and calories
- Record AEs
- Discharge subject on available UCD medication

6.2. Early Termination Procedures

Subjects who discontinue treatment with HPN-100 will have end of study procedures performed as early termination assessments (see Section 6.1.3).
7. ASSESSMENT OF EFFICACY

No formal assessment of efficacy will be performed. Blood samples will be collected for assessment of venous ammonia levels at office visits in accordance with the Schedule of Study Assessments (Appendix A) and the Laboratory Manual.
8. ASSESSMENT OF SAFETY

Safety laboratory tests, amino acid panel, and vital signs will be evaluated as described in the Schedule of Study Assessments (Appendix A). Adverse events and concomitant medications will be recorded on an ongoing basis.

8.1. Adverse Events

8.1.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs will be recorded in this study from the signing of the informed consent for this study through 7 days after the last dose of study medication.

Adverse events include the following:

- Any diagnosis, sign, symptom, or abnormal laboratory value not present, detected, or complained of at the baseline assessment of the prior study (HPN-100-005, HPN-100-007, or HPN-100-012)
- Any diagnosis, sign, symptom, or abnormal laboratory value noted at baseline that increases in severity or frequency during the study

Hyperammonemia should be considered an AE if it results in a hyperammonemic crisis as defined in section 3.4.1. The investigator will be asked to assess the precipitating event, if known and record all pertinent information on specially-designed CRF for hyperammonemic crisis. Note that hyperammonemic crises can be considered expected complications of the underlying disease for many UCD patients.

Other laboratory values that are outside the laboratory reference range should be reported as AEs if considered clinically significant by the investigator.

Diseases or diagnoses present at entry into the prior study are regarded as concomitant diseases and will be documented in the medical history. Any clinically significant exacerbations of such conditions should be recorded as AEs in the current study.

AEs that emerged during the prior study and are on-going at the transition into this study should be recorded as AEs on the AE CRF for this study.

Diseases or diagnoses emerging during the study period are considered AEs and will be documented and reported accordingly.

The term AE does not imply a causal relationship to the study medication.
All subjects experiencing AEs, including abnormal laboratory values, whether or not associated with use of the study medication, must be monitored until the condition returns to normal, returns to the subject’s baseline, or until the investigator determines the AE has reached a stable outcome.

The sponsor will notify all investigators involved in the clinical investigation of important safety information regarding the study treatment as required by the applicable regulations.

Adverse events are divided into the categories “serious” and “non-serious.” This determines the procedure that must be used to report/document the AE.

8.1.2. Definition of Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability/incapacity
- Hospitalization or prolongation of an existing hospitalization
- Congenital anomaly/birth defect
- Important Medical Events
  - Important medical events are defined as those that may not result in death, be life-threatening, or require hospitalization but may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above.

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

Hyperammonemic episodes will be considered SAEs when they meet the criteria for an SAE as described above. Hyperammonemia that does not result in a serious outcome should not be considered an AE. If a hyperammonemic episode occurs, the investigator will be asked to assess the precipitating event, if known, on a specially-designed CRF.

8.1.3. Assessment of Severity

All adverse events, both serious and non-serious, will be assessed for severity using the CTCAE v3.0. The CTCAE scale includes unique clinical descriptions of adverse events that are categorized by anatomy and/or pathophysiology. The CTCAE v3.0 scale displays Grades 1 through 5 with unique clinical descriptions of severity for each AE (including abnormal laboratory values) based on this general guideline:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
• Grade 4  Life-threatening or disabling AE
• Grade 5  AE resulting in death

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

For any AEs not covered by the CTCAE, the following criteria should be used:

• Mild: Does not interfere with routine activities
• Moderate: Interferes with routine activities
• Severe: Impossible to perform routine activities
• Life-threatening: Subject was at immediate risk of death from the event at the time it occurred, or the AE caused permanent disability
• Fatal: AE with outcome of death

8.1.4.  Assessment of Relationship to Study Drug

The principal investigator must review each AE and make the determination of relationship to study drug (i.e. whether or not the study drug possibly or probably caused the AE) using the following definitions:

• Not Related: The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or injury; does not follow a known response pattern to the study drug; and/or no temporal relationship exists with the study drug. For AEs considered not related to study drug, the investigator will be asked to choose one of the following:
  – Not related (noncompliance with medication)
  – Not related (noncompliance with diet)
  – Not related (intercurrent illness)
  – Not related (symptoms of primary disease)
  – Not related (use of concomitant medication)
  – Not related (other)

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

• Probably Related: The event follows a reasonable temporal sequence from administration of the medication and is part of a known or suspected response pattern to the medication, and a plausible alternative etiology cannot be identified.
NOTE: Lack of efficacy of the study drug is not considered an adverse event or the cause of an adverse event in the clinical trial setting in which efficacy has not yet been established by any regulatory authority.

8.1.5. Recording Adverse Events

Subjects will be questioned about AEs at each study visit using nonspecific questions such as, “How have you been feeling since the last study visit?” All adverse events, irrespective of relationship to the study treatment, that begin after the signing of the informed consent for this study through 7 days after the last dose of study medication will be considered AEs in this study and must be recorded on the CRF and documented in the source record. Also, AEs from the prior study that are continuing at the signing of the Informed Consent for this study should be recorded on the Medical History CRF for this study.

8.1.6. Procedures for Reporting Adverse Events

All SAEs, including deaths from any cause that occur at any time beginning from the time informed consent is given until 7 days after the last dose of study medication should be reported to the safety contact within 24 hours of the investigator becoming aware of the event:

Phone: [Redacted]
Fax: [Redacted]
Email: [Redacted]

A written report must be sent by fax within 24 hours to the safety contact for SAE reporting. The event must also be documented in source documentation and on the CRF.

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 the safety contact for SAE reporting. Follow-up reports will be filed as necessary until the event has resolved or attained a stable outcome.

8.1.7. Post-Study Reporting for Subjects with Adverse Events

Once the study-defined AE reporting period has passed (see Section 8.1.6), further reporting is required only if an investigator becomes aware of an AE that he or she considers related to the study treatment.

8.2. Laboratory Assessments

Blood samples will be collected for assessment of subject safety at office visits in accordance with the Schedule of Study Assessments (Appendix A). Safety laboratory assessments will include:

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

Annually, ~51 mL of venous blood for safety laboratory assessments and amino acid panel will be drawn. Please note that plasma ammonia only will be processed and analyzed by the investigative site laboratory while all other safety laboratory samples and amino acid panel samples will be processed and analyzed by a central laboratory per their respective standard operating procedures (SOPs).

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

8.3. Vital Signs

Blood pressure, respiratory rate, temperature, and pulse will be measured according to the Schedule of Study Assessments (Appendix A).

8.4. Unblinding of Treatment Assignment

Not applicable; this is an open-label study.
9. OTHER ASSESSMENTS

9.1. Neuropsychological Battery

Neuropsychological testing will be administered once a year, according to the Schedule of Study Assessments (Appendix A).

These tests must be administered by a properly trained medical professional. The tests are described briefly in Appendix B.
10. STATISTICS

10.1. Sample Size and Power
No formal sample size or power calculations are proposed, as this is a long-term safety study.

10.2. Endpoints
The primary endpoint is the rate of adverse events.
Secondary endpoints include the following:
   - Venous ammonia levels
   - Number and causes of hyperammonemic events
   - Neuropsychological testing

10.3. Methods of Analysis
Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables, and frequency and percentages for categorical variables. Any statistical hypothesis testing that is performed will be exploratory in nature.

10.3.1. Analysis Populations
The following populations will be considered in the analysis of data for this study:

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

10.3.2. Baseline and Demographic Variables
Demographic data including age, race, and gender will be summarized using descriptive statistics. Baseline variables including medical history, vital signs, laboratory data, and other baseline disease characteristics will be summarized using descriptive statistics. Summaries will be provided for the safety population.

10.3.3. Safety Variables
Safety assessments will include adverse events, vital signs, and clinical laboratory measurements.

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

The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to study treatment
will also be provided. Serious AEs and AEs leading to discontinuation of study treatment will be presented by system organ class and preferred term.

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

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

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

10.3.4. Efficacy Variables

Venous ammonia levels and changes from baseline will be summarized with descriptive statistics. The percentage of venous ammonia values above the upper limit of normal (ULN) will also be summarized.

The number of hyperammonemic crises and their causes will be summarized descriptively.

10.3.5. Other Variables

Neuropsychological testing results will be summarized for each item and scale.
11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Required information will be entered into the appropriate CRFs, which will be maintained in order and up-to-date so they reflect the latest information on the subject’s study file. All records are to be kept in conformance with applicable guidelines and SOPs.

When the study 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.

11.1. Study Monitoring

The sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities, and upon request, inspecting the various records of the trial. The sponsor’s clinical monitor is responsible for inspecting the CRFs throughout the study to verify source records; adherence to the protocol; completeness, accuracy, and consistency of data; and adherence to Good Clinical Practices. The monitor should have access to subject medical records and other study-related records needed to verify entries on the CRFs.

The investigator agrees to cooperate with the monitor.

11.2. Audits and Inspections

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

11.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

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

The investigator and appropriate representatives from the sponsor will sign the protocol to document their willingness to adhere to this protocol and to conduct the study in accordance with Good Clinical Practices.
12. QUALITY CONTROL AND QUALITY ASSURANCE

Data will be entered into a password-protected database in accordance with the Study Operations Manual. After resolution of any discrepancies and a combination of manual and automated data-review procedures, the final data sets will be subject to a quality assurance audit.

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

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

Corrections to the CRFs will be made in accordance with the Study Operations Manual. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Delegation of Responsibilities form. No erasures, correction fluid, or correction tape may be used.

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

The principal investigator will sign and date the indicated places on the CRF. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF and the data queries, and that the investigator agreed with the content.
13. ETHICS

13.1. Ethics Review

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

13.2. Ethical Conduct of the Study

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

13.3. Written Informed Consent

In accordance with ICH GCPs, written informed consent must be obtained prior to a subject’s participation in the study.
14. DATA HANDLING AND RECORDKEEPING

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

14.1. Inspection of Records

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

14.2. Retention of Records

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


Maestri NE, g D, Brusilow SW. Neonatal onset ornithine transcarbamylase deficiency: a retrospective analysis.


16. **APPENDICES**
### APPENDIX A. SCHEDULE OF STUDY ASSESSMENTS

<table>
<thead>
<tr>
<th>Month</th>
<th>0 Month</th>
<th>Every 3 months</th>
<th>Every 6 months</th>
<th>Unscheduled Visits</th>
<th>Every 12 months/Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion / Exclusion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical and Neurological Exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height and Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Safety Labs</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urine Pregnancy Test</td>
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<td>X</td>
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</tr>
<tr>
<td>Venous Ammonia</td>
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<td>X</td>
<td></td>
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<tr>
<td>Amino Acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Record prescribed dietary protein and calories</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological Battery</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Study Drugs**

| Dispense HPN-100             | X       | X              |               |                    |
| Resume Off-study Treatment   |         |                |               |                    |

- **Visit window** is +/- 30 days.
- **Month 0 visit** of this study may be combined with the Month 12 visit for subjects who completed HPN-100-005, HPN-100-007, or HPN-100-012. Common assessments between these visits do not have to be repeated; however, these data must be recorded on both Month 0 of this study and the Month 12 CRF for HPN-100-005, HPN-100-007, and HPN-100-012.
- **Routine Study Visits** must occur every 6 months.
- **Unscheduled Visits** may occur due to a hospitalization, a visit to the emergency room, or at the discretion of the investigator between routine study visits. In each case the reason for the unscheduled visit should be documented (e.g., hyperammonemic crisis, vomiting, lethargy, seizure, fever, diarrhea, dehydration, anorexia, or other).
- Subjects who exit the protocol will have the same procedures as the Month 12 visit.
- Subjects must follow their prescribed diet and at the discretion of the investigator, changes in dietary protein may be prescribed as necessary throughout the study. Changes in dietary protein and calories (increases or decreases) should be recorded at each visit (scheduled or unscheduled) along with reason for the change.
- **Vital signs** include blood pressure, respiratory rate, temperature, and pulse.
- **Neuropsychological battery** (Appendix B) will be administered once every 12 months.
APPENDIX B. NEUROPSYCHOLOGICAL BATTERY

These tests must be administered by a properly trained medical professional.

Neuropsychological Battery Tests for Adults

Wechsler Abbreviated Scale of Intelligence (WASI): Assesses general test of intelligence (IQ)

Grooved Pegboard: This test is used to test motor and visual skills through manual dexterity in adults, adolescents, and children. It consists of 25 holes with randomly positioned slots. This test requires complex visual-motor coordination; for example, pegs with a key on one side must be rotated to match the hole before they can be inserted. The time during which the task is completed is recorded.

The California Verbal Learning Test (CVLT): The California Verbal Learning Test (CVLT) assesses verbal memory abilities through testing immediate and delayed recall. Several lists of words are read to the subject. These lists contain sixteen common words, each of which belongs to one of four categories such as fruits, herbs, etc. The subject is then asked to recall as many of these items as possible. There is a short delay of 20 minutes, during which the subject is given other tasks to perform, and then the tester again asks the subject to recall the first list. The number of correct answers is recorded for both immediate and delayed recall tasks.

Digit Span: The digit span test is a common measure of attention and short-term memory. The subject is given a list of digits and then asked to recall them in correct sequential order. The number of correct digits is recorded.

Neuropsychological Battery Tests for Pediatrics

Wechsler Abbreviated Scale of Intelligence (WASI): This test is a general assessment of intelligence (IQ).

The Child Behavior Checklist (CBCL): (Thomas M. Achenbach, PhD, Leslie A. Rescorla, PhD) CBCL is a device by which parents rate a child’s problem behaviors and competencies. This instrument can either be self-administered or administered through an interview. The CBCL can also be used to measure a child’s change in behavior over time or following a treatment. The first section of this questionnaire consists of 20 competence items and the second section consists of 120 items on behavior or emotional problems during the past 6 months. Teacher Report Forms and Youth Self-Report Forms are available. Two versions of this instrument exist: one for children aged 1 1/2 to 5 years and another for ages 6 to 18 years.

Behavior Rating Inventory of Executive Function® (BRIEF®): (Gerard A. Gioia, PhD, Kimberly Andrews Espy, PhD, Peter K. Isquith, PhD) The BRIEF is designed to assess executive functioning in children and adolescents ages 5 to 18 years. It consists of 2 rating forms, a parent questionnaire and a teacher questionnaire, which require only 10 to 15 minutes to administer and 15 to 20 minutes to score. Suited for both home and school settings, the BRIEF is useful in evaluating children with a wide spectrum of developmental and acquired neurological conditions.
APPENDIX C. PROTOCOL REVISION HISTORY

Protocol HPN-100-011 version 1.0 (dated 24 September 2010) was amended in the following sections:

<table>
<thead>
<tr>
<th>Protocol Section</th>
<th>Revised Text</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1.2</td>
<td>Removed footnote of “*n=9”</td>
<td>The footnote was listed in error. The sample sizes are listed at the top of each column.</td>
</tr>
<tr>
<td>various</td>
<td>Revised various sections throughout the document to allow subjects who complete Study HPN-100-012 entry into Study HPN-100-011.</td>
<td>Patients who complete Study HPN-100-012 are eligible for continued access to HPN-100 via Study HPN-100-011.</td>
</tr>
<tr>
<td>Section 5.3.3. Study Drug Dispensing and Disposal</td>
<td>The maximum supply of HPN-100 for a single shipment will be a 3 to 6-month supply.</td>
<td>Some patients travel by airplane to study sites and are unable to visit the clinic every 3 months.</td>
</tr>
<tr>
<td>Section 6.1.4 Annual (12 Month)/End of Study Visit</td>
<td>Inquiry about a hyperammonemic crisis since the last visit. Record necessary information per Study (Reference) Manual</td>
<td>Study Manual was renamed Study (Reference) Manual</td>
</tr>
</tbody>
</table>

Protocol HPN-100-011 version 2.0 (dated 21 August 2012) was amended in the following sections:

<table>
<thead>
<tr>
<th>Protocol Section</th>
<th>Revised Text</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>various</td>
<td>Revised various sections throughout the document to allow subjects to stay on this study until HPN-100 is available through the Health Canada Special Access Program</td>
<td>After HPN-100 commercialization in US, patients will have access to HPN-100 through the Health Canada Special Access Program.</td>
</tr>
</tbody>
</table>
Protocol HPN-100-011 Amendment 3 Version 4.0 (Canada only - dated 12 February 2013) was amended in the following sections:

Protocol HPN-100-011 version 3.0 (Amendment 2, dated 21 August 2012) was revised with the following rationale:

**Rationale:** To allow subjects to continue on this study until HPN-100 is available through the Health Canada Special Access Program.

A detailed revision history of the protocol is provided below.

Deletions are marked with a strikethrough, and insertions are shown in bold text. The rationale for the changes in the protocol sections outlined below is as follows:

**Protocol Section: Synopsis (relevant section outlined)**

**SYNOPSIS**

| Mode of Administration | Subjects who have completed Study HPN-100-005, HPN-100-007, or HPN-100-012 will continue to receive open-label HPN-100, initially at the same dose which they were receiving at the time they completed study HPN-100-005, HPN-100-007 or HPN-100-012. The investigator may subsequently adjust the dose for any subject if judged clinically appropriate [the dose should not exceed the equivalent of 20 grams (g) of NaPBA (~17.4 milliliters (mL) total daily dose of HPN-100)]. |
| Duration of Study | Until HPN-100 is commercially available in the US through the Health Canada Special Access Program |

**Protocol Section 3.3: Duration of the Study**

3.3. **Duration of the Study**  
Subjects will stay on this study until HPN-100 is commercially available in the US through the Health Canada Special Access Program.

**Protocol Section 6.1.2: Routine Clinic Visit (Every 6 Months)**

6.1.1. **Routine Clinic Visit (Every 6 Months)**  
Subjects should visit the clinic as prescribed by the Investigator, but at a minimum a visit must occur every 6 months until the HPN-100 is commercially available to the subject through the Health Canada Special Access Program or the subject terminates HPN-100 for other reasons. At each clinic visit the following will be recorded:
Protocol Section 6.1.4: Annual (12 Month) / End of Study Visit

6.1.4. Annual (12 Month) / End of Study Visit

Subjects will visit the clinic a minimum of every 6 months until HPN-100 is commercially available through the Health Canada Special Access Program in the US.

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

- Inquiry about a hyperammonemic crisis since the last visit. Record necessary information per Study (Reference) Manual
- Record concomitant medications (including any HPN-100 dose adjustment. If dose adjustment is made, record reason)
- Physical and neurological exam
- Measure height and weight
- Measure vital signs: blood pressure, respiratory rate, temperature, and pulse
- Collect single blood sample for venous ammonia level assessment
- Collect blood for safety laboratory assessments and amino acid panel (see Section 8.2)
  - Note: if labs were drawn within 30 days of study visit (e.g., as part of another study or standard of care), only the research labs not drawn need to be administered.
- Perform urine pregnancy test
  - Note: Animal reproductive studies are in progress. It is not known whether HPN-100 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Should a subject become pregnant while taking HPN-100, continued administration should be at the discretion of the Investigator in consultation with the study subject; taking into account the risk/benefit of continued administration and with prior approval from the Sponsor.
- Administer neuropsychological battery (Appendix B)
- Record prescribed protein and calories
- Record AEs
- Discharge subject on commercially available UCD medication