Common Drug Review
Clinical Review Report

April 2017

Drug	Glycerol phenylbutyrate (Ravicti)
Indication	Use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥ 2 years of age with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone
Reimbursement request	As per indication
Dosage form(s)	Oral liquid, 1.1 g/mL
NOC Date	March 18, 2016
Manufacturer	Horizon Therapeutics Canada

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ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ASS	argininosuccinate synthetase
BRIEF	Behavior Rating Inventory of Executive Function
CBCL	Child Behavior Checklist
CI	confidence interval
CORD	Canadian Organization for Rare Disorders
CPS1	carbamoyl phosphate synthetase 1
CVLT-II	California Verbal Learning Test
DB	Double blind
GI	gastrointestinal
GPB	glycerol phenylbutyrate
HAC	hyperammonemic crises
HC	Health Canada
HRQoL	health-related quality of life
ITT	intention-to-treat
IQ	intelligence quotient
NaPBA	sodium phenylbutyrate
OTC	ornithine transcarbamylase
PedsQL SF15	Pediatric Quality of Life Inventory Generic Core Scales SF15 (short form 15)
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
TNAUC	time-normalized area under the curve
UCD	urea cycle disorder
ULN	upper limit of normal
WASI-II	Wechsler Abbreviated Scale of Intelligence
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence

EXECUTIVE SUMMARY

Introduction

Urea cycle disorders (UCDs) result from genetic mutations that cause defects in any of the five enzymes of the urea cycle in the liver: carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase, and arginase; in the co-factor producer *N*-acetyl glutamate synthetase; or in the ornithine transporter and citrin. The estimated incidence of UCDs ranges from one in 22,179 births to one in 53,717 births. The most recent estimate of incidence of UCDs for the US is around one in 35,000 births. It is estimated that approximately 11 new cases of UCDs will be diagnosed each year in Canada. The incidence of OTC deficiency (one in 56,500 live births) is higher than other UCDs. Deficiencies in the urea cycle may result in excessive ammonia levels due to impaired metabolism, which can be life-threatening and result in permanent neurological damage if left untreated. Treatment should be initiated as soon as a diagnosis of a UCD is suspected and should proceed simultaneously with the diagnostic evaluation.

The goals of long-term management of UCDs are to achieve normal development, to prevent hyperammonemia, and to maintain a good quality of life (QoL). These are achieved through a low-protein diet (and sometimes essential amino acids and other essential nutrients supplementation), pharmacotherapies to increase waste nitrogen excretion, and liver transplantation in selected patients. Sodium phenylbutyrate (NaPBA) is the mainstay of pharmacological therapy in chronic management of UCDs; however, its use is associated with decreased appetite, taste disturbances, body odour and menstrual dysfunction/amenorrhea. More recently, glycerol phenylbutyrate (GPB, brand name Ravicti) was approved as a nitrogen-scavenging therapy. This is a triglyceride containing three molecules of phenylbutyric acid. Its major metabolite, phenylacetic acid, conjugates with glutamine through acetylation in the liver and kidneys to form phenylacetylglutamine, which is excreted by the kidneys. GPB is administered orally with a recommended total dose ranging from 4.5 mL/m^2 per day to 11.2 mL/m^2 per day (5.0 g/m^2 per day to 12.4 g/m^2 per day). For patients who have been previously treated with NaPBA, the total daily dose of GPB can be calculated based on the total daily dose of NaPBA.

The objective of this systematic review is to examine the beneficial and harmful effects of GPB as a nitrogen-binding agent adjunctive to dietary protein restriction and dietary supplements for chronic management of adult and pediatric (at least two years of age) patients with UCDs.

Results and Interpretation

Included Studies

HPN-100-006 was a phase III, multi-centre, randomized, double-blind (DB), crossover, active-controlled, noninferiority trial that met the inclusion criteria for this systematic review. The primary objective of this study was to assess the noninferiority of GPB to NaPBA by evaluating blood ammonia levels in adult patients with UCDs. The study population included adult patients with a confirmed diagnosis of a UCD and on a stable dose of NaPBA (the mean baseline NaPBA dose was 14.54 ± 6.808 g [mean ± standard deviation] per day) for at least one week before study entry. Excluded were patients with baseline ammonia level ≥ 100 µmol/L or signs and symptoms indicative of hyperammonemia during the two-week period preceding screening or with any clinical or laboratory abnormality or medical condition that may put the patient at increased risk by participating in the study. Eligible patients were randomly assigned to two groups in a DB manner: Arm A — two-week NaPBA followed by two-week GPB, and Arm B — two-week GPB followed by two-week NaPBA. The dose of GPB was calculated from the NaPBA dose determined by the investigator for each patient. The maximum allowed GPB dose was 17.4 mL per day,

which was equivalent to 20 g per day of NaPBA. The dose of NaPBA was determined by the investigator at the screening visit and was based on a variety of factors, including severity of the patient's enzyme deficiency and diet. The maximum dose levels were 600 mg/kg per day in patients weighing less than 20 kg, and 13 g/m^2 per day in patients weighing 20 kg or more. There were no washout periods between the two treatments because of safety considerations. The primary outcome was the mean of the 24-hour area under the curve ($AUC_{0–24}$) for blood ammonia on days 14 and 28. Other efficacy outcomes included maximum blood ammonia values observed on NaPBA versus GPB, and percentage of blood ammonia values above the upper limit of normal (ULN) on NaPBA versus GPB. The number and severity of hyperammonemic crises (HACs) were assessed as well. Safety outcomes measured included adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events. In total, 46 patients were randomized, and 44 patients completed the study. Treatment compliance was high in both treatment groups, with 97.7% and 100% of patients being at least 80% compliant with the NaPBA and GPB treatments, respectively.

Efficacy

No deaths were reported in study HPN-100-006.

No patients had an HAC during GPB treatment. One patient on NaPBA treatment had an HAC.

In the per-protocol (PP) population, the mean $AUC_{0–24}$ values for blood ammonia were 12% lower with GPB treatment compared with NaPBA (868.29 ± 668.145 µmol·h/L versus 985.47 ± 873.578 µmol·h/L, respectively). GPB achieved noninferiority to NaPBA, as the upper bound of the 95% confidence interval (CI) of the ratio of the geometric means of blood ammonia $AUC_{0–24}$ between GPB and NaPBA was 1.030, which was below the predefined noninferiority margin of 1.25. Consistent results were observed in the intention-to-treat (ITT) population.

Twenty-four-hour C_{max} values for blood ammonia were numerically lower with GPB treatment compared with NaPBA treatment in the patient populations. In the ITT population, mean C_{max} values for blood ammonia were 14% lower with GPB treatment compared with NaPBA (60.94 ± 46.213 µmol/L versus 70.83 ± 66.71 µmol/L, respectively). The between-group difference did not reach statistical significance.

The number of ammonia samples above the ULN was similar with GPB and NaPBA treatments in the ITT population (35.6% and 36.2% of samples, respectively).

Cognitive development, anthropometric measurements, and health-related quality of life (HRQoL) were not assessed in study HPN-100-006.

Findings from three longer-term, open-label, non-comparative studies suggested that, after one year of treatment with GPB, the effects of GPB on blood ammonia and glutamine levels appeared to be maintained in both children and adults. In addition, the number of HACs per patient reduced compared with the values 12 months before screening. HRQoL improved in children, whereas it appeared to decrease in adults assessed using generic QoL assessment tools. Neuropsychological testing results were inconsistent across trials, age groups, and across assessment tools.

Harms

Overall, the proportion of patients reporting an AE was higher in the GPB group compared with the NaPBA group. Most AEs were considered mild. Treatment of GPB was associated with more lower gastrointestinal (GI) tract disorders, whereas treatment with NaPBA was associated with more upper GI tract disorders. Two patients reported treatment-emergent SAEs: one patient reported acute gastroenteritis on GPB treatment, and one patient reported a grade 3 HAC on NaPBA treatment. No patients discontinued GPB treatment, whereas one patient discontinued NaPBA treatment because of high ammonia levels on day 1. After the treatment with GPB, the report on UCD treatment-specific symptoms such as decreased appetite and body odour reduced compared with baseline.

In the longer-term extension studies, almost all patients experienced AEs after one year of treatment with GPB. Infections, infestations, and GI tract disorders were the most frequently experienced AEs.

Conclusions

One phase III, DB, crossover randomized controlled trial (RCT) conducted in the US and Canada that evaluated the noninferiority of GPB to NaPBA in adult patients with UCDs was included in this review. Study HPN-100-006 enrolled patients with a diagnosis of CPS1, OTC, or ASS deficiencies who had been on dietary protein restriction and/or amino acid supplementation. The patients were required to be on a stable dose of NaPBA at least one week before study entry. A total of 46 patients were randomized (44 evaluable) to receive two weeks NaPBA followed by two weeks GPB, or two weeks GPB followed by two weeks NaPBA. Results from this study suggest that GPB is noninferior to NaPBA in ammonia control, measured with $AUC_{0–24}$ for blood ammonia levels at study end points, according to the predefined noninferiority margin of 1.25. GPB also showed similar effects on maximum blood ammonia values and the percentage of ammonia samples above the ULN when compared with NaPBA. However, interpretation of results is limited, as no minimal clinically important difference is available to evaluate changes in ammonia levels. There were no HACs during the treatment of GPB, whereas one HAC occurred during the treatment of NaPBA, which led to treatment discontinuation. Cognitive development and HRQoL were not assessed in this study. Patients in the GPB group reported higher risks of AEs compared with those in the NaPBA. These events were generally mild. GPB treatment was associated with more symptoms of lower GI tract disorders, whereas the NaPBA treatment was associated with more symptoms of upper GI tract disorders. One HAC that led to treatment discontinuation was observed in the NaPBA group. After being treated with GPB, patients reported fewer UCD treatment-specific symptoms such as bad taste and body odour.

Findings from longer-term, open-label, non-comparative studies suggested that, after one year of treatment with GPB, the effects of GPB on blood ammonia and glutamine levels appeared to be maintained in both children and adults. The number of HACs per patient reduced compared with the values 12 months before screening. Almost all patients experienced AEs after one year of treatment with GPB. The interpretation of results from these long-term studies is challenging because of several important limitations, such as the study design, sample size, and the study duration.

TABLE 1: SUMMARY OF RESULTS FROM STUDY HPN-100-006

	GPB (N = 44)	NaPBA (N = 45)
Efficacy[a]		
$AUC_{0–24}$, µmol·h/L (PP Population[b]**)**		
Mean, SD	868.29 (668.15)	985.47 (873.58)
Difference between GPB and NaPBA, mean (SD)	–117.18 (584.22)	
Ratio of geometric means (95% CI)	0.90 (0.792 to 1.030)	
P value [c]	0.196	
24-h C_{max}, µmol/L (ITT Population)		
Mean, SD	60.94 (46.21)	70.83 (66.71)
Difference between GPB and NaPBA, mean (SD)	–9.89 (43.10)	
P value	0.135	
Percentage of Blood Ammonia Values Above the ULN (ITT Population)		
Number of samples > ULN (%)[d]	122 (35.6)	125 (36.2)
Harms		
N	44	45
Deaths	0	0
AEs, n (%)	27 (61.4)	23 (51.1)
SAEs, n (%)	1 (2.3)	1 (2.2)
WDAEs, n (%)	0	1 (2.2)

AE = adverse event; AUC = area under the curve; CI = confidence interval; GPB = glycerol phenylbutyrate; ITT = intention-to-treat; NaPBA = sodium phenylbutyrate; PP = per-protocol; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

[a] Results were presented by treatment; therefore, week two and week four data were combined if they derived from the same treatment group.

[b] Per-protocol population: GPB, N = 43; NaPBA, N = 43.

[c] *P* value for between-group comparison.

[d] Samples from all time points at day 14 and day 28 were analyzed.

1. INTRODUCTION

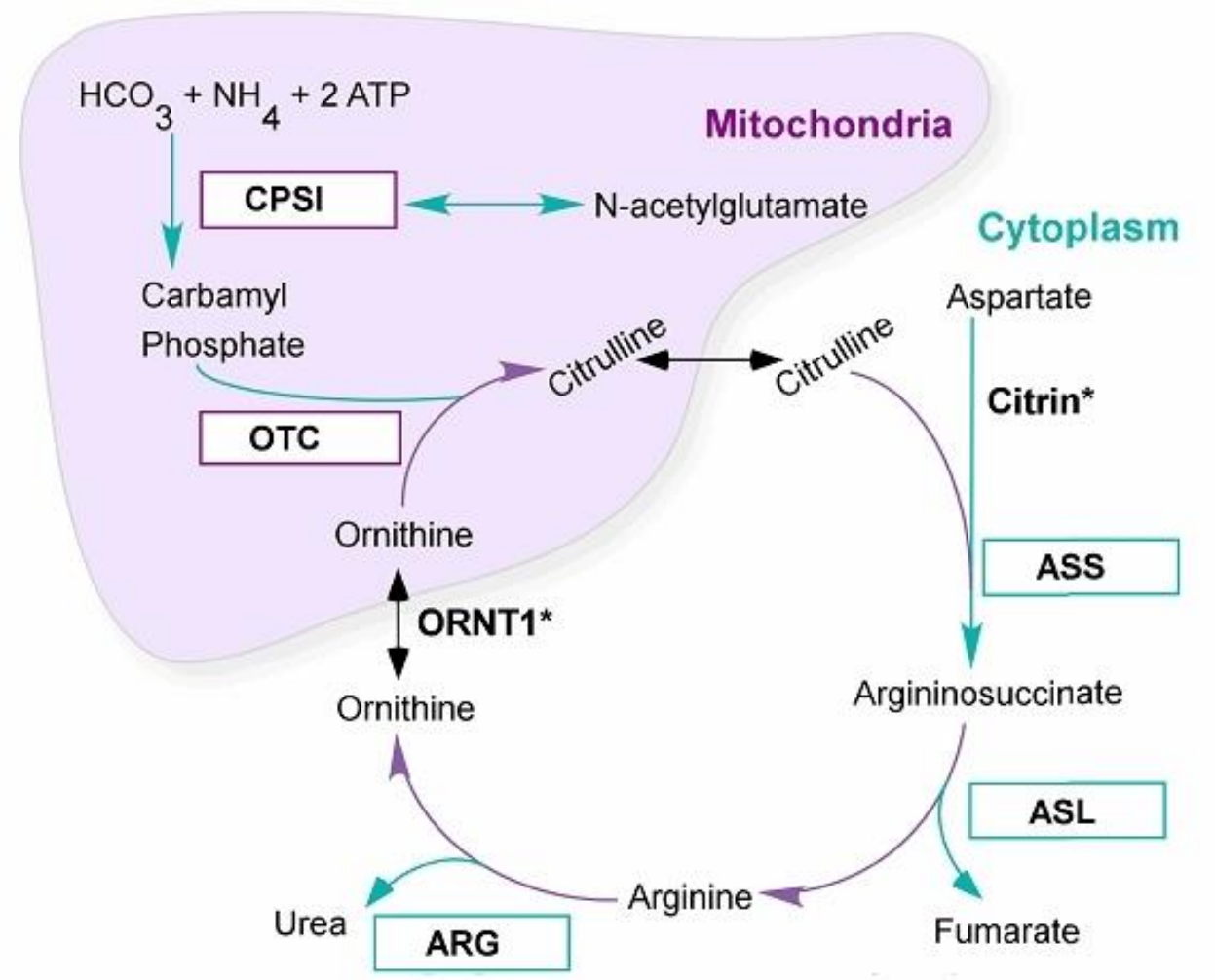
1.1 Disease Prevalence and Incidence

The urea cycle is responsible for the metabolism of nitrogen produced through the breakdown of protein and other nitrogen-containing molecules. It accomplishes this by converting ammonia to urea, which is excreted from the body (Figure 1).[1,2] Urea cycle disorders (UCDs) result from genetic mutations that cause defects in any of the five enzymes of the urea cycle in the liver: carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase, and arginase; in the co-factor producer *N*-acetyl glutamate synthetase; or in ornithine transporter and citrin. Deficiencies of CPS1, ASS, argininosuccinate lyase, arginase, *N*-acetyl glutamate synthetase, ornithine transporter, and citrin are inherited in an autosomal recessive manner, while OTC deficiencies are inherited in an X-linked manner.[1,3] The incidence of UCDs is difficult to determine owing to the rarity of the condition and undiagnosed cases, but estimates ranging from one in 22,179 births to one in 53,717 births have been reported.[4] The most recent estimate of incidence of UCDs for the US is around one in 35,000 births.[5] Assuming the same incidence in Canada and using a birth rate of 380,863 live births per year, it is estimated that approximately 11 new cases of UCDs will be diagnosed each year in Canada.[6] The incidence of OTC deficiency (one in 56,500 live births) is higher than other UCDs.[5]

Deficiencies in the urea cycle may result in excessive ammonia levels due to impaired metabolism, which can be life-threatening and result in permanent neurological damage if left untreated. Infants with a complete enzyme deficiency in a urea cycle (other than arginase) often present in the newborn period (neonatal-onset) with hyperammonemic coma, and the mortality rate is 50% after five years.[7] Survivors often experience severe developmental delay and recurrent hyperammonemic episodes.[8] Patients with partial deficiencies have variable clinical presentations and later onset, but still have a 10% risk of mortality and a significant risk of developmental disabilities.[7,9] OTC deficiency affects males and females differently as a result of its X-linked inheritance, with affected males being more likely to present neonatally with severe hyperammonemia, and female carriers presenting with a later onset.[5,10]

UCDs are diagnosed using a combination of clinical parameters, laboratory parameters, family history, and genetic testing.[8] Since hyperammonemia is the hallmark for most UCDs and may cause permanent damage, blood ammonia levels should be taken to evaluate a patient with a suspected UCD in an emergency setting if there is an unexplained change in consciousness, unusual neurological illness, liver failure, or suspected intoxication. If hyperammonemia is confirmed, plasma amino acids, blood or plasma acylcarnitines, urinary organic acids, and orotic acids should be determined, along with basic laboratory investigations, in order to differentiate between hyperammonemia due to inborn errors from other conditions. The specific UCD can be determined using laboratory parameters based on argininosuccinate, citrulline, arginine, ornithine, and orotic acid levels. For confirmation of diagnosis, genetic testing or enzymatic assays using liver biopsy samples should be performed.[8] According to the Urea Cycle Disorders Consortium, an elevated plasma ammonia level of ≥ 150 µmol/L in neonates or > 100 µmol/L in older children and adults is a strong indication for the presence of a UCD.[11]

FIGURE 1: THE UREA CYCLE



ARG = arginase; ASL = argininosuccinate lyase; ASS = argininosuccinate synthetase; ATP = adenosine triphosphate; CoA = coenzyme A; CPS1 = carbamoyl phosphate synthetase 1; ORNT1 = ornithine transporter; OTC = ornithine transcarbamylase.
Note: Transporters are indicated with a* symbol.
Source: Ah Mew N, Lanpher BC, Gropman A, Chapman KA, Simpson KL, Summar ML. Figure 1. The urea cycle. From: Urea cycle disorders overview. 2015 Apr 9 [cited 2016 Nov 17]. In: GeneReviews at GeneTests Medical Genetics Information Resource [database on the Internet]. Seattle (WA): University of Washington; c1993-2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1217/ (© 1993-2016 University of Washington).

1.2 Standards of Therapy

Neurologic abnormalities and impaired cognitive function are significantly correlated with the frequency, severity, and duration of hyperammonemia; therefore, treatment should be initiated as soon as a diagnosis of a UCD is suspected and should proceed simultaneously with the diagnostic evaluation.[10,12]

Emergency management of patients in hyperammonemic coma resulting from UCD includes removing ammonia from the body using medications and/or dialysis, stopping protein intake and minimizing catabolism, and stimulating anabolism and uptake of nitrogen precursors by muscle.[1,8,12] Medication for hyperammonemia consists of administering a combination of sodium phenylacetate and sodium

benzoate (i.e., Ammonul used in Europe), arginine, citrulline (for OTC or CPS1 deficiency), and carglumic acid (for *N*-acetyl glutamate synthetase deficiency).[12] In European guidelines, in which the majority of recommendations are based on low levels of evidence because of the rarity of UCDs, the recommended first-line medications for initial management of hyperammonemia are sodium benzoate, sodium phenylbutyrate/phenylacetate, and L-arginine. Protein intake should be minimized temporarily, but feeding needs to commence to meet metabolic demands. Following improvement of hyperammonemia (less than 100 µmol/L), reintroduction of protein and essential amino acids should not be delayed beyond 24 hours to 48 hours, increasing daily to the required amount.[8]

As there is no cure for UCDs, the goals for the long-term management of UCDs are to achieve normal development, to prevent hyperammonemia, and to maintain a good quality of life (QoL). These are achieved through a low-protein diet (and sometimes essential amino acids and other essential nutrients supplementation), pharmacotherapies to increase waste nitrogen excretion for patients with persistently higher ammonia levels (such as ammonia levels greater than 150 µmol/L), and liver transplantation in selected patients.[4,8] Diet therapy alone is insufficient in the majority of cases, and nitrogen scavengers are usually necessary.[13,14] Nitrogen scavengers used as an adjunct to diet for the long-term management of UCDs include sodium benzoate and sodium phenylbutyrate (NaPBA). In Europe, sodium benzoate is the preferred drug, whereas in North America NaPBA (Buphenyl in the US or Pheburane in Canada) is recommended as chronic maintenance therapy.[8,11] Although NaPBA is considered the mainstay of pharmacological therapy in chronic management of UCDs, its use is associated with decreased appetite, taste disturbances and body odour, and it causes menstrual dysfunction/amenorrhea in one-fourth of postpubertal females.[9,15] More recently, glycerol phenylbutyrate (GPB) was approved as a nitrogen-scavenging therapy.[16,17] All patients should be monitored for plasma arginine and given arginine and citrulline supplementation to address impaired synthesis in the urea cycle.[8] Liver transplantation is a potentially curative option for patients with UCDs, but it cannot reverse established neurologic sequelae and is associated with significant morbidities. It is recommended to be performed in patients without irreversible neurological damage who are in a stable metabolic condition, generally between three and 12 months of age.[8,9]

Patients with UCDs require lifelong monitoring, including anthropometric data, biochemical tests, dietary and drug review, history of intercurrent illness, and use of the emergency regimen. Visit intervals should be individualized on the basis of age, growth, severity, metabolic stability, and compliance with diet and drug therapy. Young and severely affected patients may need monitoring every three months, while annual reviews may be enough for older or less severely affected patients.[8]

1.3 Drug

GPB (Ravicti) is a triglyceride containing three molecules of phenylbutyric acid. Phenylacetic acid, a major metabolite of phenylbutyric acid, conjugates with glutamine through acetylation in the liver and kidneys to form phenylacetylglutamine, which is excreted by the kidneys. This provides an alternative nitrogen elimination pathway.[16] After oral administration, an action of pancreatic lipases in the gastrointestinal (GI) tract is required to convert GPB into phenylacetic acid. During the absorption of NaPBA, it is rapidly metabolized to phenylacetic acid without the involvement of pancreatic lipases. Therefore, GPB acts as a slow-release form of NaPBA, achieving more stable control of ammonia levels over a 24-hour period.[12,16,18] In addition, it may offer advantages with regard to tolerability and palatability, as it is a colourless and tasteless oil with no sodium content. However, its use is contraindicated in infants under two months of age because their immature pancreatic exocrine function could lead to insufficient drug metabolism.[12] In March 2016, Ravicti received a Notice of

Compliance by Health Canada (HC) for use as a nitrogen-binding drug for chronic management of adult and pediatric patients two years of age or older with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[17]

Ravicti is available as oral liquid with 1.1 g of GPB per mL. The daily dose should be individually adjusted according to the patient's estimated urea synthetic capacity (if any), protein tolerance, and daily dietary protein intake. An initial estimated dose for GPB during a 24-hour period is 0.6 mL/g of dietary protein ingested per 24-hour period, assuming all the waste nitrogen is covered by GPB and excreted as phenylacetylglutamine. The recommended total daily dose range of GPB is 4.5 mL/m^2 per day to 11.2 mL/m^2 per day (5.0 g/m^2 per day to 12.4 g/m^2 per day), and should be divided into equal amounts in a day, such as three times to six times per day. For patients who have been previously treated with NaPBA, the total daily dose of GPB can be calculated based on the total daily dose of NaPBA.[12] Treatment with GPB must be combined with dietary protein restriction and, in some cases, dietary supplements.

Indication Under Review
As a nitrogen-binding agent for chronic management of adult and pediatric patients greater than and equal to two years of age with UCDS who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.
Listing Criteria Requested by Sponsor
Per indication.

The objective of this systematic review is to examine the beneficial and harmful effects of GPB as a nitrogen-binding drug adjunctive to dietary protein restriction and dietary supplements for chronic management of adult and pediatric (at least two years of age) patients with UCDs.

TABLE 2: KEY CHARACTERISTICS OF NITROGEN-SCAVENGING THERAPIES FOR UREA CYCLE DISORDERS

	GPB (Ravicti)	NaPBA (Pheburane)
Mechanism of action	Metabolized to release phenylbutyrate, which is then oxidized to phenylacetate. Phenylacetate conjugates with glutamine to form PAGW to be excreted by the kidneys, providing another route of nitrogen elimination.	Prodrug metabolized to phenylacetate, which conjugates with glutamine to form phenylacetylglutamine to be excreted by the kidneys, providing another route of nitrogen elimination.
Indication[a]	For the chronic management of adult and pediatric patients ≥ 2 years of age with UCDs who cannot be managed by dietary protein restriction and/or dietary supplements.	As adjunctive therapy in the chronic management of UCDs, involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininesuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.
Route of administration	Oral (nasogastric or gastrostomy tube for patients unable to take product orally)	Oral (nasogastric or gastrostomy tube for patients unable to take product orally)

	GPB (Ravicti)	NaPBA (Pheburane)
Dosage form	**Ravicti:** liquid (1.1 g/mL)	**Pheburane:** coated granules with 483 mg NaPBA per gram of granules
Recommended dose	**Initial estimated dosage:** 0.6 mL/24-hour period. Recommended starting dosages for patients switching from NaPBA and NaPBA-naive patients may be different. **Recommended total daily dosage:** 4.5 mL/m^2/day to 11.2 mL/m^2/day (5.0 g/m^2/day to 12.4 g/m^2/day) **Daily dosage of Ravicti (mL) for patients switching from NaPBA:** total daily dose of NaPBA tablets (g) × 0.86, or total daily dose of NaPBA powder (g) × 0.81. Liquid should be divided into 3 equal doses to 6 equal doses per day. The daily dose of Ravicti should be individually adjusted.	**Patients < 20 kg:** 450 mg/kg/day to 600 mg/kg/day **Patients ≥ 20 kg:** 9.9 g/m^2/day to 13.0 g/m^2/day The total daily dosage of Pheburane should be divided into equal amounts and given with each meal or feeding. The daily dose of Pheburane should be individually adjusted.
Serious side effects / safety issues	High levels of phenylacetate may result in neurotoxicity (somnolence, fatigue, lightheadedness, etc.).	Decreased appetite, body odour, taste aversion, amenorrhea/menstrual dysfunction (females) High levels of phenylacetate may result in neurotoxicity (somnolence, fatigue, lightheadedness, etc.).
Other	Not indicated for management of acute hyperammonemia. Contraindicated in patients < 2 months of age.	Should not be used for management of acute hyperammonemia.

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; PAGW = phenylacetylglutamine; UCD = urea cycle disorder.
[a] Health Canada indication.
Source: Health Canada product monograph for Ravicti[16] and Pheburane.[18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of GPB for the treatment of UCDs.

2.2 Methods

All manufacturer-provided trials considered pivotal by HC were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult and pediatric patients ≥ 2 years of age with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. **Subgroups:** Age (adult patients; pediatric patients) Time of presentation (early-onset; late-onset) Disease severity (mild; moderate; severe) UCD subtypes (deficiency of CPS1, OTC, ASS, ASL, NAGS, or arginase)
Intervention	Glycerol phenylbutyrate
Comparators	Sodium phenylbutyrate Sodium benzoate Sodium benzoate/sodium phenylacetate Carglumic acid Best supportive care (e.g., dietary control, amino acid supplementation alone, dialysis) Liver transplant
Outcomes	**Key efficacy outcomes:** Mortality (all-cause, disease-related) Hyperammonemic crises[a] Cognitive development (e.g., IQ test scores, developmental delays) Anthropometric measurements (e.g., weight, height, head circumference) Plasma ammonia levels[a] Glutamine levels HRQoL with a validated scale (caregiver and/or patient)[a] **Other efficacy outcomes:** Hospitalization Patient adherence Patient/caregiver satisfaction **Harms outcomes:** AEs, SAEs, WDAEs, notable harms (e.g., gastrointestinal reactions, neurological reactions, body odour, and abnormal hematologic findings such as abnormal ALT, AST, or potassium)
Study Design	Published and unpublished phase III RCTs

AE = adverse event; ALT = alanine aminotransferase; ASL = argininosuccinate lyase; AST = aspartate aminotransferase; ASS = argininosuccinate synthetase; CPS1 = carbamoyl phosphate synthetase 1; HRQoL = health-related quality of life; IQ = intelligence quotient; NAGS = *N*-acetyl glutamate synthetase; OTC = ornithine transcarbamylase; RCT = randomized controlled trial; SAE = serious adverse event; UCD = urea cycle disorder; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups (this will be completed once we finalize patient input summary).

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: Medline (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings, and keywords. The main search concept was GPB (Ravicti).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2 for the detailed search strategies.

The initial search was completed on September 22, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on February 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings from the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 2). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 2: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

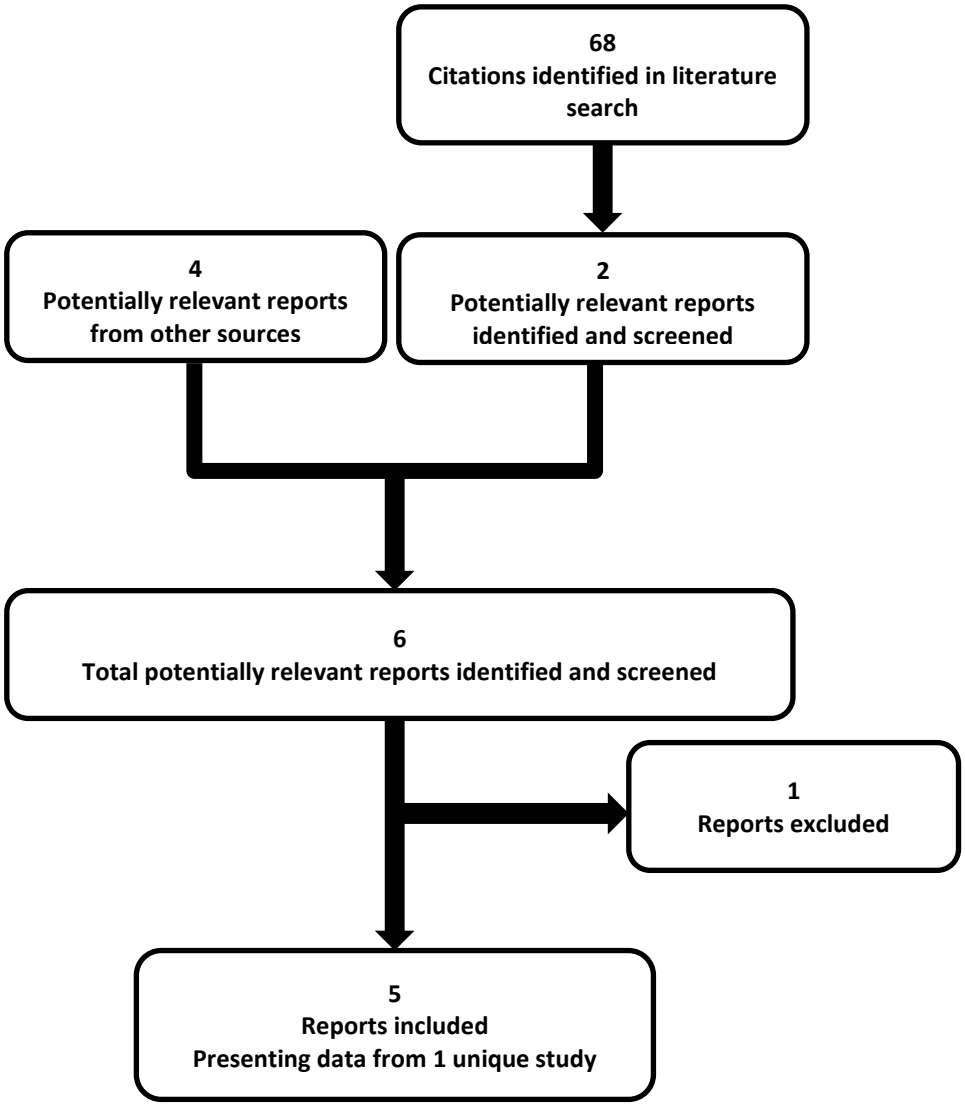


TABLE 4: DETAILS OF INCLUDED STUDIES

		HPN-100-006
DESIGNS & POPULATIONS	**Study Design**	DB, crossover, active-controlled RCT
	Locations	19 sites in Canada and US
	Randomized (N)	46
	Inclusion Criteria	Age ≥ 18 years; diagnosis of UCD involving deficiencies of CPS1, OTC, or ASS; on a stable dose of NaPBA for their UCD for at least 1 week before day 1 visit, or if not previously treated, could be started on NaPBA during screening period and enrolled in study as long as on stable dose of NaPBA for at least 1 week before day 1; no clinical evidence of hyperammonemia associated with ammonia levels of ≥ 100 µmol/L 2 weeks before screening
	Exclusion Criteria	Baseline ammonia level ≥ 100 µmol/L or signs and symptoms indicative of hyperammonemia during the 2-week period preceding screening or enrolment; use of any investigational drug within 30 days of day 1; active infection or any other intercurrent condition that may have increased ammonia levels; ≥ grade 3 clinical or laboratory abnormality except for elevated liver enzymes; any clinical or laboratory abnormality or medical condition that may put the patient at increased risk by participating in the study; use of any medication known to affect renal clearance, increase protein catabolism, or increase ammonia levels < 24 hours before day 1 and throughout the study; use of sodium benzoate < 1 week of day 1; liver or hepatocellular transplant
DRUGS	**Intervention**	GPB, administered orally t.i.d., at a daily PBA-equivalent dose (i.e., a dose that delivered the same amount of PBA to the patient's prescribed NaPBA dose before enrolment)
	Comparator(s)	NaPBA: administered orally t.i.d., at the same stable doses patients were receiving before enrolling in the study
DURATION	**Phase**	
	Screening	Within 30 days of day 1. Patients who were not on stable dose of NaPBA at screening received NaPBA for ≥ 1 week before day 1
	Double-blind	4 weeks: 2 weeks on NaPBA and 2 weeks on GPB. No washout periods
	Follow-up	1 day after end of each treatment period; final study visit was planned for day 29
OUTCOMES	**Primary End Point**	Blood ammonia AUC_{0-24} on day 14 and day 28
	Other End Points	Maximum blood ammonia values observed on NaPBA and GPB % of blood ammonia values above ULN on NaPBA versus GPB Number and severity of symptomatic hyperammonemic crises Safety
NOTES	**Publications**	Diaz et al. 2013[19]

ASS = argininosuccinate synthetase; AUC = area under the curve; CPS1 = carbamoyl phosphate synthetase 1; DB = double-blind; GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; OTC = ornithine transcarbamylase; PBA = phenylbutyrate; RCT = randomized controlled trial; t.i.d. = three times daily; UCD = urea cycle disorder; ULN = upper limit of normal.
Note: Four additional reports were included (FDA Medical Review,[20] FDA Statistical Review,[21] European Medicines Agency report,[22] and CDR submission[23]).
Source: Clinical Study Report of Study HPN-100-006.[24]

3.2 Included Studies

3.2.1 Description of Studies

One phase III randomized, double-blind (DB), double-dummy, active-controlled crossover study[24] (HPN-100-006) met the inclusion criteria for this systematic review.

This study assessed the noninferiority of GPB to NaPBA by evaluating blood ammonia levels in adult patients with UCDs who had been on a stable dose of NaPBA (the mean baseline NaPBA dose was 14.54 ± 6.808 g per day [mean ± standard deviation (SD)]) for at least one week before study day 1. Eligible patients were randomly assigned at a 1:1 ratio to one of two treatment arms, using a computer-generated central randomization schedule. All investigators and study personnel, including the site pharmacist, were blinded to the study drug assignment. In the case of a medical emergency, when knowledge of the treatment assignment was essential to the well-being of the patient, the investigator or designee may have requested unblinding of the patient's treatment assignment. In Arm A, patients received NaPBA plus GPB placebo for two weeks followed by GPB plus NaPBA placebo for two weeks; in Arm B, patients received GPB plus NaPBA placebo for two weeks followed by NaPBA plus GPB placebo for two weeks. There were no washout periods between the two treatments because of safety reasons.

No interim analysis was performed. The Data and Safety Monitoring Board (DSMB) convened on May 17, 2010, as planned, after approximately 50% of patients had received treatment, and reviewed available data on 19 of the 23 enrolled patients. No safety concerns were noted, and the DSMB recommended continuation of patient enrolment in the study. The final study visit was planned on day 29. Patients who completed the study and met study entry criteria were offered the opportunity to enrol in an open-label, long-term safety study of GPB (HPN-100-007).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

To be eligible, patients were required to be at least 18 years of age and to have a confirmed diagnosis of a UCD. Deficiencies of CPS1, OTC, or ASS were included. Patients should have been on a stable dose of NaPBA for at least one week before day 1. For patients who were NaPBA-naive at the initial screening visit but had the potential to benefit from treatment, they could have started receiving NaPBA during the screening period and been enrolled in the study as long as they were on a stable dose of NaPBA for at least one week before day 1. Patients were excluded if their baseline ammonia level was greater than or equal to 100 µmol/L or if they had signs and symptoms suggesting hyperammonemia two weeks before screening; active infection or any other intercurrent condition that may have increased ammonia levels; any clinical or laboratory abnormality or medical condition that may put them at increased risk by participating in the study; investigational drug intake within 30 days of the study; or liver or hepatocellular transplant.

b) Baseline Characteristics

The mean age of patients was 32.73 years in HPN-100-006. In general, most patients were female (68.9%), white (77.8%), and had OTC deficiency (88.9%). Most patients had childhood (44.4%) or adult onset of a UCD (33.3%). Approximately 20% of the study participants had experienced at least one hyperammonemic crisis (HAC) within one year before the study. The mean ammonia level at the time of disease diagnosis was 165 µmol/L. The mean duration of previous treatment with NaPBA was 129 months. Details of patients' baseline characteristics are presented in Table 5.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS IN STUDY HPN-100-006 (SAFETY POPULATION)

	Overall N = 45
Age, Years	
Mean (SD)	32.73 (13.53)
Median (range)	28 (18.0, 75.0)
Gender, n (%)	
Male	14 (31.1)
Female	31 (68.9)
Race, n (%)	
White	35 (77.8)
Black/African-American	3 (6.7)
Asian	1 (2.2)
American Indian/Alaskan Native	2 (4.4)
Native Hawaiian/other Pacific Islander	0
Hispanic or Latino	3 (6.7)
Other	1 (2.2)
UCD Subtypes, n (%)	
OTC deficiency	40 (88.9)
ASS deficiency	3 (6.7)
CPS1 deficiency	2 (4.4)
UCD Onset, n (%)	
≤ 2 years	10 (22.2)
> 2 years and < 18 years	20 (44.4)
≥ 18 years	15 (33.3)
Duration of Prior NaPBA Treatment, Months	
Mean (SD)	128.57 (97.41)
NaPBA Daily Dose, g	
Mean (SD)	14.54 (6.81)
Number of Patients With ≥ 1 Hyperammonemic Crisis Within 12 Months Before Study Entry	
n (%)	9 (20.0)
Ammonia Level at Admission, µmol/L	
Mean (SD)	164.72 (40.68)
Peak Blood Ammonia Levels at Hospital Admission, µmol/L	
Mean (SD)	167.94 (36.45)

ASS = argininosuccinate synthetase; CPS1 = carbamoyl phosphate synthetase; NaPBA = sodium phenylbutyrate; OTC = ornithine transcarbamylase; SD = standard deviation.
Source: Clinical Study Report of Study HPN-100-006.[24]

3.2.3 Interventions

In study HPN-100-006, patients randomized to Arm A received NaPBA plus GPB placebo for two weeks followed by GPB plus NaPBA placebo for two weeks. In Arm B, patients received GPB plus NaPBA placebo for two weeks followed by NaPBA plus GPB placebo for two weeks. There was no washout period between the two treatment periods.

Each millilitre of Ravicti equals 1.1 g GPB and delivers 1.02 g PBA. Dose of GPB was calculated from the NaPBA dose determined by the investigator for each patient, such that each patient received the same amount of PBA during treatment with both drugs. The formula was: NaPBA dose (grams) × 0.95/1.1 = total daily GPB dose (millilitres). No adjustment to the dose or schedule of GPB was allowed during the study. The maximum allowed GPB dose was 17.4 mL per day, which was equivalent to 20 g per day of NaPBA. GPB and GPB placebo were supplied as liquid to be administered undiluted orally (by mouth or through gastrostomy, or nasogastric tube.

The NaPBA formulation used in study HPN-100-006 was marketed in the US as Buphenyl. Each gram of NaPBA contained 0.88 g of PBA. Dose of NaPBA was determined by the investigator at the screening visit and was based on a variety of factors including severity of the patient's enzyme deficiency and diet. No changes in the patient's dosage regimen were required for entry and no changes were permitted during the study. The maximum dose levels were 600 mg/kg per day in patients weighing less than 20 kg, and 13 g/m^2 per day in patients weighing 20 kg or more. NaPBA and NaPBA placebo were supplied as a tablet for oral administration or as a powder for oral, nasogastric, or gastrostomy tube administration.

In this study, GPB and GPB placebo were identical in appearance, as were NaPBA and NaPBA placebo.

Rescue medication (such as intravenous sodium phenylacetate/sodium benzoate), with or without hemodialysis, was allowed during HACs. Each patient was required to follow a low-protein diet and amino acid supplements throughout the study, as assessed by the investigator and/or dietician.

3.2.4 Outcomes

a) Mortality

This outcome was reported in the safety analysis in study HPN-100-006.

Hyperammonemic crises

The number and severity of symptomatic HACs were reported. HAC was defined as clinical symptoms associated with ammonia levels greater than or equal to 100 µmol/L. Clinical symptoms included vomiting, protein intolerance (becoming physically ill after high protein intake on multiple occasions leading to a self-imposed low-protein diet), lethargy, psychosis, abnormal neurological examination (hypotonia, spasticity, hyper-reflexia, and/or clonus), brain edema (evidence on magnetic resonance imaging or computed tomography scan), and headaches.

Cognitive development

These outcomes were not evaluated in the included study.

Anthropometric measurements

These outcomes were not evaluated in the included study.

Plasma ammonia levels

Ammonia levels were measured as: (1) 24-hour area under the curve ($AUC_{0–24}$) for blood ammonia on days 14 and 28 (this was the primary outcome measure in study HPN-100-006); (2) maximum blood ammonia values observed on NaPBA versus GPB; and (3) percentage of blood ammonia values above the upper limit of normal (ULN) on NaPBA versus GPB at all time points of sample collection. On days 14 and 28, blood samples were collected at multiple time points for ammonia assessments (before first dose and after first dose at two, four, eight, 12, 16, 20, and 24 hours), and were processed by the laboratory at the investigator site per the facility standard operating procedures. $AUC_{0–24}$ and 24-hour

C_{max} for blood ammonia levels were also assessed by age of UCD onset (two years old or younger, older than two years) on NaPBA versus GPB in post-hoc evaluation.

b) Glutamine levels

Blood samples for the glutamine levels were collected before first dose on day 1, day 14, and day 28. Glutamine levels on NaPBA versus GPB were assessed in post-hoc evaluation.

c) Health-related quality of life

These outcomes were not evaluated during the four-week treatment period.

d) Safety

Adverse events (AEs), serious adverse events (SAEs), as well as withdrawals due to adverse events were evaluated in the included study. An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product; the occurrence did not necessarily need to have a causal relationship with this treatment. An SAE was defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, resulted in a congenital anomaly/birth defect, or was deemed serious for any other reason based on appropriate medical judgment. An independent DSMB was chartered to oversee the safety of study participants.

3.2.5 Statistical Analysis

In study HPN-100-006, a sample size of 44 patients was planned in order to provide 90% power at a one-sided significance level of 0.025 to demonstrate noninferiority of GPB to NaPBA, assuming an SD of the within-patient differences (natural log scale) of 0.225 and an expected ratio of the group means of 1.

An analysis of variance (ANOVA) model for the natural log-transformed blood ammonia $AUC_{0–24}$ (primary efficacy end point) was constructed with factors for treatment, sequence, patient nested in sequence (as a random effect), and period in the intention-to-treat (ITT) population. The 95% confidence intervals (CIs) for the difference between GPB and NaPBA (GPB minus NaPBA) on the natural log scale were constructed using the least squares means from the ANOVA model. The difference and related CIs were exponentiated to express the results as geometric means, ratio of geometric means, and corresponding CI on the original scale. A one-sided alpha of 0.025 and 95% CIs were employed in assessing the noninferiority of GPB to NaPBA. Noninferiority of GPB to NaPBA was concluded when the upper bound of the 95% CI of ratio of the geometric means of blood ammonia $AUC_{0–24}$ between GPB and NaPBA did not exceed 1.25. The margin of 1.25 was selected based on standard bioequivalence rules (i.e., the 95% CI for the ratio of mean AUCs being within 0.80 and 1.25); in addition, US Food and Drug Administration recommended that the manufacturer use 1.25 as the upper confidence limit (ratio of 24-hour AUC values for blood ammonia levels).[20] All statistical comparisons for inequality between treatment groups were performed using two-sided alpha of 0.05 and 95% CIs.

The two-sample *t*-test and Wilcoxon rank sum test were used to analyze the maximum blood ammonia levels observed during the study, the number and percentage of ammonia values above the ULN, and the change from baseline in blood ammonia levels. The number of patients with at least one HAC was compared by treatment group using Fisher's exact test.

Hochberg's procedure was used to control for overall type I error. No adjustment for covariates was performed. Missing data were assumed to be missing at random. For patients who had incalculable blood ammonia $AUC_{0–24}$ for both GPB and NaPBA treatment periods (completely missing data), their

ammonia data were not imputed and were excluded from the analysis; for other patients who did not have a calculable blood ammonia $AUC_{0–24}$ value for one but not both treatment periods, the missing ammonia data were handled using various methods, such as the last-observation-carried-forward approach. Sensitivity analyses were conducted to determine the effect of missing data on blood ammonia $AUC_{0–24}$.

e) Analysis Populations

In HPN-100-006, the analysis set was defined as:

ITT population: including all patients who received any amount of either study treatment (NaPBA or GPB). The ITT population was used for the analysis of efficacy and pharmacokinetic parameters. Patients were included based on randomization assignment.

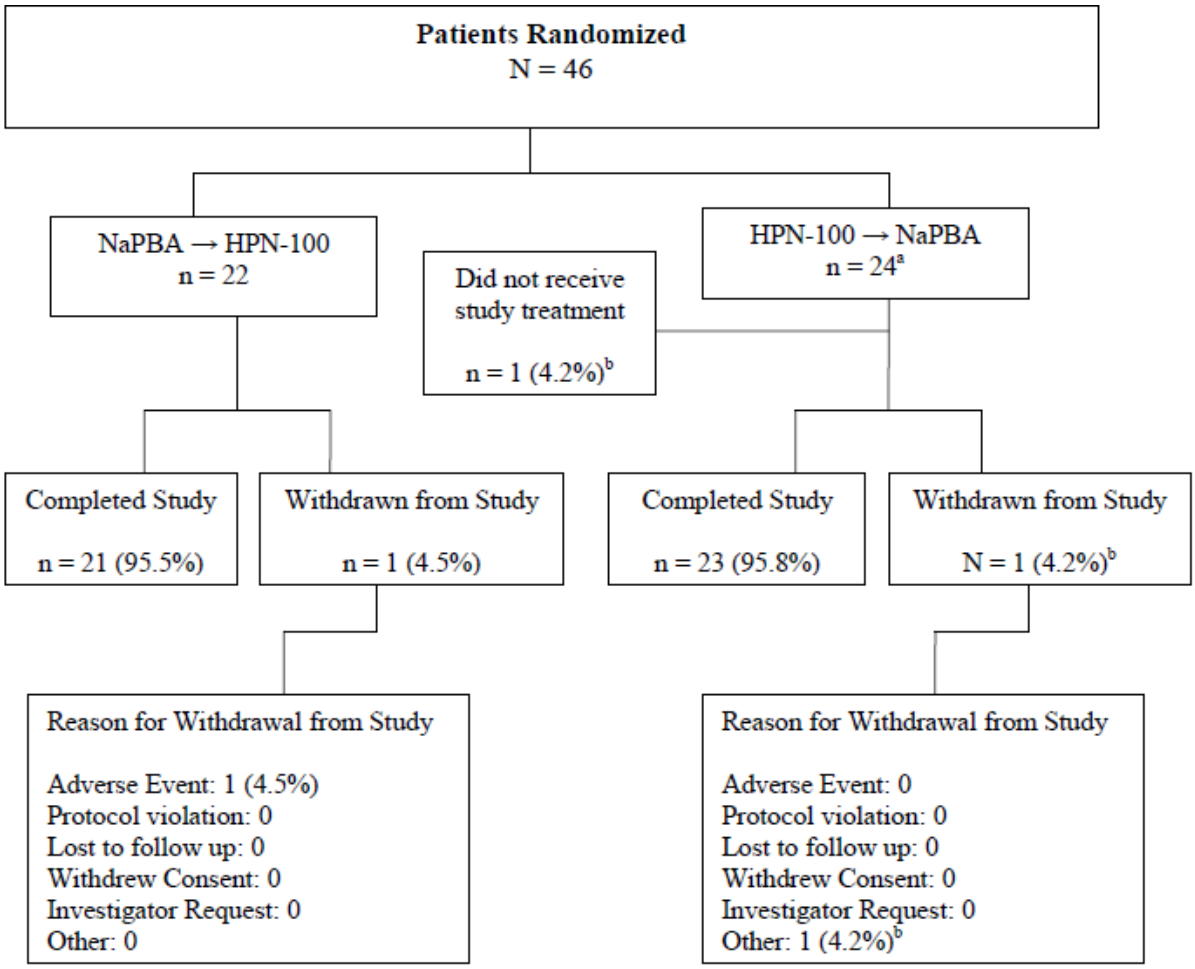
Per-protocol (PP) population: including all patients from the ITT population who received both study treatments (NaPBA and GPB) and 1) had a calculable blood ammonia AUC for both treatment periods; 2) had at least four blood ammonia samples, one of which was at either the eight-hour or 12-hour time point; 3) had the time zero blood ammonia sample drawn not more than 60 minutes after drug dosage and breakfast and the 24-hour blood ammonia sample drawn not more than 60 minutes after drug dosage and breakfast; 4) were compliant with study medication greater than 80% on day 14 and day 28; and 5) had not used sodium benzoate on either day 14 or day 28.

Safety population: including all patients who received any amount of study treatment. This was the primary population for all safety analyses. Patients were included based on study treatment received.

3.6 Patient Disposition

In total, 46 patients were randomized (Figure 3 and Table 6). One patient randomized to Arm B (GPB followed by NaPBA) withdrew before receiving any study treatment; therefore, 45 patients received at least one dose of study treatment (22 NaPBA followed by GPB, 23 GPB followed by NaPBA). One patient randomized to Arm A (NaPBA followed by GPB) withdrew on day 1 because of AEs (non-compliance with diet, including high blood ammonia levels [123 µmol/L], and headache). Another patient did not have a calculable $AUC_{0–24}$ because they withdrew from the study after receiving one dose of NaPBA. Therefore, 44 patients in the ITT population completed the study and had evaluable data for the primary efficacy analysis. No patients in the safety population withdrew during the GPB treatment. No patients discontinued NaPBA or GPB treatment because of an HAC.

FIGURE 3: PATIENT DISPOSITION IN STUDY HPN-100-006



HPN-100 = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate.
Source: Clinical Study Report of Study HPN-100-006.[24]

TABLE 6: PATIENT DISPOSITION

	Study HPN-100-006	
	Arm A: NaPBA → GPB	**Arm B: GPB → NaPBA**
Screened, N	46	
Randomized, N (%)	46	
	22	24
Discontinued, N (%)	1	1
Reason for withdrawal:		
Due to AE	1 (4.5)	0
Protocol violation	0	0
Lost to follow-up	0	0
Withdrew consent	0	0
Other	0	1 (4.2; withdrew before taking study drug)
ITT population, N (%)	45 (97.8)	
PP population, N (%)	43 (93.5)	
Safety population, N (%)	45 (97.8) for NaPBA; 44 (95.7) for GPB	

AE = adverse event; GPB = glycerol phenylbutyrate; ITT= intention-to-treat; N = number of patients; NaPBA = sodium phenylbutyrate; PP = per-protocol.
Source: Clinical Study Report of Study HPN-100-006.[24]

3.7 Exposure to Study Treatments

In study HPN-100-006, treatment compliance was assessed based on the study drug compliance diaries collected from the patients at each visit, as well as visual inspection of the returned study drug.

Forty-five of the 46 randomized patients received at least one dose of NaPBA study treatment. One patient withdrew before receiving any study treatment, and another patient, randomized to Arm A (NaPBA followed by GPB), withdrew from the study on day 1 and received only NaPBA. Therefore, 44 patients received at least one dose of GPB. Overall treatment compliance was high in the study, with 97.7% and 100% of patients being at least 80% compliant with the NaPBA and GPB treatments, respectively. The total mean dose of each study treatment was similar between the NaPBA and GPB treatment period (Table 7).

TABLE 7: EXTENT OF EXPOSURE TO STUDY DRUGS IN STUDY HPN-100-006 (SAFETY POPULATION)

	GPB N = 44	NaPBA N = 45
Actual Total Daily Dose (g/day)		
Mean (SD)	13.49 (5.96)	14.01 (6.34)
Actual Total Daily Dose (mg/kg/day)		
Mean (SD)	196.10 (90.71)	203.55 (95.87)
Total Daily Dose (g/m^2/day)		
Mean (SD)	7.55 (3.21)	7.85 (3.42)

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; SD = standard deviation.
Source: Clinical Study Report of Study HPN-100-006.[24]

3.8 Critical Appraisal

3.8.1 Internal Validity

HPN-100-006 was a phase III, DB, double-dummy, crossover randomized controlled trial (RCT) evaluating the noninferiority of GPB to NaPBA in blood ammonia $AUC_{0–24}$ in patients with UCDs. NaPBA is an appropriate comparator in the study population. Treatment allocation was carried out using a computer-generated central randomization schedule. The method of blinding was questionable because NaPBA has an unfavourable taste and odour, while GPB and GPB placebo supplied in study HPN-100-006 was odourless and almost tasteless. This may have allowed some patients (and/or investigators) to surmise that they were randomized to receive a certain treatment. However, the primary outcome, change in blood ammonia levels, is an objective outcome measure. Therefore, it is unlikely that the method of blinding had an important impact on the study results for the primary analysis. In the case of a medical emergency, unblinding of the patient's treatment assignment could be requested by the investigator for the well-being of the patient; however, no cases of unblinding occurred during the study. Forty-four out of 46 randomized patients completed the study; the overall loss to follow-up was low and treatment compliance was high. Because of the ethical consideration, there was no washout period between the two treatments. The potential carry-over effect may complicate the interpretation of the study findings, such as the comparison of drug-related AEs between treatment groups. A previous study demonstrated that, in healthy volunteers, after NaPBA administration, the mean plasma half-life of PBA was 0.7 ± 0.1 hours; after GPB administration, the mean plasma half-life of PBA was 1.9 ± 1.7 hours.[25] Given the short half-lives of GPB and NaPBA, the carry-over effect would not be considered significant.

The primary outcome of this study was $AUC_{0–24}$ for blood ammonia levels. Blood samples were drawn and processed by the laboratory at the investigator site rather than a central laboratory. Although the facility standard operating procedures were adopted for the process, there may still be discrepancies among the various sites, which may affect the accuracies of the results. Furthermore, important clinical outcomes such as cognitive development, anthropometric measurements, and health-related quality of life (HRQoL) were not measured, probably because of the short duration (four weeks) of HPN-100-006. The relationship between ammonia levels and clinical outcomes among patients with UCDs was not well established and there was conflicting evidence in previous research. While general trends suggest that higher levels of blood ammonia are associated with higher risks of HAC, identifying quantitative levels for targets and minimal clinically important differences remains elusive.[26,27]

In terms of the methods of statistical analysis, the method for the sample size calculation was described. The planned sample size was considered to provide 90% power to demonstrate noninferiority of GPB to the comparator. There was no rationale provided for the use of 0.225 as an SD. This is key information to be able to assess whether the sample size was determined in a proper manner. Due to the small sample size, analyses of some important subgroups (such as UCD subtypes and age) predefined in the research protocol were not feasible. The clinical expert consulted for this review noted that the current sample size is acceptable, given that a UCD is a rare disease. Missing data were assumed to be missing at random; however, this may not be an appropriate assumption because patient dropout may be due to differences in the treatment effects between the two groups. Sensitivity analyses were conducted by excluding patients with incalculable blood ammonia $AUC_{0–24}$ to determine the effect of missing data on the primary study end point, and the results were consistent with the primary analysis, which was conducted in a PP or ITT population.

In HPN-100-006, efficacy and safety of GPB and NaPBA were assessed up to two weeks after the randomization. There was a lack of longer-term comparative efficacy and safety data available for GPB in the study population. Open-label extension studies were conducted to explore the treatment effect of GPB in adult and pediatric populations up to one year without comparing with a currently available active treatment (APPENDIX 7).

3.8.2 External Validity

The study participants were recruited from one Canadian centre and 21 US centres. The NaPBA formulation used in study HPN-100-006 was marketed in the US as Buphenyl. This was a taste-unmasked formulation that is not the same formulation as the taste-masked formulation (Pheburane) available in Canada. The active component in both formulations is NaPBA; the dose of Buphenyl was the same as the HC-approved dosage for Pheburane. It is uncertain whether this would limit the generalizability of the study results to current Canadian clinical practice.

The baseline patient characteristics were somewhat different from a typical Canadian population with UCDs. According to the clinical expert consulted for this review, due to the restricted inclusion criteria and extensive exclusion criteria, patients in the included study had milder disease (such as lower baseline ammonia levels and less comorbidity) compared with the patients who are usually seen in clinical practice. This can limit the generalizability of the study results to a broader UCD population. The clinical expert noted that, through clinical experience, the results would be translated to the more severe UCD population. On the other hand, not all subtypes of UCDs were included in the study.

The study enrolled adult patients only; therefore, the clinical benefits and harms in pediatric patients cannot be examined. In addition, only patients with CPS1, OTC, and ASS subtypes were enrolled; thus the treatment effect of study medication on other UCD subtypes was uncertain. Generalizability of the study results would also be limited due to lack of evidence on some hard clinical outcomes, short study duration, and uncertain sustained effect of the study medication.

3.9 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4 or detailed efficacy data.

3.9.1 Mortality

No deaths occurred in the study.

3.9.2 Number of Hyperammonemic Crises

No patients had an HAC during GPB treatment.

One patient had elevated blood ammonia levels that met the definition of an HAC while on NaPBA treatment; the elevated levels were due to noncompliance with the study treatment. This was also considered an SAE.

3.9.3 Cognitive Development

This was not assessed as an outcome in HPN-100-006.

3.9.4 Anthropometric Measurements

This was not assessed as an outcome in HPN-100-006.

3.9.5 Plasma Ammonia Levels

$AUC_{0–24}$ for Blood Ammonia on Day 14 and Day 28

In the PP population, the mean $AUC_{0–24}$ values for blood ammonia were 12% lower with GPB treatment compared with NaPBA (868.29 ± 668.145 µmol·h/L versus 985.47 ± 873.578 µmol·h/L, respectively). Consistent results were observed in the ITT population, with mean $AUC_{0–24}$ values for blood ammonia 11% lower with GPB treatment compared with NaPBA (865.85 ± 660.529 µmol·h/L versus 976.63 ± 865.352 µmol·h/L, respectively). None of the differences between the GPB and NaPBA treatments with respect to blood ammonia assessed as $AUC_{0–24}$ were statistically significant.

In the PP population, GPB achieved noninferiority to NaPBA. The upper bound of the 95% CI of ratio of the geometric means of blood ammonia $AUC_{0–24}$ between GPB and NaPBA was 1.030, which was below the predefined noninferiority margin of 1.25. A consistent treatment effect was seen in the ITT population, in which GPB was shown to be noninferior to NaPBA in controlling blood ammonia (upper bound of the 95% CI of 1.034) (Table 8).

Post-hoc analysis in subgroups suggested that mean blood ammonia $AUC_{0–24}$ with GPB treatment was 17% lower compared with NaPBA treatment in patients who were diagnosed with a UCD during infancy (UCD onset at two years old or younger) and 10% lower in patients who were diagnosed with a UCD after infancy (UCD onset older than two years). The between-group differences in the subgroup analysis were not statistically significant APPENDIX 4.

TABLE 8: PLASMA AMMONIA LEVELS IN STUDY HPN-100-006 ($AUC_{0–24}$, µMOL·H/L)

	GPB	NaPBA
PP Population	N = 43	N = 43
Mean, SD	868.29 (668.15)	985.47 (873.58)
Difference between GPB and NaPBA, mean (SD)	–117.18 (584.22)	
Ratio of geometric means (95% CI)	0.90 (0.792 to 1.030)	
P value[a]	0.196	
ITT Population	N = 44	N = 45
Mean, SD	865.85 (660.53)	976.63 (865.35)
Difference between GPB and NaPBA, mean (SD)	–110.78 (578.95)	
Ratio of geometric means (95% CI)	0.91 (0.799 to 1.034)	
P value	0.211	

AUC = area under the curve; CI = confidence interval; GPB = glycerol phenylbutyrate; ITT = intention-to-treat; NaPBA = sodium phenylbutyrate; PP = per-protocol.

[a] *P* value for between-group comparison.

Source: Clinical Study Report of HPN-100-006.[24]

a) Maximum Blood Ammonia Values

Twenty-four–hour C_{max} values for blood ammonia were numerically but not statistically significantly lower with GPB treatment compared with NaPBA treatment in the patient populations. In the PP population, mean C_{max} values for blood ammonia were 14% lower with GPB treatment compared with NaPBA (61.33 ± 46.686 µmol/L versus 71.47 ± 67.355 µmol/L, respectively), and it was 14% lower with GPB treatment compared with NaPBA treatment in the ITT population (60.94 ± 46.213 µmol/L versus 70.83 ± 66.71 µmol/L, respectively) (Table 9).

The mean blood ammonia C_{max} levels were 14% lower with GPB treatment versus NaPBA treatment in patients who were diagnosed with a UCD during infancy (UCD onset at two years or younger) and in patients who were diagnosed with a UCD after infancy (UCD onset older than two years). The between-group differences in the subgroup analysis were not statistically significant APPENDIX 4.

TABLE 9: PLASMA AMMONIA LEVELS IN STUDY HPN-100-006 (24-HOUR C_{MAX}, µMOL/L)

	GPB	NaPBA
PP Population	N = 43	N = 43
Mean (SD)	61.33 (46.69)	71.47 (67.36)
Difference between GPB and NaPBA, mean (SD)	–10.14 (43.57)	
P value	0.134	
ITT Population	N = 44	N = 44
Mean, SD	60.94 (46.21)	70.83 (66.71)
Difference between GPB and NaPBA, mean (SD)	–9.89 (43.10)	
P value	0.135	

GPB = glycerol phenylbutyrate; ITT = intention-to-treat; NaPBA = sodium phenylbutyrate; PP = per-protocol; SD = standard deviation.
Source: Clinical Study Report of HPN-100-006.[24]

b) Percentage of Blood Ammonia Values Above the Upper Limit of Normal on NaPBA Versus GPB

The number of ammonia samples above the ULN was similar with GPB and NaPBA treatments in the PP populations (35.4% and 36.8%, respectively; *P* > 0.05). The number of ammonia samples above the ULN was also similar with GPB and NaPBA treatments in the ITT population (35.6% and 36.2% of samples, respectively; *P* > 0.05) (Table 10).

TABLE 10: AMMONIA VALUES ABOVE THE UPPER LIMIT OF NORMAL IN STUDY HPN-100-006

	GPB	NaPBA
PP Population	**N = 43**	**N = 43**
Number of total samples	336	337
Number of samples > ULN (%)	119 (35.4)	124 (36.8)
P value for between-group comparison	0.835	
ITT Population	**N = 44**	**N = 44**
Number of total samples	343	345
Number of samples > ULN (%)	122 (35.6)	125 (36.2)
P value for between-group comparison	0.905	

GPB = glycerol phenylbutyrate; ITT = intention-to-treat; NaPBA = sodium phenylbutyrate; PP = per-protocol; ULN = upper limit of normal.
Source: Clinical Study Report of HPN-100-006.[24]

c) Glutamine Levels

Glutamine levels were assessed in a post-hoc evaluation. Results of this outcome are presented in APPENDIX 4.

3.9.6 Health-Related Quality of Life

This was not assessed during the four-week treatment period in HPN-100-006.

3.9.7 Other Efficacy Outcomes

a) Hospitalization

Not assessed.

b) Patient Adherence

Not assessed.

c) Patient/Caregiver Satisfaction

Not assessed.

3.10 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol).

3.10.1 Adverse Events

At least one treatment-emergent AE was reported in 27 (61.4%) and 23 (51.1%) patients on GPB and NaPBA treatment, respectively (Table 11). Most treatment-emergent AEs were considered by the investigator to be mild, although one was a grade 3 hyperammonemia. Symptoms of lower GI tract disorders (diarrhea and flatulence) were reported more frequently on GPB treatment, whereas symptoms of upper GI disorders (abdominal discomfort, dyspepsia, nausea, and oral discomfort) were more likely to be reported during the NaPBA treatment. These events were generally mild. Dizziness was reported by more patients treated with NaPBA than GPB (8.9% versus 0).

3.10.2 Serious Adverse Events

Two patients reported treatment-emergent SAEs: one patient reported acute gastroenteritis on GPB treatment, and one patient reported a grade 3 hyperammonemia on NaPBA treatment.

3.10.3 Withdrawals Due to Adverse Events

No patients discontinued from GPB treatment, whereas one patient discontinued from NaPBA treatment because of high ammonia levels on day 1.

3.10.4 Mortality

No deaths occurred during the four-week treatment periods.

3.10.5 Notable Harms

During the baseline assessments, patients were queried regarding common symptoms associated with the use of NaPBA (decreased appetite/food aversion, increased appetite, body odour, burning sensation in mouth or throat, abdominal pain/distress, nausea, vomiting, heartburn, headache, amenorrhea/ menstrual dysfunction, dizziness, or fatigue) and asked to record the frequency of their occurrence. The same set of inquiries was given to patients on day 14 and day 28 after treatment with NaPBA and GPB. If such symptoms were detected at baseline, they were to be also recorded as medical history before enrolling in the study. The symptoms were not reported as AEs if they existed at baseline. If these symptoms were first detected after the baseline visit, they were recorded as AEs and attributed to the last treatment received, either NaPBA or GPB.

In total, 33 patients reported “yes” to at least one of the UCD symptoms at baseline, while on day 14 and day 28, 21 of them did not report a UCD symptom after treatment with GPB. With the exception of amenorrhea/menstrual dysfunction, which showed no change in the reporting frequency, there was an overall numerical reduction in the number of patients still reporting “yes” to any of the UCD symptoms

after treatment with GPB. Frequencies of these symptoms were less than 5%; therefore, they are are not presented in Table 11. In addition, mean changes from baseline in selected liver-function parameters were similar with NaPBA treatment and GPB treatment (data not presented). There were no clinically significant changes in liver-function values and potassium level during the study with either treatment.

TABLE 11: HARMS

	HPN-100-006	
	GPB N = 44	**NaPBA N = 45**
AEs [a]		
Patients with > 0 AEs, N (%)	27 (61.4)	23 (51.1)
Abdominal discomfort	0	3 (6.7)
Abdominal pain	3 (6.8)	2 (4.4)
Diarrhea	7 (15.9)	3 (6.7)
Dyspepsia	2 (4.5)	3 (6.7)
Flatulence	6 (13.6)	1 (2.2)
Nausea	1 (2.3)	3 (6.7)
Vomiting	3 (6.8)	2 (4.4)
Dizziness	0	4 (8.9)
Headache	6 (13.6)	4 (8.9)
Fatigue	3 (6.8)	1 (2.2)
Decreased appetite	3 (6.8)	2 (4.4)
SAEs		
Patients with > 0 SAEs, N (%)	1 (2.3)	1 (2.2)
	1 acute gastroenteritis	1 grade 3 hyperammonemia
WDAEs		
WDAEs, N (%)	0	1 (2.2)
		High blood ammonia levels and headache
Notable Harms		
GPB-treated patients reported fewer UCD symptoms than NaPBA-treated patients. No significant changes in liver function and blood potassium level in either group.		
Death		
Number of deaths, N (%)	0	0

AE = adverse event; GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency greater than or equal to 5%.

Source: Clinical Study Report of Study HPN-100-006.[24]

4. DISCUSSION

4.1 Summary of Available Evidence

One manufacturer-sponsored, phase III, DB, crossover RCT (HPN-100-006, N = 46) was included in this review. The study evaluated the efficacy and safety of GPB compared with NaPBA administered orally in adult patients with UCDs who had been on a stable dose of NaPBA for at least one week before study entry. The primary objective was to establish the noninferiority of GPB to NaPBA, as assessed by blood ammonia. HPN-100-006 was designed as a crossover study, and there was no washout period between NaPBA and GPB treatment periods because of safety reasons. Due to the short half-lives of GPB and NaPBA (after NaPBA administration, the mean plasma half-life of PBA was 0.7 ± 0.1 hours; after GPB administration, the mean plasma half-life of PBA was 1.9 ± 1.7 hours), the carry-over effect from the study drugs is less likely to significantly bias the study results. The efficacy analysis therefore involved comparison of data from the final 24 hours of each treatment period (day 14 and day 28) with either 100% NaPBA or 100% GPB, by which time steady-state metabolite plasma levels would have been achieved. The primary outcome in this study was $AUC_{0–24}$ for blood ammonia at the end of each treatment period. After randomization, patients received two weeks NaPBA followed by two weeks GPB, or two weeks GPB followed by two weeks NaPBA. The NaPBA formulation used in HPN-100-006 was Buphenyl, which is marketed in the US but not in Canada. Phenurane is the NaPBA formulation available in Canada. The dose of Buphenyl was the same as the HC-approved dosage for Pheburane.

The main limitations of this study were the lack of data regarding cognitive impairment or HRQoL, short study duration, and small sample size, which made the study unable to demonstrate any potential differences; in other words, the assay sensitivity is a significant issue with this study. $AUC_{0–24}$ for blood ammonia was assessed in patients with early onset versus late onset of disease. Due to the smaller number of patients in the subgroups, the results of subgroup analyses should be interpreted with caution. Moreover, the possibility of carry-over effect could not be ruled out, and the impact of sequence effect was unknown.

Based on the eligibility criteria of HPN-100-006, patients with the following were excluded: a baseline ammonia level greater than and equal to 100 µmol/L or signs and symptoms indicative of hyperammonemia during the two-week period preceding screening or enrolment; active infection or any other intercurrent condition that may have increased ammonia levels; greater than and equal to grade 3 clinical or laboratory abnormality; any clinical or laboratory abnormality or medical condition that may put them at increased risk by participating in the study. The recruited patient population had milder disease. In addition, only adult patients with certain UCD subtypes (CPS1, OTC, and ASS) were enrolled in the study. Therefore, the generalizability of the study results to a broader UCD population is uncertain. Findings from short-term, non-randomized studies enrolling patients with all UCD subtypes are summarized in APPENDIX 6 and APPENDIX 7.

4.2 Interpretation of Results

4.2.1 Efficacy

Previous studies evaluating the relationships between ammonia levels and clinical outcomes suggested that, although a “threshold” of blood ammonia level has not been established to indicate a definite change in health outcomes in patients with UCDs, higher initial ammonia concentrations (i.e., greater than 300 µmol/L) were found to be associated with higher risks of severe neurologic damage, cognitive impairment, HAC, or even death (APPENDIX 5). A more recent pooled analysis using data from four short-term and three long-term HPN-series studies indicated that a 10 µmol/L or 25 µmol/L increase in

ammonia exposure increased the relative risk of a HAC by 50% and greater than 200%.[26] Results from HPN-100-006 suggest that GPB is noninferior to NaPBA in lowering blood ammonia levels. This was a crossover RCT without a washout period between treatment with GPB and NaPBA. There was a potential carry-over effect, which may have an impact on the study results. A previous study indicated that, in healthy volunteers, both GPB and NaPBA have short half-lives, and phenylacetic acid and phenylacetylglutamine reached steady state in two to three days after administration of multiple doses of GPB.[20,25] The clinical expert consulted for this review noted that, given the safety considerations, no washout period is common in UCD trials to avoid uncontrolled ammonia levels and related consequences; however, the carry-over effect would be minimal due to the short half-life of the drug, when the study end point was the end of the two-week treatment period. Occurrence of HAC was rare during the four-week treatment period. The 24-hour C_{max} values for blood ammonia in the GPB group were approximately 10 µmol/L lower compared with the NaPBA group. The between-group difference did not reach statistical significance. Insufficient power could partially explain the statistically insignificant change in this outcome between the two groups. According to the clinical expert, the 10 µmol/L difference in maximum blood ammonia level would not be considered a clinically meaningful change. In addition, the percentage of ammonia samples above the ULN was similar with GPB and NaPBA treatments. Clinical outcomes such as cognitive development and HRQoL were not assessed during the short treatment periods.

The effect of GPB on blood ammonia levels was also assessed in patients who were diagnosed with a UCD during their infancy and in those who were diagnosed with a UCD after infancy. The results from subgroup analysis implied that adults with early onset of a UCD (two years of age or younger) responded better to GPB treatment in ammonia control than adults with onset of a UCD at ages older than two, although the numbers of patients in the subgroups were very small and prevent drawing solid conclusions with respect to the effect of GPB in the subpopulation (APPENDIX 4).

Results from three short-term, non-randomized trials enrolling adults and children suggested that GPB had a similar effect in lowering the blood ammonia levels as NaPBA, after one week to 10 days of treatment. The risk of AEs was comparable between GPB and NaPBA, and the majority of reported AEs were of mild intensity. However, these small trials did not have sufficient power to detect clinically or statistically meaningful differences between GPB and the comparator. The results should be interpreted with caution (0). Post-hoc pooled analyses of short-term studies of GPB were conducted in order to increase the study power. The results suggested that GPB exhibited favourable pharmacokinetic and ammonia control relative to NaPBA in patients with a UCD.[19] However, the results should be interpreted with caution due to the heterogeneity among the individual studies, such as study design and varied baseline patient characteristics. Results from three long-term, open-label, non-comparative studies indicated that the effects of GPB on blood ammonia and glutamine levels appeared to be maintained after 12 months of treatment in both children and adults. In addition, the number of HACs per patient was reduced compared with the values 12 months before screening. HRQoL improved in children, while it appeared to decrease in adults according to generic QoL assessment tools. Neuropsychological testing results were inconsistent across trials, age groups, and assessment tools. Considering the limitations of these long-term studies (open-label, lack of comparator, short duration, and small sample), the findings should be interpreted with caution (APPENDIX 7).

The clinical expert indicated that the duration of the included RCT and non-randomized trials was not long enough to appropriately assess clinical outcomes. Duration of at least eight weeks to six months would be required to evaluate the benefits and harms of study drug.

Treatment compliance was high in both treatment groups during the four-week periods.

4.2.2 Harms

No death occurred during the DB treatment period. Overall, patients treated with GPB were more likely to complain about AEs (61.4%) than those treated with NaPBA (51.1%). Symptoms of lower GI tract disorders were reported more frequently on GPB treatment, whereas symptoms of upper GI disorders were more likely to be reported during the NaPBA treatment. These events were generally mild. There was one case of hyperammonemia that led to treatment discontinuation with NaPBA. Compared with baseline (all patients received prior NaPBA treatment), there was a reduction in the number of patients still reporting any of the UCD treatment-specific symptoms (bad taste, body odour, etc.) after treatment with GPB. Because of the small number of study participants, it is challenging to make a definite conclusion on the safety of GPB.

As well, because of the relatively milder conditions of the patients recruited in HPN-100-006, AEs, and especially SAEs, would have been limited.

Longer-term safety was explored in extension studies (APPENDIX 7),which included patients from original pivotal study as well as new patients. The findings suggested that the overall frequency of AEs gradually increased. Almost all patients experienced AEs after one year of treatment with GPB. Infections and infestations, as well as GI disorders, were still the most frequently experienced AEs. Newly emerging AEs included nervous system disorders and general disorders as well as administration-site conditions.

5. CONCLUSIONS

One phase III, DB, crossover RCT conducted in the US and Canada that evaluated the noninferiority of GPB to NaPBA in adult patients with UCDs was included in this review. Study HPN-100-006 enrolled patients with a diagnosis of CPS1, OTC, or ASS deficiencies who had been on dietary protein restriction and/or amino acid supplementation. The patients were required to be on a stable dose of NaPBA for at least one week before study entry. A total of 46 patients were randomized (44 evaluable) to receive two weeks NaPBA followed by two weeks GPB, or two weeks GPB followed by two weeks NaPBA. Results from this study suggested that GPB was noninferior to NaPBA in ammonia control, measured with AUC_{0-24} for blood ammonia levels at study end points, according to the predefined noninferiority margin of 1.25. GPB also showed similar effects on maximum blood ammonia values and on the percentage of ammonia samples above the ULN when compared with NaPBA. However, interpretation of results is limited, as no minimal clinically important difference is available to evaluate changes in ammonia levels. There were no HACs during the GPB treatment, whereas one HAC occurred during the NaPBA treatment, which led to treatment discontinuation. Cognitive development and HRQoL were not assessed in this study. Patients in the GPB group reported higher risks of AEs compared with those in the NaPBA. These events were generally mild. GPB treatment was associated with more symptoms of lower GI tract disorders, whereas NaPBA treatment was associated with more symptoms of upper GI tract disorders. One case of hyperammonemia that led to treatment discontinuation was observed in the NaPBA group. After being treated with GPB, patients reported fewer UCD treatment-specific symptoms such as bad taste and body odour.

Findings from three longer-term, open-label, non-comparative studies suggested that, after one year of treatment with GPB, the effects of GPB on blood ammonia and glutamine levels appeared to be maintained in both children and adults. The number of hyperammonemic episodes per patient was reduced compared with the values 12 months before screening. Almost all patients experienced AEs after one year of treatment with GPB. The interpretation of results from these long-term studies is challenging because of several important limitations such as the study design, sample size, and the study duration.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Canadian Organization for Rare Disorders (CORD), provided input for this submission. CORD is Canada's national network for organizations representing those with rare disorders. CORD serves as the voice for patients where there is no existing patient group and provides training and support to patient organizations serving rare diseases, including the preparation of submissions for drug review processes or other activities on behalf of the patients and families.

CORD receives funding from several pharmaceutical companies including Horizon (the manufacturer of Ravicti) and Medunik Canada (provider of Pheburane). CORD declared no conflict of interest with respect to compiling this submission.

2. Condition-Related Information

Information was gathered from one-on-one interviews with patients and parents, leads of patient advocacy groups in the US, health care professionals, surveys, websites, and emails from both Canada and the US. More than 80% of those responding were diagnosed as children and approximately 80% have been living with a urea cycle disorder (UCD) diagnosis for more than five years.

A UCD is a genetic condition that can manifest with variable severity and characteristics. The impact of the condition can depend on the specific genetic mutation as well as other factors. Symptoms typically vary from birth to adulthood and were described by more than half of respondents to affect their lives "much or very much." According to CORD, most respondents reported fatigue, lethargy, or weakness, and 30% conveyed that hospitalizations affect their lives "much or very much." Two-thirds of respondents reported abdominal symptoms such as cramps, pain, diarrhea, vomiting, and eating disorders, and 20% experienced serious medical conditions (e.g., liver complications or coma). Approximately 30% of the respondents believed a UCD was associated with serious behavioural problems, whereas another 50% believed there was some impact. Serious learning or cognitive disorders were reported. Twenty per cent of the respondents described the effect of a UCD on learning or cognitive development as "much or very much" affected, whereas 50% reported there was "some" effect. Approximately 35% reported that school or work life was "much or very much" affected; the same percentage reported serious impact on home and/or social life.

Respondents expressed the impact of a UCD as follows: *"I missed many school days due to being in the hospital. When I returned, I was constantly behind and felt like a failure. As I grew older, it started to affect [sic] the ability for me to keep a job due to doctor appointments, hospitalizations, lack of energy. It has caused severe anxiety at times not knowing when the next flair up may be. It has affected my ability to remember things at times. It is an ongoing struggle and I hope they find a cure. My veins are completely gone more or less. I have had IV all over since so many hospital stays."* One patient stated that *"Urea Cycle Disorder has not affected my life --it IS my life…"*

3. Current Therapy-Related Information

All respondents reported prior experiences with UCD treatments. Approximately 80% of respondents had previously taken sodium benzoate/sodium phenylacetate (Ammonul), and nearly 8% reported use

at the time of survey. Approximately 80% of respondents had previously taken sodium phenylbutyrate (NaPBA) powder or pills (Buphenyl). A newer drug, sodium phenylbutyrate granules (Pheburane), was taken by nearly 8% of respondents at the time of the survey, all within Canada. About 25% of respondents also reported use of L-arginine hydrochloride (Citrulline).

The introduction of Buphenyl was considered to be a significant improvement on previous medication and diet alone with respect to ammonia level mitigation: *"[With] Buphenyl, sodium benzoate, and Citrulline-L have kept my daughter's ammonia relatively controlled for about six years."* However, all patients acknowledged that NaPBA was far from an ideal treatment, mainly due to the poor treatment compliance, a direct consequence of the drug's terrible taste, the difficulty in taking medication, the resulting body odour and vomiting. According to some patients, ammonia levels were not consistently sustained at target levels when taking Buphenyl, *"The absorption rate was also inconsistent, causing her ammonia levels to have distinct peaks and valleys, rarely level."* As well, approximately 60% of respondents on Buphenyl reported side effects such as stomach aches, cramps, and diarrhea. Patients reported similar issues with Pheburane. In addition, respondents complained about the inconvenient liquid formulation of Pheburane.

Caregivers expressed that caring for a child with a UCD is a "full-time job" and most expect that they will be caring for their "adult" child for the rest of their lives. Respondents expressed the tremendous impact of caring for someone with a UCD: *"It has changed every part of my life and my daughter's! She was in and out of the hospital about every three weeks. She lost her speech and ability to walk because of brain damage from the high ammonia and so much time in hospital. I do not work because UCD is a full-time job; it was too much for her father and we got a divorce and my mom has moved in with me to help so I can have some respite care."*

4. Expectations About the Drug Being Reviewed

Information was gathered from the feedback of 52 families (patients and parents). Of those individually interviewed, 12 families lived in the US and six in Canada. Six health care providers, including clinicians, nurses, and dieticians, were consulted to obtain contextual information and to seek referrals to patients. Overall, 75% of patients were currently taking glycerol phenylbutyrate (GPB; Ravicti) and 12% had taken it in the past.

GPB-naive respondents expected improvement in symptoms, fewer side effects, better quality of life (QoL), and improved compliance with Ravicti. One patient stated that "[Ravicti will] *… stabilize ammonia levels, restore energy, eliminate or reduce cramps and diarrhea, allow return to normal activities and support compliance because it is easy to take."* Patients also expected odour problems to be resolved: "*No bad odour makes life easier. Relationships are no longer as difficult because you are not always worried about how you may be smelling if you are exerting yourself*."

GPB-experienced respondents generally expressed positive experiences with Ravicti. Patients reported a more stable ammonia level that reduces anxiety and fear, especially overnight. According to CORD, most patients reported almost no side effects. Of those who experienced side effects, the most frequently mentioned were stomach cramps, nausea, diarrhea, headaches, swelling, vomiting, and anemia. All respondents said that the symptoms were reduced over time or were manageable with other strategies, such as eating with the medication. CORD reported no discontinuations in patients taking Ravicti. Some respondents were concerned about accessibility to Ravicti. Patients (12%) who had previously received Ravicti in clinical trials but no longer had access stated: *"I can only hope that it will be available soon."* They also indicated, *"There are so many benefits that everyone should have access to it! I wish that it didn't all come down to the mighty dollar…very sad!"*

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid
Date of Search:	September 22, 2016
Alerts:	Weekly search updates until February 15, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Strategy**
1	(ravicti* or glycerol phenylbutyrate or "glycerol tri(4 phenylbutyrate)" or "glycerol tris(4 phenylbutanoate)" or "glycerol tris(4 phenylbutyrate)" or "glyceryl tri(4 phenylbutyrate)" or "glyceryl tris(4 phenylbutyrate)" or "tris(4-phenylbutyryl)glycerol" or hpn 100 or hpn100 or "propane 1,2,3 triyl tris(4 phenylbutanoate)" or ZH6F1VCV7B or 611168-24-2).ti,ab,ot,kf,hw,rn,nm.
2	1 use ppez
3	glycerol phenylbutyrate/
4	(ravicti* or glycerol phenylbutyrate or "glycerol tri(4 phenylbutyrate)" or "glycerol tris(4 phenylbutanoate)" or "glycerol tris(4 phenylbutyrate)" or "glyceryl tri(4 phenylbutyrate)" or "glyceryl tris(4 phenylbutyrate)" or

MULTI-DATABASE STRATEGY	
#	**Strategy**
	"tris(4-phenylbutyryl)glycerol" or hpn 100 or hpn100 or "propane 1,2,3 triyl tris(4 phenylbutanoate)" or ZH6F1VCV7B or 611168-24-2).ti,ab,ot,kw.
5	or/3-4
6	5 use oemezd
7	6 not conference abstract.pt.
8	2 or 7
9	remove duplicates from 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 2016
Keywords:	Ravicti, glycerol phenylbutyrate urea cycle disorder, urea cycle disorders
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Glycerol phenylbutyrate (Ravicti) for urea cycle disorders. Med Lett Drugs Ther. 2014 Aug 18;56(1449):77-8.	Not randomized controlled trial (RCT)

APPENDIX 4: DETAILED OUTCOME DATA

Post-hoc evaluations of blood ammonia levels were performed in patients who were diagnosed with urea cycle disorders (UCDs) during infancy (early onset) and after infancy (late onset). For patients with UCD onset at two years of age or younger, the mean blood ammonia $AUC_{0–24}$ levels were 17% lower with glycerol phenylbutyrate (GPB) treatment versus sodium phenylbutyrate (NaPBA) treatment. For patients with UCD onset after two years of age, the mean blood ammonia $AUC_{0–24}$ levels were lower by 10% with GPB versus NaPBA.

TABLE 12: BLOOD AMMONIA LEVELS IN STUDY HPN-100-006, SUBGROUP ANALYSES BY ONSET OF UCD (INTENTION-TO-TREAT POPULATION) — POST-HOC ANALYSIS

	Onset ≤ 2 years		Onset > 2 years	
	GPB (n = 10)	**NaPBA (n = 10)**	**GPB (n = 34)**	**NaPBA (n = 34)**
$AUC_{0–24}$ of Blood Ammonia Levels, µmol h/L				
Mean (SD)	732.84 (604.13)	878.91 (586.41)	904.97 (679.73)	1005.37 (937.14)
Between-group difference	–146.07 (205.85)		–100.40 (651.70)	
P value for between-group comparison	0.052		0.376	
C_{max} of Blood Ammonia Levels, µmol/L				
Mean (SD)	51.62 (36.92)	60.23 (45.27)	63.68 (48.76)	73.94 (72.08)
Between-group difference	–8.61 (23.11)		–10.27 (47.68)	
P value for between-group comparison	0.269		0.218	

AUC = area under the curve; GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; SD = standard deviation; UCD = urea cycle disorder.
Source: Clinical Study Report of HPN-100-006.[24]

A post-hoc analysis of glutamine levels was conducted in HPN-100-006. Mean ± standard deviation (SD) glutamine values were statistically significantly lower (*P* = 0.031, paired *t*-test; *P* = 0.017, Wilcoxon signed rank test) after GPB treatment compared with NaPBA treatment (757.7 ± 237.44 µmol/L versus 808.9 ± 251.48 µmol/L, respectively) in the safety population.

TABLE 13: MEAN CHANGES IN GLUTAMINE LEVELS IN STUDY HPN-100-006 (µMOL/L) — POST-HOC ANALYSIS

	GPB	NaPBA
Safety population	**N = 44**	**N = 44**
Mean (SD)	757.7 (237.44)	808.9 (251.48)
Change from baseline to study end point	–57.1 (202.88)	41.7 (163.11)
Difference between GPB and NaPBA, mean (SD)	–51.2 (152.23)	
P value	0.031	

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; SD = standard deviation.
Source: Clinical Study Report of HPN-100-006.[24]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize evidence that evaluates the extent to which ammonia and glutamine levels correlate with clinical outcomes among patients with urea cycle disorders (UCDs). To summarize the measurement properties (e.g., reliability, validity, minimal clinically important difference) of the Pediatric Quality of Life Inventory Generic Core Scales SF15 (PedsQL SF15) version 4 and the Short Form (36) Health Survey (SF-36) version 2 and to describe the following neuropsychological tests:

- Wechsler Abbreviated Scale of Intelligence (WASI-II)
- Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)
- Grooved Pegboard Test
- Digit span
- California Verbal Learning Test (CVLT-II)
- Child Behavior Checklist (CBCL)
- Behavior Rating Inventory of Executive Function (BRIEF)

Ammonia and Glutamine

Six studies were identified that investigated the relationship between ammonia levels and/or glutamine and clinical outcomes among patients with UCDs.

Bachmann and colleagues (2003) evaluated 88 patients (41 females) with a UCD in Switzerland.[28] The most common UCDs were ornithine transcarbamylase (OTC) deficiency – hemizygous (20%), OTC deficiency – heterozygous (20%), citrullinemia type I (16%), and argininosuccinic aciduria (16%). Forty-four patients (50%) received conservative long-term management using protein restriction, and the other half received protein restriction combined with more extensive therapy (i.e., arginine/citrulline, essential amino acid supplements, and sodium benzoate) as alternative pathway therapy. The authors concluded that all patients with normal developmental outcome had initial ammonia concentrations less than 300 µmol/L and peak ammonia concentrations less than 480 µmol/L. The authors did not describe the how they evaluated psychomotor outcome; instead, they classified patients as “normal,” “retarded,” and “dead.”

Uchino et al. (1998) evaluated 108 patients with a UCD in Japan.[29] No information was provided about the demographic or disease characteristics of the patients. The researchers noted that patients did not develop severe neurological damage when their peak blood ammonia concentration during the initial hyperammonemic episode was less than 180 µmol/L, but when it exceeded 350 µmol/L, all patients sustained severe brain damage or died. Patients whose peak ammonia concentration ranged from 180 µmol/L to 350 µmol/L had variable outcomes. The authors did not describe the how they evaluated cognitive outcome.

Msall et al. (1984) studied 26 children with inborn errors of urea synthesis who survived neonatal hyperammonemic coma in the US.[30] The distribution of patients by enzyme deficiencies were as follows: three patients with carbamoyl phosphate synthetase, seven with OTC, eight with argininosuccinate synthetase (ASS), and eight with argininosuccinase. The age of the children ranged from 12 months to 74 months. Two patients with deficiencies in OTC died of hyperammonemic coma before one year of age. The researchers did not find a statistically significant correlation between peak ammonium level (351 µmol/L to 1,800 µmol/L) and intelligence quotient (IQ) scores at 12 months — as measured by the Bayley Scales of Infant and Toddler Development among those six months to 30 months, Stanford-Binet

Intelligence Scales among those 30 months to 54 months, and WPPSI-III among those 54 months to 74 months. They conducted IQ testing at least six months after the neonatal hyperammonemic episode and during a period of normal or nearly normal ammonium levels (i.e., less than 60 µmol/L).

Kido et al. (2012) studied 151 patients with a UCD in Japan.[31] No information was provided about the demographic or disease characteristics of the patients. Overall, they found that, among the 77 patients whose maximum ammonia concentration during the first hyperammonemic attack was less than 360 µmol/L, no patient died. Furthermore, of the 74 patients with a maximum ammonia concentration greater than 360 µmol/L, 11 (15%) died, 38 (51%) developed mental retardation, 11 (15%) did not develop mental retardation but had abnormal brain computed tomography and magnetic resonance imaging results or an abnormal electroencephalogram, 6 (8%) did not develop mental retardation and had normal brain computed tomography and magnetic resonance imaging results and a normal electroencephalogram. There were eight (11%) patients for whom information about mental retardation was unknown.

Lee et al. (2015, 2016) evaluated data from up to 114 adult and pediatric patients with UCDs in Canada and the US.[26,27] The distribution of patients by enzyme deficiencies were as follows: 1% of patients with carbamoyl phosphate synthetase, 69% with OTC, 12% with ASS, 13% with argininosuccinase lyase, 2% with arginase, and 3% with hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Approximately half (51%) of the include patients were adults and 49% were children. To assess the importance of the correlation between ammonia or glutamine levels and clinical outcomes during hyperammonemic crises (HACs), data on ammonia and glutamine were collected during three 12-month studies and analyzed. The authors stated that patients with greater upper limits of normal baseline ammonia levels experienced more HACs and that the time to the first HAC was significantly shorter when compared with those with lower upper limits of normal baseline ammonia levels. Additionally, the authors stated that there were no significant correlations between glutamine levels and the number of HACs or the time to first event during the 12 months of dosage.

Quality of Life

Pediatric Quality of Life Inventory Generic Core Scales SF15

The PedsQL SF15 version 4.0 was used to assess quality of life (QoL) in children with UCDs.[32-35] The PedsQL SF15 is typically reported using two forms: one self-reported component and one parent-reported component in children (aged five years to 18 years).

The PedsQL SF15 questionnaire consists of 15 questions that assess the following dimensions: physical functioning (five questions), emotional functioning (four questions), social functioning (three questions), and school functioning (three questions). Items are scored using a five-point Likert scale ranging from 0 (never) to 4 (almost always) or a three-point scale ranging from 0 (not at all) to 4 (a lot). Items are then reverse-scored and linearly transformed to a scale from 0 to 100 in the following manner: 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0. Higher scores indicate better QoL. Dimension scores are calculated as the mean of the items within the respective domain. In addition to the dimension scores, a psychosocial health summary score is also evaluated and consists of the emotional, social, and school-functioning dimensions. The physical health summary score is also evaluated as the average of the physical functioning scale scores. The total score was calculated as the sum of all the items over the number of items answered on all the scales.

Short Form (36) Health Survey
The SF-36 version 2.0 was used to assess QoL in adults with UCDs. SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). SF-36 consists of eight domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. SF-36 also provides two component summaries: the physical component summary (SF-36-PCS) and the mental component summary (SF-36-MCS). The SF-36 PCS, SF-36-MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of two points to four points in each domain or two points to three points in each component summary indicates a clinically meaningful improvement as determined by the patient.[36]

Neuropsychological Tests
Wechsler Abbreviated Scale of Intelligence (WASI-II)
The WASI-II is a nationally standardized abbreviated general assessment of IQ based on the Wechsler Adult Intelligence Scale and is used in clinical, educational, and research settings. The WASI-II provides three scores based on verbal comprehension, perceptual reasoning, and full-scale IQ for children and adults from six to 89 years of age.[32-34,37,38]

The WASI-II includes four subtests based on vocabulary (31 items), similarities (24 items), block design (13 items), and matrix reasoning (30 items) and can be administered in 30 minutes. The verbal comprehension score is based on the vocabulary and similarity subtests measuring knowledge, verbal concept formation, fund of knowledge, verbal reasoning, and concept formation. The perceptual reasoning score is based on the matrix reasoning and block design subtests measuring visual information processing, abstract reasoning skills, ability to analyze and synthesize abstract visual stimuli, non-verbal concept formation, visual perception and organization, simultaneous processing, visual-motor coordination, learning, and the ability to separate figure and ground in visual stimuli. An approximation of the full-scale IQ can be obtained based solely on the vocabulary and matrix reasoning subtests in 15 minutes.

Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)
The WPPSI-III is a measure of cognitive development for preschoolers and young children. The WPPSI-III provides five scores based on verbal IQ, performance IQ general language, processing speed index, and full-scale IQ for children from two to seven years of age.[39,40,41,42]

The WPPSI-III includes 14 subtests in total that are composed of one item per subtest. Children under the age of four are typically evaluated based on five (receptive vocabulary, block design, information, object assembly, and picture naming) of the 14 subtests, whereas children older than four years of age are evaluated based on all 14 subtests, which include vocabulary, picture concepts, symbol search, word reasoning, coding, comprehension, picture completion, and similarities, and can be administered between 25 and 50 minutes depending on age (more time for older children). The verbal IQ score is based on the information, vocabulary, and word reasoning; the performance IQ is based on block design, matrix reasoning, and picture concepts; and the processing speed index is based on coding and symbol search. The full-scale IQ is established using the vocabulary and performance score summaries as well as the coding subtest.

Grooved Pegboard Test

The Grooved Pegboard Test is used to test motor and visual skills through manual dexterity in children five years of age and older as well as in adults and is typically used in neuropsychological test batteries, student labs, and as a screening technique in industrial environments.[33,43,44] The test requires manipulative dexterity and contains 25 holes with randomly positioned slots and pegs that have an accompanying key. Pegs are rotated to match their hole counterpart before they can be inserted. This task is performed and evaluated using both the patient's dominant and non-dominant hand. Performance is measured based on the time required to complete the task, the number of unintentional peg drops, and the number of correct pegs inserted in the board upon completion. Results are then compiled and compared with tabulated means and standard deviations (SDs) in the local population categorized by age group.

Digit Span Test

The digit span test is a common measure of attention and short-term memory in both adults and children seven years of age and older.[33,45,46] The evaluations of both the forward and backward digit span are commonly used neuropsychological tests and are typically included in a component of the Wechsler memory scales and Wechsler intelligence scales. The patient is given a list of digits and then asked to recall them in correct sequential order (forward) and in reverse order (backward). Two trials are presented for each digit sequence and begin with a length of two digits per sequence. With every successful sequence, patients are presented with increasing digit sequence lengths. The digit span test ends when the patient fails to accurately report either of the two trials for a given sequence length or when the maximum sequence length is reached (nine digits forward and eight digits backward). The numbers of correct forward and backward sequences are combined to produce the Wechsler total correct score. Typically, three metrics can be used to assess the digit span test results: the maximum span, which consists of the longest sequence of digits correctly reported after two consecutive failures; the mean span, which is the mean of correctly reported digits; and the sequence length in which 50% of the digits were correctly reported.

California Verbal Learning Test

The CVLT-II assesses verbal memory abilities through testing immediate and delayed recall in adults and children 16 years of age and older. The CVLT-II provides seven scores based on the list A total recall, short delay free and cued recall, long delay free and cued recall, learning slope and total recognition discriminability.[33,47,48]

Several lists containing 16 common words are read to the patients. Each word belongs to one of four categories, such as fruits and herbs. Patients are then asked to recall as many of these words as possible. The standard and alternative forms can be administered in 30 minutes of testing with a 30-minute delay, and the short form can be administered in 15 minutes of testing with a 15-minute delay. During the delay, patients are given other tasks to perform. The tester again asks the patients to recall the list. The number of correct answers is recorded for both immediate and delayed recall tasks. The list A total recall is based on the number of words in list A recalled in trials one through five. The short delay free recall is based on the number of words in list A recalled immediately after another trial using words from list B, whereas the short delay cued recall counterpart presents the category names of the words used in list A. The long delay free recall is based on the number of words in list A recalled after a delay of non-verbal testing is imposed following the short delay cued recall trial, whereas the long delay cued recall counterpart presents the category names of the words used in list A. The learning slope score is based on the slope of the least squares regression for correct response scores through trials one to five.

Child Behavior Checklist

The CBCL is an instrument used to rate a child's problem behaviours and competencies. The preschool form is intended for children aged one year to five years, and the school-age form is intended for children under 18 years of age. The CBCL provides three summary scores categorized under internalizing problems, externalizing problems, and total problems.[32,33,34,39,40,49,50]

The CBCL is completed by parents or teachers who are familiar with the patient. The first section of this questionnaire consists of 20 competence items, while the second section consists of 120 items on behaviour or emotional problems during the past six months. Items are scored using a three-point Likert scale in which 0 signifies "not true," 1 signifies "somewhat or sometimes true," and 2 signifies "very true or often true." The CBCL is based on eight domains, which include the following: aggressive behaviour, anxious/depressed, attention problems, rule-breaking behaviour, somatic complaints, social problems, thought problems, and withdrawn/depressed. The internalizing problems summary score is based on the sum of the anxious/depressed, withdrawn/depressed, and somatic complaints domain scores, whereas the externalizing problems summary score is based on the sum of rule-breaking behaviour and aggressive behaviour domain scores. The total problem summary score is based on the sum of all domains.

Behavior Rating Inventory of Executive Function

The BRIEF is designed to assess executive functioning. The preschool form consists of 63 items and is intended for children aged two years to five years, whereas the standard form consists of 86 items and is intended for children aged five years to less than 18 years of age. The BRIEF provides three summary scores categorized under a behavioral regulation index, metacognition index, and global executive composite.[32,33,34,39,40,51,52,53,54,55]

The BRIEF is completed by parents or teachers who are familiar with the patient. Items are scored using a three-point Likert scale — "never," "sometimes," and "often," — in which higher scores reflect higher levels of reported problems. The BRIEF is based on eight domains, which include the following: inhibit, shift, emotional control, monitor, organization of materials, plan/organize, working memory, and initiate. The behavioural regulation index score is based on the inhibit, shift, and emotional-control domains, and the metacognition index score is based on the monitor, organization of materials, plan/organize, working memory, and initiate domains. The global executive composite score considers all domains and represents the child's overall executive function.

The BRIEF can be assessed using *t* scores, with a score of 50 points typically considered the mean and a difference of 10 points from the mean as one SD. A clinically important difference for the BRIEF was identified as a change of 15 points (1.5 SDs) in the *t* score in a study by Waisbren et al. evaluating the validity of the BRIEF in a pediatric population with UCDs. However, the methodology used to establish the clinically important change in the study by Waisbren is unclear.[56]

APPENDIX 6: SUMMARY OF EFFICACY AND SAFETY RESULTS IN THREE SHORT-TERM, NON-RANDOMIZED STUDIES: UP 1204-003, HPN-100-005, AND HPN-100-012

Objective

To summarize the results from three short-term, switch-over studies comparing glycerol phenylbutyrate (GPB) with sodium phenylbutyrate (NaPBA) in adult or pediatric patients with urea cycle disorders (UCDs).

Findings

Study Design

Study design and characteristics of the three short-term, non-randomized trials are summarized in Table 14.

TABLE 14: SUMMARY DESIGN AND CHARACTERS OF SHORT-TERM, NON-RANDOMIZED STUDIES

		UP 1204-003	HPN-100-005	HPN-100-012
DESIGNS & POPULATIONS	**Study design**	Multi-centre, phase II, OL, fixed sequence, SO study		Multi-centre, phase III, OL, SO study
	Number of patients (N)	10	11	15
	Eligibility	Adult patients taking a stable dose of NaPBA t.i.d. for at least 2 weeks before day 1	Children 6 years old to 17 years old who had been on a stable dose of NaPBA for at least 1 week before day 1; patients with a history of ≥ 4 hyperammonemic events in the preceding 12 months were excluded	Children aged 29 days to < 6 years, who were followed by or referred to the investigator for management of their UCD or assessment of high blood ammonia; were on a stable dose of NaPBA powder for at least 5 days before enrolment
	Primary objective	To evaluate the safety and tolerability of GPB compared with NaPBA in patients with UCDs	To evaluate the safety and PK characteristics of GPB compared with NaPBA in pediatric patients with UCDs	To assess safety, PK and ammonia control in pediatric patients with UCDs aged 29 days to < 6 years

		UP 1204-003	HPN-100-005	HPN-100-012
DRUGS	Intervention and comparator	• 1 week of NaPBA t.i.d. • During a dose-escalation phase: switched over to GPB t.i.d.; for patients received up to 200 mg/kg of NaPBA, switched to 100% GPB; for those received more than 200 mg/kg NaPBA, dose of GPB was increased and the dose of NaPBA was correspondingly decreased each week by the mole-equivalent of 50 mg/kg/day of GPB until the entire PBA-equivalent dose was provided by GPB • Following dose escalation, patients received steady state GPB for 1 week • After 1 week of stable dose of GPB, patients were switched back to original NaPBA treatment	• 1 week of NaPBA t.i.d. • Switched to 1 week of GPB t.i.d. The 100% GPB equivalent dose was calculated from the 100% NaPBA dose determined by the investigator such that patients received the same amount of PBA during treatment with both study drugs. Transition from NaPBA to GPB could have occurred in a single step or in 2 steps	• 5 days of NaPBA, t.i.d. or q.i.d. • Switched to 10 days of GPB t.i.d. or q.i.d., with a dose delivered the same amount of PBA
DURATION	**Phase**			
	Run-in	1 week on NaPBA	1 week on NaPBA	5 days on NaPBA
	Treatment period	Dose-escalation period: varied depending on dose. Patients on 100% GPB for 1 week	1 week on GPB	10 days on GPB
	Follow-up	Follow-up visit for safety 1 week after switching back to NaPBA	Upon study completion, patients were allowed to enter a 12-month extension study	

	UP 1204-003	HPN-100-005	HPN-100-012	
OUTCOMES	**Primary end point**	Safety	Safety	Safety
	Other end points (review relevant outcomes)	Blood ammonia levels Blood glutamine levels PK	Blood ammonia levels PK/PD	Blood ammonia levels Hyperammonemic crisis PK

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; OL = open-label; PBA = phenylbutyrate; PD = pharmacodynamics; PK = pharmacokinetic; q.i.d. = four times daily; SO = switch-over; t.i.d. = three times daily; UCD = urea cycle disorder.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005[32] and HPN-100-012.[39]

Patients who completed the switch-over phase of studies HPN-100-005 and HPN-100-012 were offered the opportunity to continue in the safety-extension phase to receive open-label GPB for up to 12 months. Results of the safety-extension phase are presented in APPENDIX 7. Because of the small sample size, no adjustment for covariates was considered.

UP 1204-003: All efficacy analyses were performed using the intention-to-treat (ITT) population, which consisted of all patients who received any amount of both study drugs. For the primary analysis of ammonia levels using time-normalized area under the curve (TNAUC), patients with missing TNAUC at visit 2-1 (steady-state NaPBA) or with missing TNAUC at visit 11-1 (steady-state GPB) were excluded. The last-observation-carried-forward method was planned for imputation of data, but was not used (all 10 patients had available data to calculate TNAUC). Peak venous ammonia was also imputed using the last-observation-carried-forward method if there was at least one post-first GPB dose peak venous ammonia level. A formal testing of hypotheses was not performed for this study. The study was not powered to demonstrate equivalence between GPB and NaPBA. Subgroup analysis was not conducted due to the small sample size.

HPN-100-005: Descriptive statistics were used to summarize study data. An analysis of variance (ANOVA) model was constructed with factors for treatment and patient to assess the noninferiority of GPB to NaPBA in ammonia control (as blood ammonia $AUC_{0–24}$ levels) in the ITT and per-protocol (PP) populations. Noninferiority was concluded when the upper bound of the 90% confidence interval (CI) was less than and equal to 1.25. Missing ammonia data were imputed for patients who did not have a calculable venous ammonia $AUC_{0–24}$ value. The relative effect of GPB and NaPBA on glutamine levels was evaluated post hoc. A post-hoc evaluation of blood ammonia $AUC_{0–24}$ and C_{max} levels was conducted in children (aged six years to 11 years) and adolescents (aged 12 years to 17 years).

HPN-100-012: The study was not powered to detect a statistically significant difference between GPB and NaPBA. Given the small number of patients, all hypothesis tests were interpreted as exploratory in nature. An ANOVA model was constructed with factors for treatment and patient to assess the noninferiority of GPB to NaPBA in ammonia control (as blood ammonia $AUC_{0–24}$ levels) in the ITT and PP populations. Noninferiority was concluded when the upper bound of the 90% CI was less than and equal to 1.25.

Disposition

The disposition of patients across the three switch-over studies (UP 1204-003, HPN-100-005, and HPN-100-012) is summarized in Table 15.

TABLE 15: DISPOSITION OF PATIENTS IN STUDIES UP1204-003, HPN-100-005, AND HPN-100-012

	UP 1204-003	HPN-100-005	HPN-100-012
Enrolled	15	11	15
Withdrawals n (%)	5[a]	0	0
Adverse events, n (%)	1 (6.7)	–	–
Treatment failure, n (%)	0	–	–
Non-medical reason, n (%)	1 (6.7)	–	–
Withdrew consent n (%)	2 (13.3)	–	–
Protocol deviation n (%)		–	–
Investigator discretion n (%)	1 (6.7)	–	–
Completed n (%)	10 (66.7)	11 (100)	15 (100)
ITT population	10	11	15
PP population	NA	9	13
Safety population	14	11	15

ITT = intention-to-treat; NA = not applicable; PP = per-protocol.
[a] Two patients withdrew and were then re-screened and re-enrolled under new patient ID numbers.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005,[32] and HPN-100-012.[39]

Results

The main demographic and baseline characteristics of patients were similar across treatment arms within studies, but were variable across studies. Patient characteristics are summarized in Table 16.

TABLE 16: DEMOGRAPHICS AND MAIN BASELINE CHARACTERISTICS IN STUDIES UP1204-003, HPN-100-005, AND HPN-100-012 (INTENTION-TO-TREAT POPULATION)

	UP 1204-003	HPN-100-005	HPN-100-012
	N = 10	**N = 11**	**N = 15**
Age, Years			
Mean (SD)	38.2 (17.9)	10.2 (3.95)	2.87 (1.89)
Gender			
Number of males (%)	4 (40)	1 (9.1)	8 (53)
Race, n (%)			
Caucasian/White	6 (60)	9 (81.8)	12 (80)
Non-Caucasian	4 (40)	2 (18.2)	3 (20)
UCD Diagnosis, n (%)			
OTC deficiency	8 (80)	9 (81.8)	3 (20)
ASS deficiency	1 (10)	1 (9.1)	3 (20)
HHH syndrome	1 (10)	–	–
CPS1 deficiency	–	0	–
ASO deficiency	–	1 (9.1)	–
ASL deficiency	–	–	8 (53)
ARG deficiency	–	–	1 (7)
UCD Onset, n (%)			
Neonatal (0 days to ≤ 30 days)	1 (10)	3 (27.3)	13 (87)
Infantile (> 30 days to ≤ 2 years)	2 (20)	3 (27.3)	2 (13)

	UP 1204-003	HPN-100-005	HPN-100-012
	N = 10	**N = 11**	**N = 15**
Childhood or adult onset (> 2 years)	7 (70)	5 (45.5)	0
Duration of NaPBA Treatment			
Mean (SD)	9.04 (8.00) years	74.68 (48.22) months	19.29 (17.15) months
NaPBA Daily Dose			
Mean (SD)	190.79 (44.64) mg/kg	12.41 (4.39) g	5.28 (2.45) g
Number of Hyperammonemic Episodes in Last 12 Months Before Screening			
Mean (SD)	0.7 (0.82)	4 patients had a history of hyperammonemic crises within 12 months before screening	10 patients had at least 1 hyperammonemic crisis within 12 months before screening

ARG = arginase; ASS = argininosuccinate synthetase; ASL = argininosuccinate lyase; CPS1 = carbamoyl phosphate synthetase 1; HHH = hyperomithinemia, hyperammonemia, and homocitrullinuria; ITT = intention-to-treat; NaPBA = sodium phenylbutyrate; OTC = ornithine transcarbamylase; SD = standard deviation; UCD = urea cycle disorder.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005,[32] and HPN-100-012.[39]

In UP 1204-003, all patients reported high compliance with the study medication (93% to 100% of planned doses were taken). Four patients reported missing doses and no patient reported missing more than two doses of study drug. Compliance with the dietary regimen was variable and ranged from 1% of prescribed protein/kg per day to 215% of prescribed protein/kg per day, and from 3% of calories/kg per day to 127% of calories/kg per day.

In HPN-100-005, among the 11 patients enrolled in the switch-over phase, 10 were 100% compliant with their prescribed NaPBA treatment and nine were 100% compliant with their GPB treatment.

Details of treatment compliance are presented in Table 17.

TABLE 17: COMPLIANCE TO STUDY DRUGS DURING TREATMENT (%)

	UP 1204-003	HPN-100-005	HPN-100-012
Compliance During NaPBA Treatment			
Mean (SD)	99.49 (1.10)	98.7 (4.31)[a]	NR
Compliance During GPB Treatment			
Mean (SD)	98.33 (3.09)	99.5 (1.51)[a]	NR

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; NR = not reported; SD = standard deviation.
[a] Measured at day 7 and day 14.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005,[32] and HPN-100-012.[39]

A summary of the results of blood ammonia levels after treatment with GPB and NaPBA in the adult or pediatric patients with UCDs is presented in Table 18.

In UP 1204-003, the TNAUC for blood ammonia after seven days of treatment with NaPBA (at steady state) was higher (mean value was 38.40 µmol/L) compared with after seven days of treatment with GPB (26.5 µmol/L). The overall difference in ammonia values (TNAUC) measured after NaPBA treatment and after GPB treatment did not reach statistical significance. The mean peak ammonia level was higher with steady-state NaPBA (79.14 µmol/L) compared with the mean peak ammonia level with GPB

treatment (56.31 µmol/L) at steady state. Glutamine decreased after switch to GPB in eight patients who had values at both visits 2-1 and 11-1. On average, there was a mean decrease from visit 2-1 to visit 11-1 (–87 µmol/dL) in these eight patients.

In HPN-100-005, the difference in blood ammonia $AUC_{0–24}$ levels was not statistically different between the GPB and NaPBA treatments (*P* = 0.1028). However, in the PP population, blood ammonia $AUC_{0–24}$ levels were statistically lower with GPB treatment than with NaPBA treatment (*P* = 0.0304). In the ITT and PP populations, blood ammonia $AUC_{0–24}$ levels with GPB treatment compared with NaPBA treatment met the predefined noninferiority criteria. There were no statistically significant differences between the treatments in mean C_{max} concentrations in either the ITT (*P* = 0.2481) or PP (*P* = 0.1441) populations.

In HPN-100-012, blood ammonia, assessed as mean $AUC_{0–24}$, was lower after GPB treatment than after NaPBA treatment (mean between-group difference –237.46 µmol·h/L, *P* > 0.05). C_{max} for ammonia was lower after GPB treatment compared with after NaPBA treatment.

TABLE 18: CHANGE IN BLOOD AMMONIA AND GLUTAMINE LEVELS IN STUDIES UP 1204-003, HPN-100-005, AND HPN-100-012 (INTENTION-TO-TREAT POPULATION)

	UP 1204-003		HPN-100-005		HPN-100-012	
	GPB N = 10	**NaPBA N = 10**	**GPB N = 11**	**NaPBA N = 11**	**GPB N = 13**	**NaPBA N = 15**
TNAUC, µmol/L						
Mean (SD)	26.49 (10.73)	38.40 (19.57)	NR		NR	
Mean difference (GPB vs. NaPBA)	–11.92 (21.24) *P* value NR		NR		NR	
$AUC_{0–24}$ for Ammonia, µmol·h/L						
Mean (SD)	NR		603.8 (187.92)	814.6 (322.36)	647.63 (379.94)	914.43 (630.21)
Mean difference (GPB vs. NaPBA)	NR		–210.8 (310.89) *P* value NR		–237.46 (439.45) *P* = 0.075	
$C_{max–ss}$, µmol/L						
Mean (SD)	56.31 (27.90)	79.14 (40.08)	47.77 (12.80)	55.66 (21.61)	39.39 (29.29)	52.74 (37.14)
Mean difference (GPB vs. NaPBA)	NR		–7.89 (23.13) *P* value NR		–13.35 (32.82) *P* = 0.138	
Glutamine level, µmol/L						
Mean (SD)	652.67 (312.93)	739.28 (293.97)	635.1 (205.29)	723.1 (198.85)	669.0 (150.69)	698.1 (118.73)
Mean difference (GPB vs. NaPBA)	–86.61 (121.70) *P* value NR		NR		–20.1 (149.99) *P* = 0.638	

$C_{max–ss}$ = maximum plasma concentration at steady state; GPB = glycerol phenylbutyrate; NaPBA = sodium pheylbutyrate; NR = not reported; SD = standard deviation; TNAUC = time-normalized area under the curve.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005,[32] and HPN-100-012.[39]

Safety of the study drugs was evaluated in these three studies. A summary of the adverse events (AEs) during the studies is presented in Table 19. There were no deaths reported in the three studies. In general, the risks of AEs were similar between GPB and NaPBA.

In UP1204-003, the occurrence of AEs was similar between 100% NaPBA treatment and 100% GPB treatment. The most frequently reported (AEs) were gastrointestinal (GI) disorders (i.e., nausea, dyspepsia, and abdominal pain), which were reported in 35.7% of patients during the study, including 21.4% during 100% NaPBA and 20% during 100% GPB. Two patients had serious adverse events (SAEs), both during NaPBA treatment, one before and one after the GPB treatment period. There were no deaths during the study.

In HPN-100-005, all but one of the AEs were considered mild, and for one patient the investigator considered the event (vomiting while on GPB) to be moderate-intensity.

In HPN-100-012, six patients reported AEs during the GPB treatment period. All AEs were mild. There were no SAEs or discontinuations due to AEs.

TABLE 19: ADVERSE EVENTS REPORTED IN STUDIES UP 1204-003, HPN-100-005, AND HPN-100-012 (SAFETY POPULATION)

	UP 1204-003		HPN-100-005		HPN-100-012	
	GPB N = 10	**NaPBA N = 15**	**GPB N = 11**	**NaPBA N = 11**	**GPB N = 15**	**NaPBA N = 15**
AEs, n (%)	5 (50.0)	7 (50.0)	4 (36.4)	2 (18.2)	6 (40)	0
GI disorders	2 (20.0)	3 (21.4)	3 (27.3)	0	3 (20)	0
Metabolism and nutrition disorders	3 (30.0)	2 (14.3)	NR	NR		
Respiratory disorders	2 (20.0)	0				
Skin disorders	0	1 (7.1)	1 (9.1)	0	1 (6.7)	0
SAEs, n (%)	0	2 (13.3), 1 before and 1 after GPB treatment, both hyperammonemia	0	0	0	0
WDAEs, n (%)	0	1 (6.7), hyperammonemia	0	0	0	0

AE = adverse event; GI = gastrointestinal; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports of Studies UP 1204-003,[57] HPN-100-005,[32] and HPN-100-012.[39]

Summary

Results from three short-term, non-randomized controlled studies suggested that GPB has similar effect in lowering ammonia levels in patients (adults or children) with UCDs when compared with NaPBA. The risk of AEs was similar between GPB and NaPBA during the one-week to two-week treatment periods, and the majority of reported AEs were mild. Because of the small sample size, the studies did not have sufficient power to detect clinically or statistically meaningful differences between GPB and the comparator in the study population. The results should be interpreted with caution.

APPENDIX 7: SUMMARY OF EFFICACY AND SAFETY RESULTS IN THREE LONG-TERM, NON-RANDOMIZED STUDIES: HPN-100-005, HPN-100-007, AND HPN-100-012

Objective

To summarize the results from three long-term, safety studies that evaluated the safety and efficacy of glycerol phenylbutyrate (GPB) in adult and/or pediatric patients with urea cycle disorders (UCDs).

Findings

Study Design

Study design and characteristics of the three long-term, open-label, non-randomized, non-comparative trials are summarized in Table 20. Both patients who were not included as well as those who completed the switch-over phase of studies HPN-100-005, HPN-100-006, and HPN-100-012 were offered the opportunity to continue in the safety-extension phase and receive open-label GPB for up to 12 months.

TABLE 20: SUMMARY DESIGN AND CHARACTERS OF LONG-TERM NON-RANDOMIZED STUDIES

		HPN-100-005	HPN-100-007	HPN-100-012
DESIGNS & POPULATIONS	**Study design**	Multi-centre, phase II OL, SO study	Multi-centre, phase III, OL, SO study	
	Number of patients (N)	17	60	23
	Eligibility	Children 6 years to 17 years old who had been on a stable dose of NaPBA for at least 1 week before day 1. Patients previously participating in the HPN-100-005 switch-over phase and new patients were included. Patients with a history of ≥ 4 hyperammonemic events in the preceding 12 months were excluded.	Adults and children (≥ 6 years old) who were either NaPBA experienced or naive. Patients previously participating in the HPN-100-006 switch-over phase and new patients were included. Patients with a history of ≥ 4 hyperammonemic events in the preceding 12 months were excluded.	Children aged 29 days to < 6 years who were followed by or referred to the investigator for management of their UCD or assessment of high blood ammonia; were on a stable dose of NaPBA powder for at least 5 days before enrolment. Patients previously participating in the HPN-100-012 switch-over phase and new patients were included.
	Primary objective	To evaluate the long-term safety of GPB and its control of blood ammonia.		To assess safety, PK and ammonia control.

		HPN-100-005	HPN-100-007	HPN-100-012
DRUGS	Intervention	1 week of NaPBA t.i.d. GPB administered orally or through G-tube t.i.d.: for patients who participated in the switch-over studies, the initial dose of GPB was equivalent to the dose they had received in the switch-over phase; for new patients, the initial GPB dose was calculated using a NaPBA equivalency formula Dose adjustments were permitted during the extension phase; maximum dose of 17.4 mL GPB equivalent to 20 g/day NaPBA.	1 week of NaPBA t.i.d. GPB administered orally or through G-tube t.i.d.: for patients who participated in the switch-over studies, the initial dose of GPB was equivalent to the dose they had received in the switch-over phase; for new patients, the initial GPB dose was calculated using a NaPBA equivalency based on the investigators assessment, the patient's ammonia scavenging needs, or based on the PBA-equivalent dose to the patient's prescribed NaPBA dose before enrolment Dose adjustments were permitted during the extension phase; maximum dose of 17.4 mL GPB equivalent to 20 g/day NaPBA.	5 days of NaPBA, t.i.d. or q.i.d. Switched to GPB t.i.d. or q.i.d., with a dose delivered the same amount of PBA.
DURATION	Run-in	1 week on NaPBA	None	5 days on NaPBA
	Treatment period	12 months	12 months	12 months
	Follow-up	Screening visit Week one visit only required for new patients Monthly visits		Visits every three months, at the least
OUTCOMES	**Primary end point**	Adverse event rates		
	Other end points (review relevant outcomes)	Blood ammonia and glutamine levels Number of hyperammonemic events QoL (SF-15) PK	Blood ammonia and glutamine levels Number of hyperammonemic events QoL (SF-36 and SF-15) PK/PD	Blood ammonia and glutamine levels Frequency of hyperammonemic crises

GPB = glycerol phenylbutyrate; G-tube = gastrostomy tube; NaPBA = sodium phenylbutyrate; OL = open-label; PBA = phenylbutyrate; PK = pharmacokinetic; q.i.d. = four times daily; QoL = quality of life; SF-15 = short form 15; SF-36 = Short Form (36) Health Survey; SO = switch-over; t.i.d. = three time daily; UCD = urea cycle disorder.
Source: Clinical Study Reports.[32,33,34,39,40]

Assessment

No adjustments for covariates were made in any of the analyses in any of the long-term treatment studies. All analyses were based on the safety population, defined as all patients who received any amount of GPB. Any missing data were not imputed. No corrections were applied to adjust for multiplicity, and all efficacy end points were considered exploratory. The primary outcome in all long-term studies was safety as measured by the rate of adverse events (AEs). Other safety end points

included serious adverse events (SAEs) and withdrawals due to adverse events. All efficacy end points evaluated in the long-term studies were considered secondary outcomes. The outcomes measured in the long-term treatment studies are detailed in Table 20.

Disposition

The disposition of patients across the three long-term studies (HPN-100-005, HPN-100-007, and HPN-100-012) is summarized in Table 21.

A total of 17 patients were enrolled in the extension phase of HPN-100-005. Eleven (65%) of the 17 were patients in the switch-over phase. There was only one (6%) withdrawal during the trial; all other patients (94%) completed the trial.

A total of 60 patients were enrolled in HPN-100-007. Forty (67%) of the 60 were patients in HPN-100-006. There was a total of seven (12%) withdrawals; all other patients (88%) completed the trial.

A total of 23 patients were enrolled in the extension phase of HPN-100-012. Fifteen (65%) of the 23 were patients in the switch-over phase. There was a total of two (9%) withdrawals; all other patients (91%) completed the trial.

TABLE 21: DISPOSITION OF PATIENTS IN STUDIES HPN-100-005, HPN-100-007, AND HPN-100-012

	HPN-100-005	HPN-100-007	HPN-100-012
Enrolled	17	60	23
≥ 18 years	NA	51 (85)	NA
< 18 years	17 (100)	9 (15)	23
Withdrawals n (%)	1(6)	7 (12)	2 (9)
Adverse events, n (%)		1 (2)	1 (4)
Withdrew consent n (%)	1 (6%)	5 (8)	
Other n (%)		1 (2)	1 (4)
Completed n (%)	16 (94)	53 (88)	21 (91)
Safety population	17 (100)	60 (100)	23 (100)

NA = not applicable.
Source: Clinical Study Reports.[32,33,34,39,40]

Results

The main demographic and baseline characteristics of patients were variable across studies and are summarized in Table 22. The extension phases of HPN-100-005 and HPN-100-012 included a younger population than the patients included in HPN-100-007 [redacted] Generally, all long-term studies included more females than males and more white patients than other ethnic groups. Both the extension phase of HPN-100-005 and HPN-100-007 included more patients with UCDs with ornithine transcarbamylase (OTC) deficiency [redacted] whereas HPN-100-012 included more patients with the arginosuccinate lyase deficiency. Both the extension phase of HPN-100-005 and HPN-100-007 included patients with childhood or adult UCD onset [redacted] whereas HPN-100-012 included more patients with neonatal UCD onset [redacted] Sodium phenylbutrate (NaPBA) exposure, NaPBA daily dose, and the number of hypoammonemic crises varied across the long-term studies.

TABLE 22: DEMOGRAPHICS AND MAIN BASELINE CHARACTERISTICS IN STUDIES HPN-100-005, HPN-100-007, AND HPN-100-012

	HPN-100-005	HPN-100-007			HPN-100-012
	N = 17	< 18 years, N = 9	≥ 18 years, N = 51	All, N = 60	N = 23
Age, Years					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender					
Number of males (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)					
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-white	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UCD Diagnosis, n (%)					
OTC deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASS deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HHH syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS1 deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASL deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARG deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UCD Onset, n (%)					
Neonatal (0 days to ≤ 30 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infantile (> 30 days to ≤ 2 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Childhood or adult onset (> 2 years to < 18 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult (≥ 18 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of NaPBA Treatment, Months					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NaPBA Daily Dose, g					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Hyperammonemic Episodes Per Patient in Last 12 Months Before Screening					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARG = arginase; ASS = argininosuccinate synthetase; ASL = argininosuccinate lyase; CPS1 = carbamoyl phosphate synthetase; HHH = hyperomithinemia, hyperammonemia, and homocitrullinuria; NA = not applicable; NaPBA = sodium phenylbutyrate; OTC= ornithine transcarbamylase; SD = standard deviation; UCD = urea cycle disorder.
Source: Clinical Study Reports.[32,33,34,39,40]

Safety

A summary of the AEs during the studies is presented in Table 23. [redacted]

[redacted]

[redacted]

TABLE 23: ADVERSE EVENTS REPORTED IN STUDIES HPN-100-005, HPN-100-007, AND HPN-100-012 (≥ 10%)

	HPN-100-005	HPN-100-007			HPN-100-012
	N = 17	< 18 years, N = 9	≥ 18 years, N = 51	All, N = 60	N = 23
AEs, n (%)	[redacted]				
GI disorders					
General disorders and administration-site conditions					
Infections and infestations					
Investigations					
Metabolism and nutrition disorders					
Nervous system disorders					
Respiratory disorders					
Skin disorders					
SAEs, n (%)					
WADEs, n (%)					

AE = adverse event; GI = gastrointestinal; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[32,33,34,39,40]

Efficacy

A summary of the blood ammonia and glutamine levels during the long-term studies is presented in Table 24. [redacted]

A summary of the number of hyperammonemic crises (HACs) during the long-term studies is presented in Table 25. [redacted]

[redacted]

Two long-term studies, HPN-100-007 and the extension phase of HPN-100-005, evaluated quality of life (QoL) using the Pediatric Quality of Life Inventory Generic Core Scales SF15 (PedsQL SF15) version 4 and/or the Short Form (36) Health Survey (SF-36) version 2, [redacted] A summary of the quality of life data is presented in Table 26 and Table 27. The PedsQL SF15 quality of life measure was evaluated in children in both HPN-100-007 and the extension phase of HPN-100-005 [redacted] The SF-36 QoL measure was evaluated in adults in HPN-100-007. [redacted]

All long-term studies performed neuropsychological testing, [redacted] The Wechsler Abbreviated Scale of Intelligence was evaluated in both HPN-100-007 and the extension phase of HPN-100-005. [redacted] Mean estimated full intelligence quotient (IQ) scores were also evaluated in adults in HPN-100-007 [redacted] A summary of the Wechsler Abbreviated Scale of Intelligence data is presented in Table 28.

The Child Behavior Checklist was evaluated in all three long-term studies. [redacted] A summary of the Child Behavior Checklist data is presented in Table 29.

The Behavior Rating Inventory of Executive Function (BRIEF) was also evaluated in all three long-term studies in children only. [redacted] A summary of the Behavior Rating Inventory of Executive Function data is presented in Table 30.

Study HPN-100-012 also evaluated the Wechsler Preschool and Primary Scale of Intelligence. [redacted] A summary of the Wechsler Preschool and Primary Scale of Intelligence data is presented in Table 31.

Study HPN-100-007 also evaluated the California Verbal Learning Test, Digit Span Test, and Grooved Pegboard Test in adults only. [redacted]

[redacted]Summaries of the California Verbal Learning Test, Digit Span Test, and Grooved Pegboard Test data are presented in Table 32 and Table 33.

TABLE 24: CHANGE IN BLOOD AMMONIA AND GLUTAMINE LEVELS IN STUDIES HPN-100-005, HPN-100-007, AND HPN-100-012

	HPN-100-005	HPN-100-007			HPN-100-012
	N = 17	< 18 years, N = 9	≥ 18 years, N = 51	All, N = 60	N = 23
Mean Ammonia, µmol/L (SD)					
Baseline	[redacted]				
Week 1					
Month 1					
Month 2					
Month 3					
Month 4					
Month 5					
Month 6					
Month 7					
Month 8					
Month 9					
Month 10					
Month 11					
Month 12					
Mean Glutamine, µmol/L (SD)					
Baseline					
Month 3					
Month 6					
Month 9					
Month 12					

GPB = glycerol phenylbutyrate; NaPBA = sodium phenylbutyrate; NR = not reported; SD = standard deviation; TNAUC = time-normalized area under the curve.
Source: Clinical Study Reports.[32,33,34,39,40]

TABLE 25: HYPERAMMONEMIC CRISES IN STUDIES HPN-100-005, HPN-100-007, AND HPN-100-012

	HPN-100-005	HPN-100-007			HPN-100-012
	N = 17	< 18 years, N = 9	≥ 18 years, N = 51	All, N = 60	N = 23
Number of patients with at least one crisis (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of crises	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of hyperammonemic episodes per patient 12 months before screening (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of hyperammonemic episodes per patient during the trial (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: Clinical Study Reports.[32,33,34,39,40]

TABLE 26: PEDIATRIC QUALITY OF LIFE INVENTORY GENERIC CORE SCALES SF15 QUALITY OF LIFE DATA IN STUDIES HPN-100-005 AND HPN-100-007 IN CHILDREN

	HPN-100-005		HPN-100-007	
	Baseline	Month 12	Baseline	Month 12
Self-Reported				
Psychosocial Health Summary	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	
Physical Health Summary	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	
Total Score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	
[redacted]				
Psychosocial Health Summary	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	
Physical Health Summary	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	
Total score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]		[redacted]	

SD = standard deviation.
Source: Clinical Study Reports. [32,33,34]

TABLE 27: SHORT FORM (36) HEALTH SURVEY (SF-36) QUALITY OF LIFE DATA IN STUDIES HPN-100-007 IN ADULTS

	HPN-100-007	
	Baseline	Month 12
Physical Component Summary	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Mental Component Summary	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	

SD = standard deviation.
Source: Clinical Study Reports.[33]

TABLE 28: WECHSLER ABBREVIATED SCALE OF INTELLIGENCE SECOND EDITION

	HPN-100-005		HPN-100-007					
			< 18 years		≥ 18 years		All	
	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12
Vocabulary	[redacted]							
Mean (SD)	[redacted]							
Change from baseline at month 12 (SD)	[redacted]							
Matrix Reasoning	[redacted]							
Mean (SD)	[redacted]							
Change from baseline at month 12 (SD)	[redacted]							
Estimated Full-Scale IQ	[redacted]							
Mean (SD)	[redacted]							
Change from baseline at month 12 (SD)	[redacted]							

IQ = intelligence quotient; SD = standard deviation.
Source: Clinical Study Reports.[32,33,34]

TABLE 29: CHILD BEHAVIOR CHECKLIST

	HPN-100-005		HPN-100-007 < 18 years		HPN-100-012	
	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12
Total Problems						
Mean (SD)						
Change from baseline at month 12 (SD)						
Internalizing Problems						
Mean (SD)						
Change from baseline at month 12 (SD)						
Externalizing Problems						
Mean (SD)						
Change from baseline at month 12 (SD)						

SD = standard deviation.
Source: Clinical Study Reports.[32,33,34,39,40]

TABLE 30: BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION

	HPN-100-005		HPN-100-007 < 18 years		HPN-100-012	
	Baseline	Month 12	Baseline	Month 12	Baseline	Month 12
Behavioral Regulation Index						
Mean (SD)						
Change from baseline at month 12 (SD)						
Metacognition Index						
Mean (SD)						
Change from baseline at month 12 (SD)						
Global Executive Composite						
Mean (SD)						
Change from baseline at month 12 (SD)						

NR = not reported; SD = standard deviation.
Source: Clinical Study Reports. [32,33,34,39,40]

TABLE 31: WECHSLER PRESCHOOL AND PRIMARY SCALE OF INTELLIGENCE THIRD EDITION

	HPN-100-012	
	Baseline	**Month 12**
Full-Scale IQ	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Verbal IQ	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Performance IQ	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
General Language	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Processing Speed Index	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	

IQ = intelligence quotient; SD = standard deviation.

[redacted]

Source: Clinical Study Reports.[39,40]

TABLE 32: CALIFORNIA VERBAL LEARNING TEST SECOND EDITION

	HPN-100-007	
	≥ 18 years	
	Baseline	**Month 12**
List A Total 1 to 5	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Short Delay Free Recall	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Short Delay Cued Recall	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Long Delay Free Recall	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Long Delay Cued Recall	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

	HPN-100-007	
	≥ 18 years	
	Baseline	Month 12
Change from baseline at month 12 (SD)	[redacted]	
CVLT-II Learning Slope	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Total Recognition Discriminability	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	

[redacted]

SD = standard deviation.
Source: Clinical Study Reports of Studies.[33]

TABLE 33: DIGIT SPAN AND GROOVED PEGBOARD TESTS

	HPN-100-007	
	≥ 18 years	
	Baseline	Month 12
Digit Span Test	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Grooved Pegboard Dominant Hand	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	
Grooved Pegboard Non-Dominant Hand	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change from baseline at month 12 (SD)	[redacted]	

SD = standard deviation.

[redacted]

Source: Clinical Study Reports of Studies.[33]

Limitations

There are several limitations to these long-term, open-label, non-randomized, non-comparative safety studies. First, given that they were uncontrolled studies, it remains unclear whether the changes observed in the safety profile were due to a natural course of the disease or were attributed to long-term treatment with GPB. Open-label trial designs in which both the investigators and the patients are unblinded to treatment allocation may have an impact on subjective outcomes, such as some patient-reported AEs. Additionally, dose adjustments were permitted during the studies; this makes it difficult to isolate the safety profile of GPB. In addition, all efficacy end points were considered exploratory and no

corrections were applied to adjust for multiplicity; therefore, any efficacy results are susceptible to inflated type I error, which can lead to uncertainty. Furthermore, no minimal clinically important differences for any of the QoL or neuropsychological scales were identified in the UCD population, making it difficult to interpret the results and whether they are clinically meaningful. Finally, patients included in all three long-term studies were mainly female, with OTC deficiency and childhood-to-adult UCD onset, which may suggest the inclusion of a less severe UCD population. Consequently, the generalizability of the results to the Canadian population is unclear.

Summary

Results from three long-term, open-label, non-randomized, non-comparative studies suggested that the effects of GPB on blood ammonia and glutamine levels appear to be maintained after 12 months of treatment in both children and adults. In addition, the number of hyperammonemic episodes per patient appears to be reduced compared with the values 12 months before screening when treated with GPB. Generally, QoL appears to increase in children when assessed with the PedsQL SF15 questionnaire. By contrast, QoL appears to decrease in adults when assessed with the SF-36 questionnaire. Generally, neuropsychological testing results were inconsistent across trials, age groups, and assessment tools. Almost all patients experienced AEs after one year of treatment with GPB. Infections and infestations (i.e., gastroenteritis, nasopharyngitis, and upper respiratory tract infection) and gastrointestinal (GI) disorders (i.e., vomiting, diarrhea, and abdominal pain) were reported as the most frequently experienced AEs. Newly emerging AEs included nervous system disorders and general disorders as well as administration-site conditions. However, because of the uncontrolled design, it is unclear whether any difference truly exists.

Considering the exploratory nature of all efficacy outcomes and the limitations of the long-term studies, the results should be interpreted with caution.

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