CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	203-284	*Submission Date(s)*	December 23, 2011, February 22, March 13, March 27, April 20, June 29, July 03, July 05, August 23, 2012
Brand Name		Ravicti®	
Generic Name		Glycerol phenylbutyrate	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
Division Director		Capt. Edward D. Bashaw, Pharm.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Gastroenterology and Inborn Errors Products	
Sponsor		Hyperion	
Submission Type;		Original	

Executive Summary

This is an addendum to the original clinical pharmacology review of NDA 203-284 dated 1/2/13 to discuss two post-marketing studies. We require a pharmacokinetic study in pediatric patients < 2 years old and recommend an in vivo drug interaction study with a sensitive CYP3A4 substrate as a post-marketing commitment as below.

Post-Marketing Requirement

Pharmacokinetic studies in pediatric patients from birth to less than 2 years of age with Urea Cycle Disorders. PK of glycerol phenylbutyrate and its metabolites (PBA, PAA and PAGN) must be characterized and the exposure-response relationship should be evaluated for safety and efficacy.

Rationale

In the NDA, Ravicti was not studied in patients younger than 2 month old and very few data on patients in the age category of 2 months to 2 years were included. Because of no or insufficient data in patients younger than 2 years old, additional clinical studies will be required in these two age groups i.e. < 2 months old and 2 months to 2 years old.

In the age category of 2 months to 2 years, two of the four patients had PAA levels ~ 500 μg/mL when on buphenyl or HPN-100. Therefore we recommend PK blood samples be collected to characterize PK of Ravicti and its metabolites, PBA, PAA and PAGN.

PAA toxicity with neurological and gastrointestinal manifestations has been demonstrated with IV administration of PAA. In cancer patients, the symptoms at PAA levels of ~500 μg/mL were somnolence, emesis and lethargy in patients with cancer who received IV PAA. More severe toxicity (confusion and psychomotor depression)

occurred in patients with mean peak PAA level of 682 μg/mL[1]. In patients with acute hyperammonemia, overdose of IV PAA in children has been reported to cause death and coma.[2] Levels of PAA in these children were > 1000 μg/mL.

Post-Marketing Commitment

In vivo drug interaction study to evaluate the effect of Ravicti on a concomitant drug that is metabolized by CYP3A4.

The highest proposed dose of Ravicti should be used to maximize the potential of in vivo drug interaction while the dose for individual patients may vary.

Rationale: Based on the in vitro studies suggested drug interaction potential with substrates of three CYP enzymes, we are requesting one in vivo study with CYP3A.

The [I]/Ki of PBA was the highest for CYP2C9 i.e. 0.451 and it was 0.393 for CYP2D6 and [I]/IC_{50} for CYP3A4 was 0.325. Although the [I]/Ki was higher for CYP2C9 than for CYP3A4, we recommend that in vivo drug interaction study with a sensitive substrate of CYP3A4/5 based on following:

1) The wider range of drugs that are metabolized by CYP3A4
2) The significant contribution of CYP3A4 to the metabolism in the intestine because phenylbutyrate, a metabolite of glycerol phenylbutyrate is presumably generated in the intestine.
3) Phenylacetate (PAA), which is converted from phenylbutyrate, showed an inhibitory effect on CYP3A4 and CYP2C9 at a concentration higher than the observed plasma concentrations. While the possibility of in vivo drug interaction with CYP2C9 substrate is unlikely based on the [I]/Ki of PAA for CYP2C9 determined in an additional study, the [I]/Ki of PAA for CYP3A4 was not determined. Therefore, potential effects PAA on CYP3A4 can not be ruled out.

[1] Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. Cancer 1995;75:2932-8.

[2] Parphanphoj et al (2000), Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring the treatment of acute hyperammonemia, J. Inherit. Metab. Dis 23: 129-36.

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/s/

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01/18/2013

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CLINICAL PHARMACOLOGY REVIEW

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Brand Name		Ravicti®	
Generic Name		Glycerol phenylbutyrate	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
PM Reviewer		Kevin Krudys, Ph.D.	
PM Team Leader		Nitin Mehrotra, Ph.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Gastroenterology and Inborn Errors Products	
Sponsor		Hyperion	
Submission Type;		Original	505(b)(1)
Formulation; Strengths; Regimen		Liquid for oral administration 1.1 g of glycerol phenylbutyrate (GPB) in 1 ml of Ravicti® (equivalent to 1.02 g phenylbutyric acid) • Recommended starting total daily dose is as below (b) (4) • Dose range: 4.5-11.2 ml/m^2 (5-12.4 g/m^2) • Not to exceed 17.5 ml (19 g) total • Total daily dose should be administered in three divided doses with meals	
Indication		Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders involving deficiencies of the following enzymes: Carbamyl phsphate synthetase (CPS), Ornithine transcarbamylase (OTC), Argininosuccinate synthetase (ASS), Argininosuccinate lyase (ASL), Arginase (ARG), Mitochondrial transporter ornithine translocase (HHH deficiency)	

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1 Executive Summary

This original submission is to support the approval of glycerol phenylbutyrate (GPB; HPN-100, proposed tradename:Ravicti®), as an adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders (UCD) involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (also called Hyperornithinemia-Hyperammonemia-Homocitrullinuria; HHH deficiency).

Glycerol phenylbutyrate is a prodrug of phenylbutyrate which is a nitrogen scavenger. Phenylbutyrate in a sodium salt form was approved in 1996 for use in patients ≥ 6 years of age with UCD involving deficiencies of the following enzymes: CPS, OTC, and ASS (Buphenyl® Tablets (NDA 20-572) and Powder (NDA 20-573)). In addition to the enzyme deficiencies that Buphenyl® is indicated for, use of Ravicti is proposed for other enzyme deficiencies i.e. ASL, ARG and a transporter deficiency i.e. HHH related to urea cycle disorders.

In support of this application, the sponsor conducted clinical trials in UCD patients > 6 years old. The primary efficacy endpoint was blood ammonia level at steady-state of treatment during the switch-over period. The efficacy of Ravicti to Buphenyl was based on the non-inferiority of Ravicti in maintenance of blood ammonia level in UCD patients. The control of blood ammonia level was evaluated based on the area under the curve of ammonia concentration over 24 hours.

Because of the concern of neurotoxicity associated with phenylacetate (PAA) reported in cancer patients and in animals, the evaluation of systemic exposure to PAA in UCD patients < 6 years old in comparison to that after Buphenyl was requested. The results of PK study in patients < 6 years old was submitted in April, 2012 after filing of the NDA as agreed upon prior to the NDA submission. In the initial submission, the sponsor did not seek the indication in patients < 6 years old.

1.1 Recommendations

The Division of Clinical Pharmacology 3 and the Division of Pharmacometrics reviewed the submission and found acceptable provided a mutual agreement on the labeling languages can be reached.

1.2 Post-Marketing Studies

A potential post-marketing study(ies) is currently under discussion. An addendum will be followed if a study(ies) is deemed necessary.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Throughout this review Ravicti was also referred as glycerol phenylbutyrate and by its code name HPN-100.

Exposure (Dose)-Response Relationship

- *Efficacy*

The Sponsor performed an analysis to explore the relationship between blood ammonia and exposure. Blood ammonia was represented as AUC_{0-24} or change in ammonia from time 0 to C_{max}. No consistent or strong relationship between exposure and blood ammonia was observed. The sponsor notes that the lack of a relationship is most likely due to the fact that the patients enrolled in these studies were already dosed to effect so that their ammonia levels were already within the normal range. Also, other factors contribute to ammonia levels, including residual urea synthetic capacity and dietary nitrogen intake. One way to understand the dose-response relationship would be to study patients as they are titrated to a dose of BUPHENYL or HPN-100.

- *Safety:*

In healthy subjects

In healthy subjects, a positive relationship between plasma peak PAA level and the incidence of nervous system AEs was observed. The incidence of a nervous system adverse event is elevated when the PAA C_{max} exceeds **80** µg/mL (90%) compared to when PAA levels are lower than 80 µg/mL (32%). Please see the Pharmacometrics review in the appendix by Dr. Krudys for more details.

In UCD patients

No clear relationship between PAA C_{max} and the incidence of nervous system adverse event was observed in UCD patients. The discrepancy may be because UCD patients were well-controlled on a stable dose of BUPHENYL upon entering the trial. Presumably, this dose was titrated based on safety as well as ammonia levels. Therefore, for each individual patient, the PAA levels were tolerable. This is supported by the relatively lower overall incidence of nervous system adverse events in UCD patients compared to healthy volunteers. On the other hand, Healthy subjects more sensitive or responsive to nervous system side effects of PAA.

In addition, UCD patients may be more tolerant to nervous system side effects because some of the manifestations of hyperammonemia are similar to those that can be expected at high levels of

PAA. These patients, therefore, may have become more tolerant to these adverse reactions over the course of their disease.

Effects of Ravicti on the QT interval

The review of the thorough QT study by the IRT-QT team (dated 5/30/2012) noted that there was no QTc prolongation effect of HPN-100 based on the double delta analysis. The largest upper bounds of the 2-sided 90% CI for the mean difference between HPN-100 (13.2 g/day and 19.8 g/day) and placebo were below 10 ms. However the study was considered inconclusive because the moxifloxacin time profile was not consistent with the expected moxifloxacin time course. IRT-QT team review noted that it was unexpected to see moxifloxacin peaks at 0.5 h post-dose after a single oral dose of 400 mg was administered. Therefore, IRT-QT team recommended a further evaluation of effects of Ravicti on the QT prolongation. The necessity of an additional study is under discussion.

The rationale for the proposed daily dose range

The ammonia scavenger therapy should be individualized due to various factors that contribute to the management of ammonia such as the patients' residual urea formation capacity, the age-dependent nutritional need, and intrinsic capacity elimination of PAA via conjugation with glutamine. The wide range of observed maintenance dose for sodium phenylbutyrate implicates that the starting dose should also be individualized. Nevertheless, this development program was not designed to address the starting dose for Ravicti nor the dose titration strategy. In this development program, all patients except six patients were on Buphenyl prior to the switch to Ravicti. The removal of Buphenyl was considered unethical due to a risk of hyperammonemia. The dose of Ravicti was determined based on the molar equivalent dose of phenylbutyrate to Buphenyl.

The proposed dose range i.e. 4.5-11.2 ml/m^2(5-12.4 g/m^2) is based on the dose range of observed doses for Buphenyl. The proposed lower end of the dose corresponds to the observed Buphenyl dose at 25% quartile and the proposed upper end of the dose is equivalent to the upper end of the Buphenyl dose (Table 1).

Table 1. The proposed daily starting dose and the dose range in UCD patients

BSA	Starting dose	Dose range
	(b) (4)	4.5-11.2 ml/m^2; (5-12.4 g/m^2); not to exceed 17.5 ml total (19 g)

Approved dose range for sodium phenylbutyrate

> 20 kg	No starting dose	9.9 g—13 g/m^2
< 20 kg	No starting dose	450-600 mg/kg

The proposed dose range is reasonably acceptable in UCD patients > 2 months of age.

UCD patients > 2 years of age

- The maintenance of blood ammonia during the switch-over period was comparable.
- The dosing range is based on the observed range of effective individual doses.

- The observed and simulated systemic exposure to PAA was comparable between Ravicti and Buphenyl treatments.
- The simulated mean Cmax for PAA patients ≥ 2 years old at the high end of the proposed dose was below 200 µg/ml and lower than the concentrations reported to be associated with neurotoxicity in cancer patients e.g. ~400-500 mcg/ml.

UCD patients < 2 years of age

- In patients younger than 2 years old, PK data is insufficient due to the limited number of patients (n=4), and sparse PK samplings. Therefore, modeling and simulation of PK was not reliable in this age group.
- Because there are two patients who experienced PAA concentrations higher than 400 µg/ml after Ravicti as well as Buphenyl, further PK and safety information is desired to better define the upper limit of the dose range. In the meantime, the proposed dose range is applicable to this age group based on the high end of the dose range similar to that of Buphenyl for this age group.

UCD patients < 2 months of age

Because Ravicti was not studied in newborns younger than 2 months old and the concern of inefficient hydrolysis of Ravicti due to lower lipase activity in this age group, we do not recommend that the use of Ravicti in neonates <2 months old until further information becomes available.

Starting dose

The starting dose should also be individualized based on the individual patient's needs at the time of initiation of Ravicti treatment e.g. dietary needs changes by the developmental stage. Therefore, the proposed starting dose in patients > 6 years old may not be the optimal starting dose for all patients. The initiation of treatment for individual patients should follow an established clinical treatment guideline as available. Nevertheless, it seems to be a reasonable starting point to avoid excessive under- or overdosing for majority of patients in the absence of the treatment guideline. In addition, the dose is expected to be further titrated based on the patients' response. Therefore, the median observed dose should be provided in the label but should not be recommended as a starting dose. Comments on the treatment initiation strategy are deferred to the clinical reviewers.

Patients who were not on Buphenyl

In the open-label extension period, there were a limited number of patients (n=6), were not on Buphenyl. For those patients, the starting dose of HPN-100 was to be equivalent to the lower end of the approved dose range for BUPHENYL® at the investigator's discretion. According to the comments from the six investigators who initiated HPN-100 on patients who were not on Buphenyl, the starting dose was determined taking several factors into considerations such as the prescribed dietary protein, the recommended Buphenyl dose range, UCD subtype, and supplementary amino acid intake. Among these patients, two patients who received 17.4 ml or 18 ml of HPN-100 (the proposed upper limit is 17.5 ml) discontinued after dose reduction for toxicity at 1 week or 2 months after the initiation of the treatment.

Ammonia assay in Phase 3 trial

Total eleven ammonia assay kits were used for the assay for blood ammonia in the pivotal phase 3 study. Because the cross-assay validation was not performed, the comparison of blood ammonia level between patients across study sites is not considered reliable. Nevertheless, it was concluded that the lack of the cross-assay validation did not invalidate the comparison of ammonia control during the switch-over period because blood ammonia for the each patient was measured at the same laboratory using the same assay kit and each patient served as his or her own control.

Pharmacokinetic/ Biopharmaceutics Properties

The evaluation of pharmacokinetics of Ravicti was in comparison to that after Buphenyl in all UCD patients. Upon oral administration Ravicti is hydrolyzed by lipases to release phenylbutyrate. Phenylbutyric acid (PBA) is further converted to phenylacetic acid (PAA) which is conjugated with glutamine to form phenylacetylglutamine (PAGN). Urinary excretion of one molecule of PAGN is equivalent to the elimination of two nitrogen molecules.

The systemic exposure to PBA and its active moiety, PAA was about 3-4 fold lower after Ravicti than that after Buphenyl in healthy subjects. On the other hand, in adult UCD patients, the mean systemic exposure to PBA and to PAA was 15-25% lower after Ravicti than Buphenyl while the mean blood ammonia level tended to be lower after Ravicti than Buphenyl.

PK of glycerol phenylbutyrate, HPN-100

After multiple doses, UCD patients aged 6-17 year, intact HPN-100 was not detectable in plasma samples. The evaluation of PK in UCD patients was performed only at steady-state. Intact HPN-100 was not measured in the pivotal Study HPN-100-006.

In healthy subjects intact HPN-100 was detected in plasma. However, the detectable HPN-100 in healthy subjects was attributed to the contaminated plasma samples at the study site. While there was no direct evidence to support the assertion, it makes the HPN-100 results unreliable in healthy subjects. Therefore a firm conclusion can not be drawn and the incomplete hydrolysis of HPN-100 can not be ruled out.

PK of metabolites of glycerol phenylbutyrate

In healthy subjects, after single dose administration, Tmax for PBA, PAA, and PAGN was 1 h, 4 h, and 4 h, respectively. Mean terminal half-life for PBA, PAA and PAGN was 1.9, 1.4 and 5.9 hours, respectively. The ratio of mean AUCi of PAA and PAGN to PBA is 0.58 and 2.1, respectively. In comparison to Buphenyl, the systemic exposure (AUC) to PBA and PAA of Ravicti was 75% and 73% lower, respectively. The AUC and urinary excretion of PAGN over 24 hours was also 18% and 17% lower after Ravicti. Multiple dose PK under the proposed three times daily dosing frequency was not studied in healthy subjects. After multiple doses (BID for 7 days), AUC of PBA, PAA, and PAGN was 1.4, 2.9, and 1.6 fold higher than after single dose.

In UCD patients > 2 years old, the modeling and simulation of PK suggests that the systemic exposure to PAA is similar between Ravicti and Buphenyl at the high end of the dose range and the mean peak plasma concentration is predicted to be lower than 500 μg/ml. In pediatric UCD patients, a higher variability and higher concentrations of PAA than in adult patients is predicted after administration of Buphenyl and Ravicti. The modeling and simulation was not reliable in

UCD patients < 2 years old due to the limited number of patients and sample numbers. There is no PK data available for patients < 2 months old of age.

PK in patients with hepatic impairment

In patients with hepatic impairment, mean AUC of PAA was higher than in healthy subjects and mean AUC increased as the degree of hepatic impairment increased. Of note the effects of hepatic impairment on the systemic exposure to PAA was studied under a different dosing frequency i.e. BID. Mean AUC of PAA in patients with moderate and severe hepatic impairment was 1.53-- and 1.94--fold higher than in healthy subjects. For patients with hepatic impairment Child-Pugh B and C, the dosing should be initiated at the lower end of the range. If possible, measurement of PAA concentration and the PAA/PAGN ratio at steady-state will be useful to guide further dose increase.

In vitro drug interaction studies

In vivo drug interaction via induction of CYP3A4 and CYP1A2 is not expected based on a lack of induction of CYP3A4 and CYP1A2 in in vitro studies.

In vitro PBA inhibited CYP2C9, CYP2D6, and CYP3A4/5 and potential in vivo drug interaction was suggested by the [I]/Ki > 0.1 for CYP2C9 and CYP2D6 and [I]/IC_{50} >0.1 for CYP3A4. Mean plasma peak concentration of PBA was used as [I]. Of note the likelihood of in vivo drug interaction may vary among patients depending on the dose because of the wide range of individual dose and the systemic exposure.

Plasma PAA/PAGN ratio as a biomarker to the probability of exceed 400 µg/ml PAA concentration

To mitigate a risk of exposing patients to high PAA concentration, the sponsor proposed plasma PAA/PAGN ratio as a biomarker for the lower conversion of PAA to PAGN. A high PAA to PAGN ratio could indicate inefficient conversion of PAA to PAGN in a given patient. The mean ratio of AUC of PAA to PAGN was about 0.5 in adult UCD patients and the ratio of plasma PAA to PAGN was mostly lower than 1 at any given PK sampling time point in UCD patients as well as in healthy subjects. On the other hand, in patients with hepatic impairment (Child-Pugh B and C classes), the ratio greater than 2 was common and mostly associated with peak PAA concentration higher than 100 µg/ml.

The sponsor proposes to measure PAA level when symptoms of vomiting, nausea, headache with somnolence, confusion or sleepiness are present in the absence of high ammonia. The sponsor also proposes that the Ravicti dose should be reduced if the plasma PAA level is ≥ 500 µg/mL and/or the ratio of plasma PAA to PAGN (both in µg/mL) is greater than (b) (4)

While it is reasonable to use PAA to PAGN ratio as an inherent measure of conversion efficiency, it alone should be not used as a dose reduction criteria and the dose reduction should be done based on the patient response. The ratio of PAA to PAGN may be informative to modify UCD management strategy such that when the ratio is high and the PAA level is high, modification of other aspects of management should be considered rather than an increase in dose because further increase in dose may not necessarily increase the efficiency of ammonia elimination as the conjugation of PAA with glutamine could be saturated.

However, there are no commercially available assays for PAA and PAGN.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

In this original submission, the sponsor seeks a marketing approval of glycerol phenylbutyrate (GPB; HPN-100, Ravicti®), a prodrug of phenylbutyrate as an adjunctive therapy in the chronic management of patients with urea cycle disorders. Phenylbutyrate (Buphenyl® Tablets and Powder (NDA 20-572, NDA 20-573)) is approved for the same indication. Because most of patients were likely already on Buphenyl®, the evidence of efficacy of HPN-100 was agreed to be primarily based on a comparable maintenance of blood ammonia level during the switch-over between Buphenyl® and HPN-100.

In addition to the enzyme deficiencies indicated for Buphenyl®, i.e. OTC, CPS, and ASS, the sponsor proposes to expand the indication to additional enzyme deficiencies including argininosuccinate lyase (ASL), arginase (ARG), and mitochondrial transporter ornithine translocase (HHH deficiency).

The approved product, Buphenyl® is indicated for children weighing more than 20 kg and for adults. Although Buphenyl® is not indicated for children weighing < 20 kg; dosing information is provided in the current label. The sponsor stated that HPN-100 was developed to reduce pill burden, sodium load, and to improve palatability of sodium phenylbutyrate.

The sponsor is not seeking the indication in patients younger than 6 years of age in this submission, however to address the concern of the neutrotoxicity associated with high plasma concentration of phenylacetic acid (PAA) reported in cancer patients[1,2], a PK study was conducted in patients with UCD < 6 years old. A priori agreement was made to provide PK data in patients younger than 6 years old after the NDA filling. The PK in patients younger than 6 years of age was submitted in an amendment dated April 23, 2012.

Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250–300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominately somnolence, fatigue, and lightheadedness; with less frequent headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy. These adverse events were mainly mild in severity. The reversible toxicities as reported by Thibault were reported to be temporally associated with PAA levels ranging from 499–1285 µg/mL. The acute onset and reversibility when the phenylacetate infusion was discontinued suggest a drug effect.

[1] Thibault et al. (1995) Phase I study of phenylacetate administered twice daily to patients with cancer, Cancer 75(12); 2932
[2] Thibult et al. (1994) Phase I and pharmacokinetic study of intravenous phenylacetate in patients with cancer, Cancer Res. 54, 1690

Based on the reported association between plasma PAA level and neurotoxicity and PAA being an active moiety, the systemic exposure to PAA was used for the exposure-response relationship analysis for safety.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Glycerol phenylbutyrate is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone via (b) (4) and its molecular weight is 530.67 (Figure 16). Glycerol phenylbutyrate is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide (DMSO) and > 65% acetonitrile. Upon administration, the active moiety phenylacetate (PAA) should be released following hydrolysis of phenylbutyrate (PBA) from glycerol phenylbutyrate (GPB).

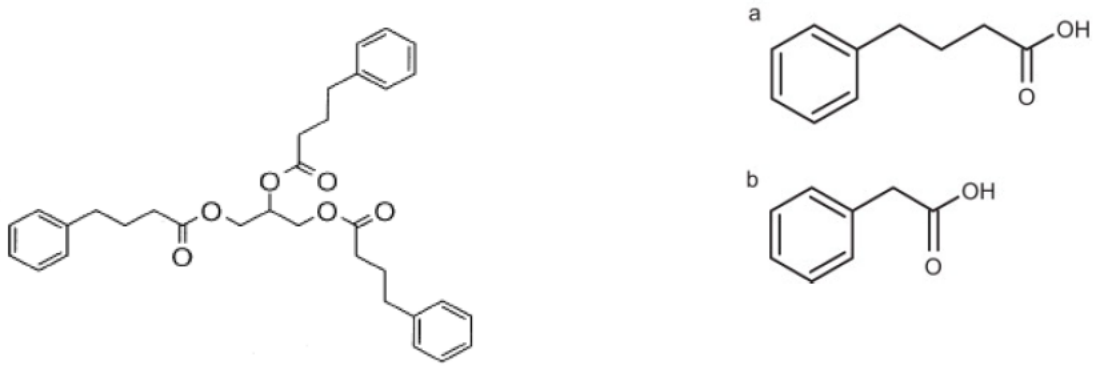


Figure 1. Structure of glycerol phenylbutyrate and its metabolites (a) PBA; (b) PAA

Ravicti® is (b) (4) in liquid form containing (b) (4)

One glycerol contains three molecule of phenylbutyrate which will be converted to phenylacetate. Each mL of liquid contains 1.1 grams of glycerol phenylbutyrate and delivers 1.02 grams of phenylbutyrate (PBA).

In clinical trials to compare the proposed Ravicti® and Buphenyl®, the dose for Ravicti was determined based on the molar content of PBA equivalent to Buphenyl.

NaPBA dose (g) x 0.95 /1.1 = Total daily HPN-100 dose (mL)

Each HPN-100 dose may have been rounded up to the nearest 0.2 mL. Disposable syringes and medication cups were provided by the sponsor.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

"The urea cycle disorders (UCD) result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules[3]. Severe deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life (Figure 2). Infants with a severe urea cycle disorder are normal at birth but rapidly develop cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. In milder (or partial) deficiencies of these enzymes and in arginase (ARG) deficiency, ammonia accumulation may be triggered by illness or stress at almost any time of life. In these disorders the elevations of plasma ammonia concentration and symptoms are often subtle and the first recognized clinical episode may not occur for months or decades."

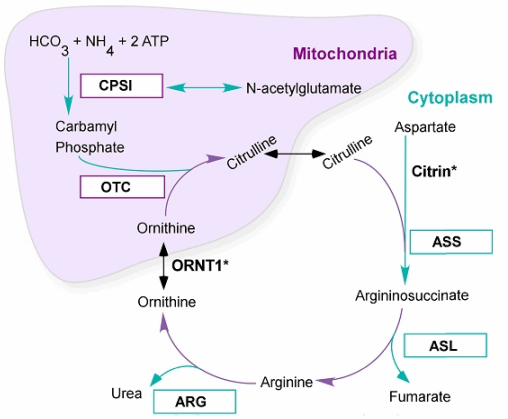


Figure 2. Urea Cycle

Glycerol phenylbutyrate is a nitrogen scavenger. Upon administration, glycerol phenylbutyrate will be mainly eliminated as phenylacetic glutamine (PAGN) following the conjugation of the active moiety PAA with glutamine. Phenylacetic glutamine will be further excreted in the urine eliminating two nitrogen molecules (Figure 3).

[3] GeneReviews™. Pagon RA, Bird TD, Dolan CR, et al., editors. Seattle (WA): University of Washington, Seattle; 1993- (http://www.ncbi.nlm.nih.gov/books/NBK1217/)

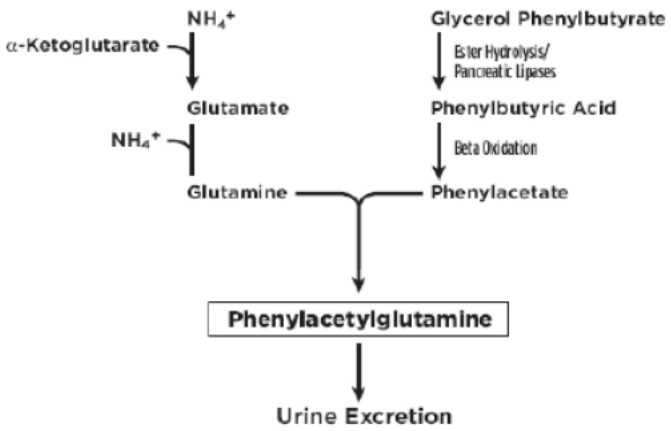


Figure 3: Mechanism of Action of Phenylbutyric acid

The proposed indication is an adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders (UCD) involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (also called Hyperornithinemia-Hyperammonemia-Homocitrullinuria; HHH deficiency).

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Ravicti® is in liquid form and is to be administered without further preparation. It is proposed to be delivered directly into the mouth with an oral syringe. The total daily dose should be divided into 3 doses and administered with meals.

TThe starting dose based on body surface area is proposed for patients older than 6 years as below.

	(b) (4)
Body surface area (m^2)	
Recommended starting dose	
Dose range	5–12.4 g/m^2 (4.5–11.2 mL/m^2); not to exceed 19 g/17.5 mL total

HPN = glycerol phenylbutyrate.

The sponsor also proposes therapeutic drug monitoring based on a fasting plasma ammonia level as well as a level of U-PAGN as follows: (b) (4) the initial dose should be titrated to produce a fasting plasma ammonia level that is less than half the upper limit of normal and a level of U-PAGN to cover dietary protein intake. The daily amount of dietary protein covered is calculated based on the 24 hour excretion of urinary PAGN (U-$PAGN_{24hr}$), whereby each gram of U-PAGN covers waste nitrogen produced by approximately 1.44 g of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein and the fasting ammonia is greater than half the upper limit of normal, the Ravicti dose should be adjusted upward.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of HPN-100, four clinical studies were conducted in 91 UCD patients (65 adults and 26 children between the ages of 6 and 17 years) with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH across four studies. In addition, three phase 1 PK studies; a relative bioavailability study, a hepatic impairment study and a thorough QT study were conducted. The sponsor also submitted PK information in patients with hepatic impairment which was conducted as a run-in study for a phase 2 study for patients with hepatic encephalopathy. In addition to the studies submitted in the initial submission, the study report entitled " A switch-over, open-label study of the safety, pharmacokinetics, and efficacy of HPN-100, followed by long-term treatment with HPN-100, in pediatric subjects under 6 years of age with Urea cycle Disorders" was submitted in April, 2012 as agreed with the Agency (Table 2).

Studies in UCD patients had a fixed sequence switch-over design from Buphenyl (sodium phenylbutyrate) to HPN-100 studies except for the HPN-100-006 which was a two sequence, crossover switch-over study design.

2.2.2 What is the primary efficacy endpoint and what is the basis for selecting the blood ammonia as primary efficacy endpoint and how are they measured in clinical studies?

Elevated blood ammonia is the common signature feature of Urea Cycle Disorders. Most ammonia in the body forms when protein is broken down by bacteria in the intestine. The absorbed ammonia undergoes urea cycle in the liver and is subsequently eliminated as urea in urine. Impairment of urea cycle consequently results in accumulation of blood ammonia. Hyperammonemia manifested by vomiting, lethargy, and neurologic impairment and control of blood ammonia is a primary objective of clinical management of UCD.

The primary efficacy endpoint was blood ammonia level assessed as AUC_{0-24} at steady-state after 2 week treatment with either Buphenyl or HPN-100.
Secondary efficacy endpoints included: Maximum blood ammonia values observed on NaPBA versus HPN-100, rate (percentage) of blood ammonia values above the upper limit of normal (ULN) on NaPBA versus HPN-100, number and severity of symptomatic hyperammonemic crises and correlation between 24-h urinary PAGN excretion ($U\text{-}PAGN_{0-24}$) and blood ammonia AUC_{0-24}.

Table 2. Summary of HPN-100 Clinical Studies

Study	Study design	Subject	Objective	Dose
UP 1204-001	Randomized, open-label, cross-over	healthy subjects (n=24)	PK Relative BA Buphenyl (n=23) HPN-100 (n=22) Ammonul (n=24)	Mole equivalents to 3g/m2 of PBA per dose Single dose PK sampling: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h
UP 1204-002	Open-label	Healthy subjects (n=8) Hepatic impairment patients CP-A (n=8) CP-B (n=8) CP-C (n=8)	Single dose PK Multiple dose PK (BID, 7 days) safety	100 mg/kg 100 mg/kg BID PK sampling: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h
HPN-100-010	Randomized, double-blind, crossover	Healthy subjects	TQT study	Arm 1 9 ml (n=4) 12 ml (n=4) Arm 1 TID (Q8h) for one day PK sampling: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 23 h Arm 2: Multiple dose for three days 4 ml TID (n=66) 6 ml TID (n=69) 9 ml TID(m=5) PK sampling: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 23 h Doses were administered every 8 hours in Arm 1 and 3 times a day with meals for Arm 2
HPN-100-008 Part A	Randomized, open-label, run-in	CP-B (n=10) CP-C (n=5)	Single dose PK after 6 ml Multiple dose PK safety	6 ml BID 9 ml BID Dose escalation to 9 ml after 1 week treatment with 6 ml

Study	Study design	Subject	UCD subtype	Objective	Dose
UP 1204-003	Non-randomized, open-label, fixed-sequence, switch-over Treatment was switched from NaPBA to HPN-100	Adult UCD (> 18 years old) (n=10)	OTC (n=8) ASL (n=1) ASS (n=1) HHH(n=1)	safety efficacy (ammonia) Multiple dose PK	NaPBA: 4-298 mg/kg/day HPN-100: 8.7-17.4 ml/day TID 7 days PK sampling: 0, 0.5, 1, 2, 4, 5, 6, 8, 10, 12, 24 h
HPN-100-005	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Pediatric UCD 6-17 years old M (n=1; ASS) F (n=10) 6-11 (n=7) 12-17 (n=4)	OTC (n=9) ASS (n=1) ASL (n=1)	Safety efficacy Multiple dose PK (TID 7 days)	NaPBA dose: 8-18 g/day HPN-100 (6.9-16.5 mL/day) TID (0, 4, 10 h) PK sampling: 0; 4, 8, 12, 16, 20, 24 h

	Treatment was switched from NaPBA to HPN-100				
HPN-100-006	Randomized, double-blind, crossover	Adult UCD (n=45) (M; n=14, F; n=35)	OTC (n=40) ASS (n=2) CPS1 (n=2)	Safety efficacy Multiple dose PK	TID for 7 days Median NaPBA dose: 15 g/day (1.5-36 g/day) Median HPN-100 dose 13.1 ml (1.2-31.2 ml/day) Median PBA dose 13.2 g/day (1.32-31.7 g/day) Dosing (0, 4, 10 h) PK sampling: 0, 2, 4, 8, 12, 16, 20, 24 h
HPN-100-012	Open-label, switch-over followed by long-term treatment	Pediatric UCD < 6 years infants/toddlers (29 days to < 2 years) (n=4) Children (2 to < 6 years) (n=11) M: (n=8) F: (n=7)	OTC (n=3) ASL (n=8) ASS (n=3) ARG (n=1)	PK	TID (one subject QID) At least 5 days treatment with NaPBA 10 days after HPN-100 NaPBA dose: 1.8-14.6g/m^2 HPN-100: 1.22-12.8 g/m^2 Dosing (0, 4, 10 hr) PK sampling: 0, 8, 12, 24 h
HPN-100-007	Open label extension	N=60 (51 adult and 9 pediatric patients)			

Measurement of blood ammonia

In each study, blood ammonia sampling was performed at steady state over 24 h. Timing of samples differed slightly among the studies and AUC_{0-24} for HPN-100-006 and HPN-100-005 (or time-normalized AUC for UP 1204-003) was calculated based on the ammonia concentrations at different time points.

At each designated time point for ammonia sampling, 2 mL of venous blood was to be drawn and processed by the laboratory at the investigator site per the facility standard operating procedures (SOPs).

Blood ammonia was measured either by colorimetric or enzymatic method using commercially available assay systems available to each study site. **Eleven assay kits** were used for the pivotal phase 3 trial, HPN-100-006. Ammonia assay kits used for the study were cleared as a device via 510(k) pathway. There was no cross assay validation performed.

Ammonia measurements in blood are known to vary with storage and handling and are, therefore, typically stored on ice and analyzed promptly. Ammonia level in plasma stored in a refrigerator or freezer for more than 1 hour falsely increases[4].

In order to minimize the possibility of inaccurate ammonia values in the pivotal study (HPN-100-006), ammonia measurements from each subject were performed by the CLIA-approved laboratory at each site. The sponsor took following two steps to minimize the potential impact of methodological differences among ammonia analyses. First, the ammonia values on Days 14 and 28 used to calculate each subject's 24-hour area under the curve were measured at the same lab. Since the efficacy analysis involved differences in daily ammonia exposure on HPN-100 as compared with NaPBA, use of the same lab mitigated inter-laboratory and/or inter-site differences in methodology. Second, the statistical analysis plan stipulated that all ammonia values be normalized to a standard laboratory reference range before conducting the primary efficacy analyses. This minimized artificial variability due to inter-laboratory differences in the normal range.

Reviewer's comments: The protocol did not specify the blood sample handling procedure for ammonia measurement and while left it up to the standard of procedure at each site. Because the cross-assay validation was not performed for the different assay kits used at each study site, a head-to-head comparison of blood ammonia values obtained using different assay kits is not considered reliable due to unaccounted inter-assay variability.

However, the lack of cross-assay validation is not considered to be critical in the comparison of blood ammonia within a patient because ammonia levels were measured by the same assay kit at the same site after treatment with Buphenyl® and HPN-100.

Regarding the normalization to the standard reference range, the biostatics reviewer found it acceptable (please see the Biostatics Review by Dr. Verang Bali for more details). While the normalization to a standard laboratory reference range may not affect the statistical comparison between products, the resulting ammonia levels are not actual readout. The normalized value in the labeling is potentially misleading. Therefore, non-normalized data was further requested. Please see section 2.6 for the normalization method.

Ammonia level by the assay type

In study HPN-100-006, blood ammonia was measured by colorimetric method or enzymatic method for 28 patients and 17 patients, respectively. When mean $AUC_{NH3\ 0\text{-}24}$ was compared by assay type, mean ammonia AUC measured by enzymatic method was about 2-2.5 fold greater than that measured by colorimetric method. Nonetheless, geometric mean ratio and associated 90% confidence interval around was similar (Table 3).

[4] Batshaw (1984) Hyperammonemia, Current Problems in Pediatrics

Table 3. Mean ammonia AUC by assay type (provided by the sponsor in response to the IR.

Assay type	Mean $AUC_{NH3\ 0\text{-}24}$ (µmol·h/ml)[§] (min, max)		
	HPN-100	NaPBA	GM ratio (90% CI) (95% CI)
Colorimetric method	600.66 (206,1556) (n=28)	597.06 (301.9,1022.8) (n=28)	0.95 (0.82, 1.087) (0.803, 1.118)
Enzymatic method	1287.03 (389,3351) (n=17)	1579.47 (434, 4665) (n=17)	0.87 (0.71, 1.07) (0.678, 1.117)

[§]Based on normalized ammonia level. From the response to IR dated June 15, 2012(NDA 203284/Seq 0007).

Normal ammonia level

The upper limit of normal ammonia is around 35-60 µmol/L depending on assay type.
In addition, normal range of blood ammonia varies by age (Table 4).

Table 4. Reference intervals for blood ammonia concentration (µmol/L)[5]

Table 1. Reference intervals for blood ammonia concentration (µmol/L).

			Reference Intervals	
Age	n	Mean	Mean ± 2SD	0.05–0.95 fractiles
<30 days	87	54.0	17–91	21–95
1–12 months	91	43.5	15–72	18–74
1–14 years	94	39.5	14–65	17–68
>14 years	182	41.0	18–64	22–66
Men	89	43.5	19–68	21–71
Women	93	38.5	17–60	19–63

The label of Carbaglu®, an approved adjunctive therapy for acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) refers ammonia normal range from 5 to 50 µmol/L.

2.2.3 Are the active moieties in the plasma and urine appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety, phenylacetate (PAA) was adequately measured in plasma and urine. In addition to phenylacetate (PAA), phenylbutyrate (PBA), its precursor and phenylacetyl glutamine (PAGN), its conjugate metabolite were measured in all PK studies. In some studies,

[5] Letters to the editors (1995) Reference Intervals for Blood Ammonia in Healthy Subjects, Determined by Microdiffusion CLINICAL CHEMISTRY, 41(7)

the parent drug, glycerol phenylbutyrate was measured in plasma (Please see section 2.6 for details about the bioanalytical assay methods. Urinary excretion of PAGN was also measured because U-PAGN is stoichiometrically related to waste nitrogen removal.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

The dose of glycerol phenylbutyrate was determined based on the mole-equivalent dose of phenylbutyrate in sodium phenylbutyrate (Buphenyl®) for the switch-over study to compare the efficacy of two products based on mean AUC of blood ammonia over 24 hours. There was no additional dose-ranging study to evaluate the dose-response relationship for HPN-100.

A relationship between PBA dose (g or g/m^2) or PAA (AUC) and plasma ammonia (AUC_{0-24}) was not identified in a pooled analysis including adult and pediatric data (Table 5). The most likely reason the lack of a relationship is that patients enrolled in the studies were already titrated to a dose of NaPBA to control ammonia levels within normal limits. Please see the Pharmacometric review for more details.

Table 5. Pearson's Correlation for Exposure-Response Relationships

Relationship	Group	Pearson's Corr. (r)	Critical Value of Pearson's r*	Statistically Significant?
Ammonia AUC versus total daily PBA	Peds: Both formulation (switch-over)	-0.29	0.360	N
	Peds: HPN-100 (switch-over)	-0.43	0.521	N
	Peds: NaPBA (switch-over)	-0.20	0.521	N
	Adults: Both formulation (switch-over)	0.31	0.173	Y
	Adults: HPN-100 (switch-over)	0.24	0.243	N
	Adults: NaPBA (switch-over)	0.38	0.231	Y
Ammonia AUC versus total daily PBA per BSA	Peds: Both formulation (switch-over)	0.10	0.360	N
	Peds: HPN-100 (switch-over)	0.15	0.521	N
	Peds: NaPBA (switch-over)	0.09	0.521	N
	Adults: Both formulation (switch-over)	0.32	0.173	Y
	Adults: HPN-100 (switch-over)	0.30	0.243	Y
	Adults: NaPBA (switch-over)	0.35	0.231	Y
Pred. ammonia AUC versus total daily PBA per BSA	Peds: Fasting state (extension studies)	-0.16	0.164	Y
	Adults: Fasting state (extension studies)	0.13	0.164	N
Pred. ammonia AUC versus total daily PBA per BSA	Peds: All state (extension studies)	-0.10	0.164	N
	Adults: All state (extension studies)	0.19	0.164	Y
Ammonia AUC (obs. or pred.) versus total daily PBA per BSA	All peds: Extension & switch-over	-0.14	0.301	N
	All adults: Extension & switch-over	0.26	0.173	Y
	All patients: Extension & switch-over	0.18	0.164	Y

p value < 0.05

Source: Ammonia Exposure-Response Report, Appendix 7.1, Page 28.

The efficacy of the HPN-100 was supported by the non-inferiority of HPN-100 to NaPBA in controlling blood ammonia assessed as AUC_{0-24}, with the upper bound of the 95% CI ranging from 1.034 and below the non-inferiority margin of 1.25 agreed upon with FDA for the pivotal study, HPN-100-006 (Tables 6, 7).

Table 6. Non-Inferiority Analysis of Blood Ammonia AUC_{0-24} (ITT Population)

Blood Ammonia$_{0-24}$ Statistic (µmol·h/L)[a]	NaPBA	HPN-100	Difference Between HPN-100 and NaPBA
ITT	**n=44**	**n=44**	**n=44**
Mean	976.63	865.85	-111
SD	865.352	660.529	579.0
Median	652.48	672.59	-47
Min, Max	301.9, 4665.9	206.0, 3351.1	-2953, 1007
Ratio of Geometric Means[b]			0.91
90% Confidence Interval[b]			(0.816, 1.012)
95% Confidence Interval[b]			(0.799, 1.034)

Source: modified from Table 15 in CSR HPN-100-006

[a] Individual missing ammonia AUC data were imputed if values were missing at 0 or 24 h or the patient had < 12 h of blood ammonia data.

[b] Results on original scale were obtained by exponentiating the corresponding log-transformed results.

Table 7. Mean Blood Ammonia AUC_{0-24} and 24-Hour C_{max} Values Following Dosing with HPN-100 or NaPBA

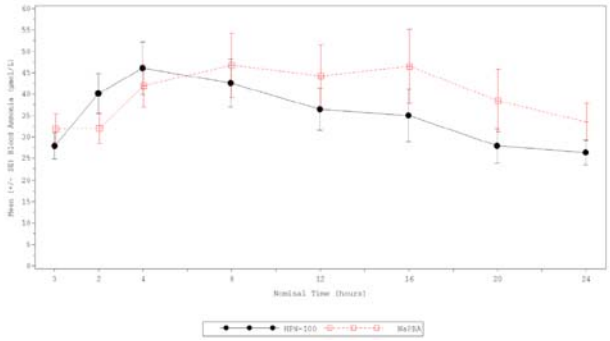
	Ammonia AUC_{0-24} (µmol·h/L)[a]			Ammonia C_{max} (µmol/L)		
	NaPBA	HPN-100	Difference between HPN-100 and NaPBA	NaPBA	HPN-100	Difference between HPN-100 and NaPBA
ITT	**n=44**	**n=44**	**n=44**	**n=44**	**n=44**	**n=44**
Mean	976.63	865.85	-110.78	70.83	60.94	-9.89
SD	865.352	660.529	578.951	66.705	46.213	43.088
Median	652.48	672.59	-46.70	45.95	50.70	-3.58
Min	301.9	206.0	-2952.9	13.5	12.1	-163.3
Max	4665.9	3351.1	1006.6	303.3	245.0	85.0

Source: modified from Table 16 in CSR HPN-100-006

[a] Individual missing ammonia AUC data were imputed if values were missing at 0 or 24 h or the patient had < 12 h of blood ammonia data

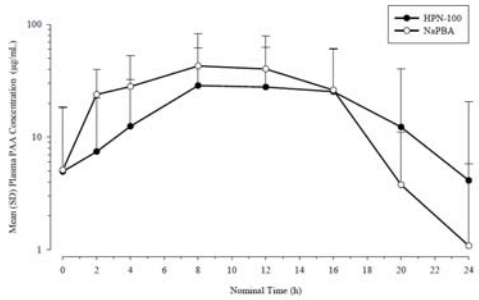
After administration of Ravicti the plasma ammonia concentration tended to be higher after the first dose of the day but tended to be lower later during the day compared to that after Buphenyl. On the other hand, plasma PAA concentration tended to be initially lower with Ravicti and tended to higher later during the day. This ammonia concentration-time profile and PAA concentration-time profile appears to correlate in a way that Ravicti exhibited a slightly delayed onset of PAA as well as a slightly delayed ammonia control.

Figure 4. Mean (SE) blood ammonia over 24 hours after treatment with NaPBA and HPN_100 ammonia value (non-normalized)



Source: Figure AH14.2.3.1. Amendment dated 8/27/12

Figure 5. Mean (+SD) PAA Plasma Concentration-Time Profiles (HPN-100 and NaPBA) (HPN-100-006)



2.2.4.2 What are the characteristics of the exposure-response relationships for neurological adverse events?

In healthy subjects

In healthy subjects, a dose-dependent increase in discontinuation and TEAEs was observed (Table 8).

Table 8. Treatment emergent adverse events by dose in healthy subjects

	Placebo	4 ml[1] TID	6 ml[2] TID	9 ml TID	12 ml TID
N exposed	84	68	75	12	4
Discontinued due to AE (%)	4 (4.8)	3 (4.4)	7 (9.3)	4 (33.3)	1 (25)
One or more neurological AE	8 (9.5)	18 (26.5)	35 (46.6)	11 (91.7)	3 (75)
One or more GI AE	9 (10.7)	8 (11.8)	24 (32)	9 (75)	4 (100)

[1]Similar to the proposed starting daily dose (b) (4) for patients with BSA of (b) (4)

[2]Similar to the proposed upper limit of the daily dose i.e. 17.5 ml/day

Similarly, a significant positive relationship between plasma peak PAA level and the incidence of nervous system AEs and gastrointestinal AEs was observed (Figure 8). The incidence of a nervous system adverse event is elevated when the PAA C_{max} exceeds **80** µg/mL (90%) compared to when PAA levels are lower than 80 µg/mL (32%). Please see the Pharmacometrics review by Dr. Krudys in the appendix for more details.

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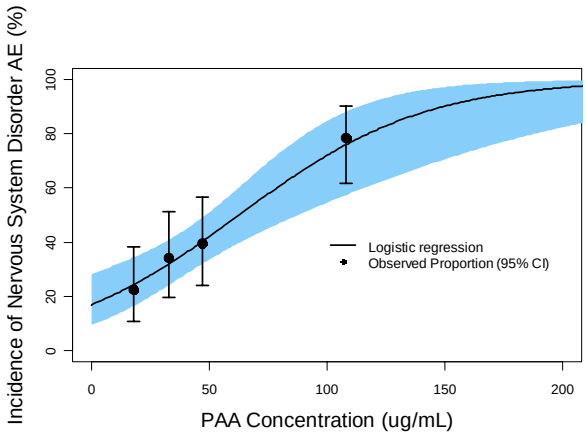
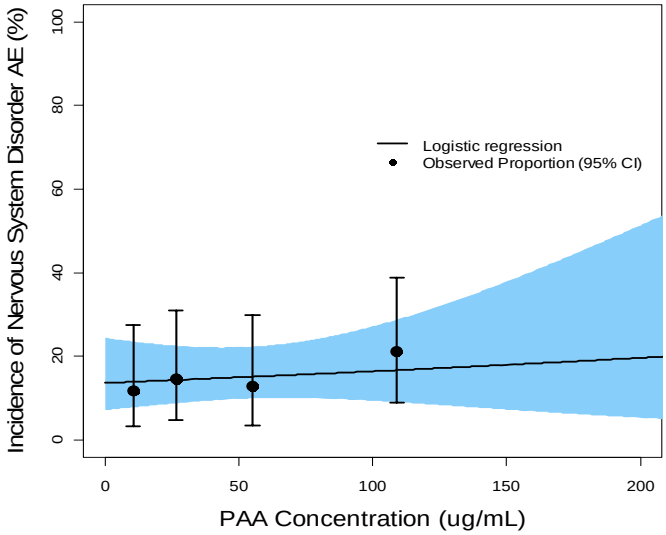
Figure 6. Relationship Between PAA C_{max} (µg/mL) and Incidence of Nervous System Adverse Events (all grades) in Healthy Volunteers



In UCD patients

No clear relationship between PAA C_{max} and the incidence of nervous system adverse event was observed in UCD patients (Figure 7).

Figure 7: Lack of Relationship Between PAA C_{max} (µg/mL) and Incidence of Nervous System Adverse Events (all grades) in UCD Patients



The discrepancy between healthy subjects and UCD patients may be due to the overall lower incidence rate of nervous system AE in UCD patients.

UCD patients were well-controlled on a stable dose of BUPHENYL upon entering the trial. Presumably, this dose was titrated based on safety as well as ammonia levels. Therefore, for each individual patient, the PAA levels were tolerable. This is supported by the relatively lower overall incidence of nervous system adverse events in UCD patients compared to healthy

volunteers. In a pooled analysis, the overall incidence rate of nervous system AE was ~16% in UCD patients while it was ~ 38 % in healthy subjects in the thorough QT study.

In addition, UCD patients may be more tolerant to nervous system side effects. Some of the manifestations of hyperammonemia are similar to those that can be expected at high levels of PAA. Therefore, these patients may have become more tolerant to these adverse reactions over the course of their disease.

On the other hand, the observed median peak plasma concentration of PAA was 25.4 µg/ml after Ravicti and 38.3 µg/ml after Buphenyl in adult UCD patients while the probability of nervous system AEs significantly increased at PAA concentration higher than 80 µg/ml in healthy subjects.

Reviewer's comments: It was noted that plasma concentration of PAA was missing from 8 healthy subjects who discontinued due to TEAE in the QT study. Therefore it is unknown if those subjects whose PAA plasma concentration is missing had a higher than the observed maximum PAA Cmax of 434.6 µg/m.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of HPN-100 on the QT interval was studied after 3 day administration 6 ml and 4 ml three times daily in a thorough QT study (HPN-100-010).

The review of the thorough QT study by QT-IRT team (dated 5/30/2012) noted that it appears that no significant QTc prolongation effect of HPN-100 was detected in this TQT study based on the double delta analysis for the study drug. The largest upper bounds of the 2-sided 90% CI for the mean difference between HPN-100 (13.2 g/day and 19.8 g/day) and placebo were below 10 ms (Table 9).

Table 9. Mean corrected QT interval after HPN-100 administration

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HPN-100 13.2 g/day,	1.5	-2.8	(-5.0, -0.7)
HPN-100 19.8 g/day,	12	-3.4	(-5.5, -1.3)
Moxifloxacin 400 mg*	2	9.5	(7.0, 11.9)

* Multiple endpoint adjustment of 3 time points was applied.

However the study was considered inconclusive because the moxifloxacin time profile was not consistent with the expected moxifloxacin time course. IRT-QT team review noted that it was unexpected to see moxifloxacin peaks at 0.5 h post-dose after a single oral dose of 400 mg was administered (Figure 8).

Figure 8. Mean and 90% CI ΔΔQTcI Time course

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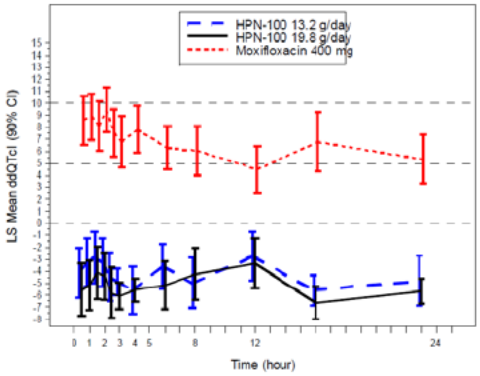


(Note: CIs are all unadjusted including moxifloxacin)

The QT-IRT team therefore suggested a PMR for further evaluation of the cardiovascular safety for the study drug. Please see the review by IRT-QT team dated 5/30/2012 for more details.

Reviewer's comments: While the necessity of additional study needs further discussion, the substantial difference in ddQTcI-time profile between moxifloxacin and HPN-100 appears to assure the negative effects of HPN-100 on QT interval. Moreover, apparently HPN-100 apparently decreases the QT interval. While the assay sensitivity remains as an issue for further discussion, the apparent decrease in the QT interval was noted. The largest lower limit of 90% CI was -9.4 ms at 16 h and -10.6 ms at 16 h after administration of 13.2 g and 19.8 g, respectively. The clinical significance of this observation is unknown.

Initially, the sponsor planed to study at 6 ml TID of HPN-100 (19.8 g total daily dose of HPN-100) and at 12 ml TID of HPN-100 (39.6 g total dose of HPN-100) as the supratherapeutic dose. Nevertheless because of tolerability issues with 9 ml TID, (29.7 g/day) and 36 mL (12 ml TID, 39.6 g/day), which include headache, nausea, dizziness, and emesis, leading to subject discontinuation, the highest dose for the evaluation of effects on the QT interval was decided at 4 ml TID of HPN-100 (13.2 g/day) and at 6 ml TID (19.8 g/day). The proposed starting dose of (b) (4)

Therefore the studied high dose may not cover a worst scenario such as elevated PAA level at the higher dose in patients with hepatic impairment.

2.2.4.4 Is proposed dose range of HPN-100 for adult and pediatric patients appropriate? The Sponsor's proposed dosing range of HPN-100 is appropriate. Even at the highest proposed dose of HPN-100, PAA levels after HPN-100 dosing are predicted to be similar to an already approved product, BUPHENYL (NaPBA) (Figure 92). Therefore, HPN-100 does not appear to provide an added risk compared to BUPHENYL. PAA levels in the youngest children, however, are expected to be higher than in adolescents or adults. Given the relatively limited data in infants, additional safety information is this population is warranted.

Figure 9: PAA Exposure from Infant to Adults using a BSA Based Dosing Regimen: Highest Labeled Dose

Source: hype-pcs-100, Figure 4.3:4, Page 33.

The proposed starting dose for HPN-100 is based on the (b) (4) observed dose of HPN-100, which was determined by the maintenance dose of Buphenyl for individual patients.
While the current development program is not designed to evaluate the starting dose for Ravicti, the starting dose for pediatric patients with BSA > (b) (4) is not supported by the current data (Table 14). It is rather extrapolated from the dose for adult patients. Discussion about the proposed starting daily dose for patients > 6 years is on-going.

Reviewer's comments: There were 7 Buphenyl® naïve patients in an open label extension study HPN-100-007. The initial dose for HPN-100 was determined by investigators based on the individual need such as disease status, treatment history, a UCD subtype and the recommended Buphenyl dose range. The initial dose ranged from 3.3-19.14 g/day for patients aged from 15 to 57 years. The dose reduction due to toxicity was noted in two adult patients who received 13.86 g/day and 19.14 g/day.

The median prescribed Buphenyl doses in the trials were 8.78 g/m^2/day for adult patients and 9.88 g/m^2/day for pediatric patients. Notably the doses were below the lower end of labeled range; i.e. 9.9 g/m^2/day in patients > 20 kg and 450 mg/kg/day in patients < 20 kg.

Table 10. The observed dose in the clinical trials by Age

Patient Age	N	HPN-100 and NaPBA Total Daily Dose g/d		mg/kg/d		$g/m^2/d$	
HPN-100		**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Ages 6–11 years	7	9.62 (1.211)	9.90	333.58 (86.970)	334.18	9.43 (1.642)	9.69
Ages 12–17 years	4	16.09 (4.203)	17.66	273.85 (87.478)	275.75	10.66 (3.328)	10.78
All pediatric (6–17 years)	11	11.97 (4.103)	9.90	311.86 (87.990)	334.18	9.88 (2.308)	9.69
Ages ≥ 18 years	54	13.46 (5.646)	14.19	192.21 (84.476)	185.01	7.45 (2.974)	7.76
NaPBA		**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Ages 6–11 years	7	9.83 (1.350)	9.50	340.56 (90.477)	341.77	9.63 (1.723)	9.91
Ages 12–17 years	4	16.85 (4.312)	18.45	286.94 (90.591)	287.52	11.17 (3.423)	11.29
All pediatric (6–17 years)	11	12.38 (4.384)	10.50	321.06 (90.031)	341.77	10.19 (2.428)	9.91
Ages ≥ 18 years	56	13.99 (5.974)	14.25	198.69 (88.149)	192.77	7.73 (3.118)	7.69

In 23 pediatric UCD patients (29 days to 5 years of age) receiving maintenance treatment with Ravicti, the median maintenance dose was 7 mL/m^2/day (7.7 g/m^2/day) with a maximum BSA of 0.92 m^2.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the single dose and multiple dose PK parameters?

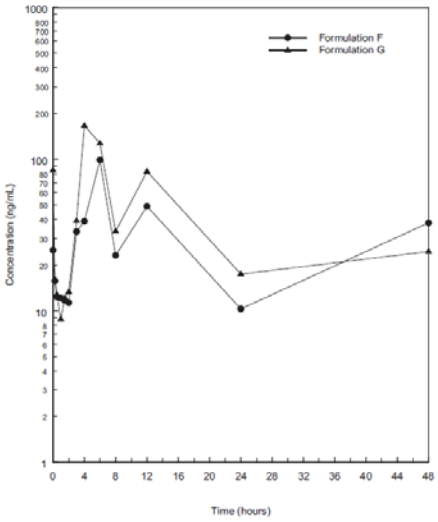
HPN-100

After 7 day treatment of HPN-100 in UCD patients aged 6-17 years, the plasma concentration of HPN-100 was below detection limit at all sampling time points (HPN-100-005). HPN-100 was also below detection limit at all sampling time points in adult UCD (Study UP 1204-003).

Reviewer's comments: *While the results of Study HPN-100-005 were found acceptable, the bioanalytical assay of HPN-100 for Study UP 1204-003 is questionable because the protocol did not specify the addition of acetonitrile to human plasma sample for HPN-100 after collection. The bioanalytical assay report (Y255-0704D) does not mention the addition of acetonitrile at the collection site either. Because the bioanalytical assay validation for HPN-100 including storage stability was conducted in presence of acetonitrile, the omission of acetonitrile invalidates the bioanalytical assay results for Study UP 1204-003.*

On the other hand, in healthy subjects after a single dose administration of 5.9 ml of HPN-100, HPN-100 (GT4P) was detectable (UP 1204-001). The PK profile of HPN-100 was somewhat erratic with several subjects with substantial pre-dose concentrations (Figure 10). The median Tmax was 5 hours which ranged from 0.5 to 48 h while median Cmax was 72 ng/ml and ranged from 12 to 2222 ng/ml.

Figure 10. Mean plasma concentrations of GT4P in healthy male subjects administered single oral doses of GT4P-F (Formulation F) and GT4P-API (Formulation G)



Reviewer's comments: *The sponsor explained the observed discrepancy of HPN-100 PK between healthy subjects and UCD patients by sample contamination at the clinical study site. The bioanalytical assay for HPN-100 was done in acetonitrile because acetonitrile stabilizes HPN-100 in plasma. Accordingly chilled 200 µl acetonitrile was added to 100 µl human plasma samples for HPN-100 analysis at the collection facility before shipping to the bioanalytical site. The sponsor speculated that acetonitrile added at the collection facility was contaminated with HPN-100.*

The sponsor could not provide any direct evidence for this speculation; nonetheless, they referred another study UP-1204-002. In Study UP 1204-002, the protocol was amended not to measure HPN-100 level due to technical difficulties. For UP-1204-002, an analysis letter was submitted, which documented the detection of HPN-100 in acetonitrile provided by the study site. Study UP 1204-002 and UP 1204-001 were conducted at the same site (PI: Igor Zupanets, National University of Pharmacy, Medical Sanitary Division #12, 4 Textylnaya Street, Kharkiv, 61011, Ukraine). If HPN-100 was detected because of the contamination, more consistent plasma concentrations would have been expected since the same volume of acetonitrile was to be added. Therefore the contamination itself is not sufficiently explaining the inconsistent observation about HPN-100 level. Therefore, a lower extent of metabolism of HPN-100 to PBA in healthy subjects in Study UP-1204-001 can not be completely ruled out considering the bioavailability of PBA after HPN-100 administration was only about 20% compared to that after Buphenyl®.

Single dose PK of PBA, PAA, and PAGN in healthy subjects

Following the oral administration of HPN-100, plasma concentrations of PBA were quantifiable in 15 out of 22 participants at the first sample time postdose (0.25 h), indicating rapid absorption and release of PBA. Mean maximum plasma concentrations of PBA were attained at 2 h postdose, followed by a rapid decline, and were below the level of quantification beyond 8 h postdose. PAA levels were quantifiable at 1 h postdose, reached a maximum at 4 h, and

decreased below the limit of quantification beyond 8 h postdose. Mean concentrations of PAGN were higher than those of PAA, were quantifiable at 0.5 h postdose, and reached a maximum at 4 h (Table 11). Mean terminal half-life for PBA, PAA and PAGN was 1.9, 1.4 and 5.9 hours, respectively. The ratio of mean AUCi of PAA and PAGN to PBA is 0.58 and 2.1, respectively.

The AUC for PBA and PAA was 75% and 73% lower after HPN-100 compared to Buphenyl®, respectively. Notably mean AUC and urinary excretion of PAGN over 24 hours was also 18% and 17% lower after HPN-100 and after Buphenyl despite significantly lower bioavailability of PBA after HPN-100 compared to Buphenyl®. The urinary excretion of PAA and PBA was about three orders of magnitude lower than that of PAGN.

Table 11. Mean (SD) PK parameters in healthy male subjects after single dose of Buphenyl® or HPN-100 at a mole equivalent dose to PBA 3 g/m2 (mean BSA 1.94 m2)

	Buphenyl® (n=23)	HPN-100 (n=22)
Mean dose[1]	3.6 g/m^2	2.9 ml/m^2
PBA equivalent dose	3 g/m^2	3 g/m^2
Mean dose (g)	7.04 (0.54)	6.43 (0.49) 5.8 ml
PBA		
Cmax (µg/ml)	221(44)	37.01 (21.74)
Tmax	0.9	2.4
AUCt (µ·h/ml)	538.2 (111.6)	132.2 (80.3)
AUCi (µg·h/ml)	556.9 (n=20)	133.5 (n=12)
$T_{1/2}$ (h)	0.7 (0.1)	1.9 (1.7) (n=12)
PAA		
Cmax (µg/ml)	58.84 (10.37)	14.92 (6.86)
Tmax	3.9	4
AUCt (µ·h/ml)	266 (57.4)	64.08 (32.13)
AUCi (µg·h/ml)	287.9 (n=15)	78.01(31) (n=8)
$T_{1/2}$ (h)	1.2 (0.2)	1.4 (0.23) (n=8)
PAGN		
Cmax (µg/ml)	63.14 (7.14)	30.18 (8.95)
Tmax	3.2	4
AUCt (µ·h/ml)	379.9 (59.4)	278.1 (99.1)
AUCi (µg·h/ml)	388.8 (64.8) (n=20)	317.9 (136.5) (n=8)
$T_{1/2}$ (h)	1.7 (0.5)	5.9 (5.2) (n=8)
Urinary excretion (Ae24)		
PAGN (g)	4.91 (1.41)	4.1(0.9)
PBA (mg)	6.3 (3)	
PAA (mg)	4.7 (2.7)	--

Multiple dose PK of PBA, PAA, and PAGN

The PK of HPN-100 in healthy male subjects after single and multiple doses of 100 mg/kg HPN-100 twice daily. The mean exposure ($AUC_{0\text{-}12}$ and C_{max}) of PBA in plasma was similar after single 100 mg/kg dose and multiple 100 mg/kg BID doses of HPN-100 for 7 days. Consistently with the short apparent half-life for this metabolite, concentrations of PBA at the end of the

dosing intervals (C_{min}) were low (< 1 µg/mL) and similar on both days, showing no accumulation of PBA in plasma in healthy subjects (Table 12). The exposure of the HPN-100 metabolites in plasma after a single dose (Day 1) was similar to that observed after a comparable mean dose of HPN-100 administered in Study UP 1204-001.

During multiple dosing, PAA and PAGN mean predose concentrations in plasma increased initially and then reached a plateau after the first 1–3 days of multiple dosing, indicating that steady state had been reached. The exposure of the metabolite PAA was greater on Day 15 as compared to single-dose levels on Day 1 across.

Urinary PAGN (U-PAGN) excretion was greater after multiple doses of HPN-100 compared with levels observed after a single dose, which is consistent with the increases in plasma PAA and plasma PAGN observed during the first 1–3 days of multiple dosing, after which steady state appeared to have been reached.

After twice daily dosing for 7 days, the systemic exposure to PBA and PAGN increased by 40-50% while approximately 300% increase in the exposure of PAA was observed.

Table 12. Pharmacokinetics of HPN-100 Metabolites in Healthy Subjects after Single and Multiple 100 mg/kg Doses of HPN-100-Study UP 1204-02

Dose	100 mg/kg	100 mg/kg BID[1]	100 mg/kg BID[1]
Mean dose	7.6 g 6.9 ml	7.6 g 6.9 ml	7.6 g 6.9 ml
	Single dose Fasting	Day 8	Day 15
PBA (n=8)			
AUC_{0-12} (µg·h/ml)	105 (83)	98 (64)	113 (48)
AUC_i (µg·h/ml)	141.71 (92.5) (n=5)	--	
Cmax (µg/ml)	27 (22)	30 (22)	30 (14)
Tmax (h)[2]	3 (2,4)	3 (2,4)	3 (2,4)
Accumulation * (AUC)			1.40 (2.07)
PAA (n=8)			
AUC_{0-12} (µg·h/ml)	67 (54)	52 (42)	127 (113)
Cmax (µg/ml)	15 (15)	13 (13)	26 (26)
Tmax (h)*	6 (4,6)	4 (3,6)	4 (3,4)
Accumulation * (AUC)			2.91 (6.13)
PAGN (n=8)			
AUC_{0-12} (µg·h/ml)	247 (93)	220 (58)	342 (88)
Cmax (µg/ml)	36 (12)	34 (8)	46 (15)
Tmax (h)*	6 (4,6)	4 (4, 6)	4 (4, 6)
Accumulation * (AUC)			1.57 (0.81)
Urinary PAGN			
Ae0-48 (g)	4.7 (1.1)		7.6 (2.2)
Fe0-48 (%)	42.2(11.4)		68.6 (21.9)

[1]Subjects received GT4P of a 100 mg/kg dose every 12 hours. On day 15, each subject received a single oral dose of GT4P 100 mg/kg in the morning at 7-8 am after overnight fasting. Subjects were also required to fast (except water) from 10 pm the night before dosing until 4 hours post-dose on day 1 and until after the morning dose on days 8–15. Meals were standardized throughout the study. Breakfast and dinner was served at 10 am and 7 pm according to the meal table. There was 7 day wash-out period between single dose administration and multiple dose administration periods. PK on day 8 was obtained after the first dose of BID dosing and PK on day 15 was obtained after 7 days of dosing.
[2]Median (min, max)
[3]Geometric mean ratio (AUC_{day15}/AUC_{day8})

Reviewer's comments: *The dosing frequency was different from the proposed dosing frequency. During the multiple dose period, subjects were allowed have breakfast after the morning dose. The timing of meal was not specified in the protocol. Based on the meal type table provided later, breakfast was apparently provided 2-3 hours after dosing. As such PK on Day 8 is considered collected under fasting condition.*

2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
The PK of HPN-100 and its metabolites were studied only at steady-state in pediatric and adult UCD patients in comparison to Buphenyl® in four studies.

Similarly in healthy subjects, the systemic exposure to PBA, PAA and PAGN was generally lower in adult UCD patients after HPN-100 than Buphenyl® at the same PBA mole-equivalent dose. Mean systemic exposure of plasma PBA (AUC_{0-24}) was also 15% and 27% lower after HPN-100 compared to Buphenyl treatment in Study UP 1204-003 and HPN-100-060, respectively (Table 13). In healthy subjects, mean systemic exposure of plasma PBA (AUC_i) was 75% lower after administration of HPN-100 compared to NaPBA treatment (Study UP 1204-001). While the differences in study design makes a head-to-head comparison of PK parameters across studies inappropriate, the trend of lower systemic exposure to PBA, PAA and PAGN after HPN-100 than Buphenyl was consistent between in healthy subjects and UCD patients. The urinary excretion of PAGN was similar between treatments.

Reviewer's comments: *In healthy subjects, the intact HPN-100 was detected in plasma suggesting a possibly lower extent of metabolism or absorption of PBA in healthy subjects compared to UCD patients. However because of the questions about the bioanalytical assay validity for HPN-100, the results are considered unreliable. In addition to the wide range of individualized dose for Buphenyl and HPN-100, the study design for PK characterization significantly varies among studies in UCD patients PK sampling interval and frequency. Because of the differences in study design, a cross-study comparison of PK parameters for each product is not considered proper and should be done with a caution.*

Table 13. Mean PK parameters (% CV) in adult UCD patients*

	Study HPN-100-006[1]		Study UP 1204-003[2]	
	HPN-100 (n=44)	Buphenyl® (n=44)	HPN-100 (n=10)	Buphenyl® (n=10)
Median daily dose	13.1 ml (1.2-31.2 ml)	15 g (1.5-36 g)		
Mean daily dose (g)	**12.50 (5.53)**	**12.33 (5.58)**	**12.3 (3.91)**	**12.6 (4.11)**
Median PBA dose	13.2 g(1.3-31.7 g)	13.2 g(1.3-31.7 g)		
PBA				
$C_{max\ ss}$ (µg/ml)	51.9 (67.2)	80.9 (64.9)	70.1 (64.7)	141 (44.3)
$T_{max\ ss}$[3]	10 (0, 20)	8 (2, 16)	6 (2, 12)	2 (0.5, 12)
$C_{min\text{-}ss}$ (µg /mL)	1.44 (201.2)	0.0905 (392.3)	2.87 (265)	0.588 (255)
$AUC_{0\text{-}24}$ (µg·h/ml)	433 (76.6)	508 (72.7)	540 (60.1)	739 (49.2)
CL_{ss} /F (mL/min)	687 (57.6)	685 (92.8)	-	-
PAA				
$C_{max\ ss}$ (µg/ml)	38.5 (102.6)	52.2 (80.2)	40.5 (147.6)	53.0 (94.7)
$T_{max\ ss}$[3]	11 (0, 19)	8 (1, 16)	8 (6, 12)	8 (6, 12)
$C_{min\text{-}ss}$ (µg /mL)	2.11 (381.3)	0.903 (377.7)	7.06 (310.7)	3.56 (194.4)
$AUC_{0\text{-}24}$ (µg·h/ml)	447 (130.4)	599 (91.6)	574.6 (168.9)	595.6 (123.9)
CL_{ss} /F (mL/min)	1136 (109.3)	722 (165.1)	-	-
PAGN				
$C_{max\ ss}$ (µg/ml)	78.6 (55.8)	86.8 (51.5)	71.9 (56)	83.3 (25.8)
$T_{max\ ss}$[3]	10 (0, 20)	8 (2, 16)	8 (4, 12)	7 (5, 12)
$C_{min\text{-}ss}$ (µg /mL)	15.1 (138.1)	9.09 (154.7)	12.1 (134.4)	16.8 (86.1)
$AUC_{0\text{-}24}$ (µg·h/ml)	1127 (61.7)	1252 (57.3)	1098 (44.2)	1133 (31.1)
CL_{ss} /F (mL/min)	346 (37.9)	297 (40.2)	-	-
Urinary excretion (Ae24)				
PAGN (g)	13.5 (52.5)	13.6 (52)	10.8 (25.9)	12.1 (48.2)
Fe % dose	68.7 (25)	71.4 (26)	NA	NA

* Dose of NaPBA was determined by the PI at screening, and the 100% HPN-100 dose-equivalent was calculated as follows: NaPBA dose (g) × 0.95/1.1 = HPN-100 dose (mL). Total daily dose was administered with meals in three divided doses at 0, 4, and 10 hours. PK parameters were determined with continued dosing over 24 hours. Because of the differences in PK sampling scheme, a cross-study comparison for each product should be done with a caution.

[1] HPN-100-006 two sequence crossover study: PK samples were collected at pre-dose and 2, 4, 8, 12, 16, 20, and 24 hours with continued dosing after the morning dose. PK sampling is not frequent enough to accurately describe PK parameters.

[2] UP 1204-003 fixed sequence switch-over study: PK samples were collected at pre-dose and 0.5, 1, 2, 4, 5, 6, 8, 10, 12, and 24 hours post-first dose with continued dosing.

[3] Median (min, max)

2.2.5.4 What are the characteristics of drug absorption?

HPN-100 was not detected in UCD patients aged 6-17 years (UP 1204-003). Nonetheless a question remains whether HPN-100 is completely hydrolyzed prior to the systemic absorption due to the issues about bioanalytical assays in adult UCD patients (Study HPN-100-005) and in healthy subjects (Study UP 1204-001). Intact HPN-100 was not measured in other studies including the pivotal study HPN-100-006 and HPN-100-012.

In healthy fasting adult subjects receiving a single oral dose of Ravicti containing $3 g/m^2$ of PBA, peak plasma levels of PBA, PAA and PAGN occurred at 2 h, 4 h and 4 h, respectively. Peak plasma levels of PBA, PAA and PAGN following multiple dosing (100 mg/kg BID) in healthy

subjects occurred at 3, 4 and 4 h, respectively. Urinary excretion of PAGN a final product for nitrogen elimination was 40% of dose after single dose administration and about 70% after multiple doses in healthy subjects.

2.2.5.5 What are the characteristics of drug distribution?

In vitro, the extent of plasma protein binding for ^{14}C- labeled metabolites was measured using ultrafiltration. The protein binding was moderate to high for PBA (80.6% to 98.0% over the concentration range 1 – 250 µg/mL), low to moderate for PAA (37.1% to 65.6% over the concentration range 5 – 500 µg/mL) and low for PAGN and no concentration effects noted (7.3-12 % over the concentration range 1-250 µg/mL) (Table 14).

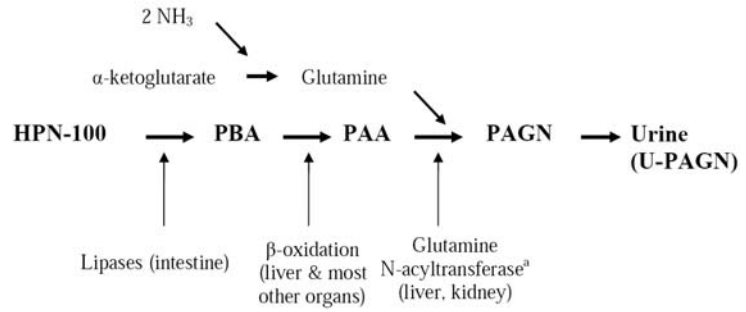
Table 14. Summary of mean plasma protein binding (%) of C^{14}-labeled PBA, PAA and PAGN

Concentration (µg/mL)	Species				
	Mouse	Rat	Rabbit	Cynomolgus monkey	Human
PBA					
1	87.9	-		98.0	98.0
2	-	-	97.8	-	-
5	87.3	93.5	98.3	97.9	97.4
10	-	-	98.2	-	-
25	83.2	88.9	97.8	97.2	97.7
50	-	-	95.8	-	-
100	70.0	72.2	-	90.6	92.3
250	57.3	56.8	-	75.4	80.6
1000	-	34.4	-	-	-
PAA					
5	15.2	26.5	76.4	46.1	65.6
25	11.7	25.7	74.8	44.7	64.2
100	13.4	21.1	69.8	38.0	57.1
250	12.8	19.1	56.2	33.2	45.8
500	-	-	-	-	37.1
1000	6.6	11.2	27.4	18.4	-
PAGN					
1	-	1.3	-	3.6	7.3
2.5	-	5.7	-	-	-
5	-	5.9	-	7.2	8.7
25	-	-	-	3.5	8.7
100	-	-	-	6.7	12.0
250	-	-	-	4.8	9.5

2.2.5.7 What are the characteristics of drug metabolism and excretion?

Upon oral administration, hydrolysis of HPN-100 releases PBA, and PBA further undergoes β-oxidation to form PAA. The active moiety PAA is conjugated with glutamine to form PAGN which is excreted in urine. PBA which could be formed in the intestine or in the systemic circulation undergoes β-oxidation to PAA which is conjugated with glutamine in the liver and kidney through the enzyme phenylacetyl-CoA: L-glutamine-N-acetyltransferase to form PAGN, which is subsequently eliminated in the urine. Because the synthesis of each molecule of glutamine requires two nitrogen molecules, the body excretes two nitrogen molecules with each molecule of PAGN. This is the same stoichiometry as for urea, each molecule of which also contains two nitrogen molecules. (Figure 11)

Figure 2.5-1: Biotransformation of HPN-100 (glycerol phenylbutyrate)



NH3 = ammonia; PAA = phenylacetic acid; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; U-PAGN = urinary phenylacetylglutamine.
[a] This conversion likely involves more than one enzyme present in liver and kidney (Moldave 1957)

Figure 11. Biotransformation of glycerol phenylbutyrate

Hydrolysis by lipase

In vitro, HPN-100 is hydrolyzed by lipases such as pancreatic triglyceride lipase (PTL), carboxyl ester lipase (CEL) and pancreatic lipase related protein 2 (PLRP2). The specific activity was determined by µmole fatty acid released/min/mg protein or Units/mg. The specific activity for HPN-100 was in order of PTL (~600 Units/mg), CEL (250 Units/mg) and PLRP2 (22 Units/mg) suggesting potentially predominant role of PTL and of CEL to a lesser degree, in hydrolysis of HPN-100 (Table 15).

Table 15. Lipase Activity for HPN-100*

Lipase	Bile Acid/Salt	Mean Units/mg Lipase	
		With Colipase	Without Colipase
PTL (3 µg)	NaTDC (0.5 mM)	618	342
PLRP2 (20 µg)		35	32.2
PTL (3 µg)	NaTDC (4 mM)	592	42
PLRP2 (20 µg)		22	10.8
CEL (10 µg)	NaCholate (10 mM)	249	

CEL = carboxyl ester lipase; GPB = glycerol phenylbutyrate; NaCholate = sodium cholate; NaTDC = sodium taurodeoxycholate; PLRP2 = pancreatic lipase related protein 2; PTL = pancreatic triglyceride lipase.
* µmol fatty acid released/min/mg protein or Units/mg

Reviewer's comments: PTL likely makes a dominant contribution to the absorption of HPN-100 in adults, but is lacking during the early neonatal period [6]. Since PLRP2 and perhaps CEL[7] are both believed to play an important role in digestion of fats during the neonatal period and prior to developmental expression of PTL, the present findings suggest that the combined activities of PLRP2 and CEL might also digest HPN-100 in newborns. In Study HPN-100-012, two patients younger than one year old (2 and 11 months old) were HPN-100. Plasma concentration for PBA was available only from 11 months old. In the 2-month old patient PAA was detected at one time point after administration of Ravicti. In both patients plasma ammonia levels were

[6] Lindquist and Hernell (2010) Lipid digestion and absorption in early life: an update, Curr Opin Clin Nutr Metab Care 13:314-320
[7] Carboxyl ester lipase is also known as bile-salt dependent lipase and its activity is dependent on bile salts. Carboxyl ester lipase is secreted in human milk.

maintained after 7 days of treatment with HPN-100 following switching from Buphenyl. HPN-100 was not studied in neonates with UCD.

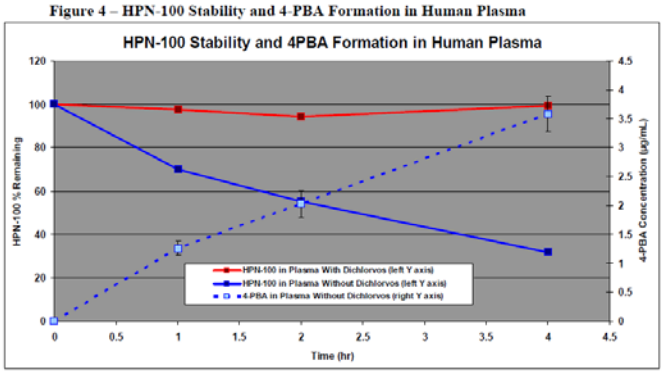
PTL converts triglyceride substrates found in ingested oils to monoglycerides and free fatty acids. In principle, hydrolysis of HPN-100 by pancreatic lipases can produce mono-ester intermediate and bis-ester intermediates also can be formed by other lipases. In vitro hydrolysis studies by lipases, the complete disappearance of HPN-100 did not produce 3 molar equivalent PBA suggesting the formation of intermediates. The pharmacokinetics of mono- or bis-ester intermediates was not studied in humans based on the non-detectable plasma level of mono- or bis-ester intermediates in animals.

Reviewer's comments: *The possibility of formation of mono- and bis-esters in humans can not be completely ruled out in humans. In non-clinical studies, mono- and bi-esters were not detected in plasma or urine of* ***rats****. However, mono- and bis-esters products of HPN-100 as well as HPN-100 were detected in urine of a monkey. The sponsor explained that this observation is likely due to contamination because HPN-100 and its mono- and bis-esters intermediates were not detected in most plasma samples. Although the plasma level of mono- and bis-ester intermediates may be too low to detect in plasma, urinary excretion of mono- and bis-esters in monkey should not be dismissed based on their non-detectable plasma levels.*

Hydrolysis by esterases

HPN-100 was hydrolyzed in human plasma in vitro and an esterase inhibitor (dichlorvos) completely prevented hydrolysis in the plasma, indicating that the degradation in plasma could be attributed to the esterase family (Figure 12).

Figure 12. HPN-100 stability and PBA formation in human plasma



2.2.5.9 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose proportionality of PBA was assessed in the thorough QT study.

After single dose and multiple doses of HPN-100, the systemic exposure to PBA, PAA and PAGN increases with an increase in dose. The HPN-100 was not measured in the thorough QT study (HPN-100-010). After single administration of 9 ml and 12 ml with a meal i.e. first dose of three repeated doses on a single day, a greater than dose-proportional increase in the systemic

exposure to PBA, PAA and PAGN was observed. Mean AUC for PBA, PAA and PAGN was about 2.2, 3.4 and 1.5 fold higher when dose was increased by 1.5 fold from 9 ml to 12 ml. Because of insufficient PK sampling, AUC of PAA and PAGN is likely underestimated. In addition, the number of subjects was too small (n=4) to draw a definitive conclusion (Table 16).

Table 16. Mean (SD) PK parameters after single dose administration (after the first dose during three times a day dosing for one day)

	9 ml (n=4)	12 ml (n=4)
Dose	9.9 g	13.2g
PBA equivalent dose	9.18 g	12.24 g
PBA		
Cmax (µg/ml)	85 (37.4)	184 (83.5)
Tmax	1.25 (1, 3)	1.50 (1, 1.5)
AUC_{0-8} (µg·h/ml)	269 (105)	589 (350)
AUCi (µg·h/ml)	273 (108)	453 (230) (n=3)
$T_{1/2}$ (h)	1.02 (0.215)	1.49 (0.554)
PAA		
Cmax (µg/ml)	22.8 (7.28)	68.2 (23.0)
Tmax	3.50 (2, 6)	5.00 (4, 6)
AUC_{0-8} (µg·h/ml)	106 (41.4)	363 (147)
PAGN		
Cmax (µg/ml)	48.4 (12.3)	66.7 (11.7)
Tmax	4 (2, 7.83)	4 (3, 7.85)
AUC_{0-8} (µg·h/ml)	244 (66.3)	371 (73.2)

After multiple doses (7 doses), mean Cmax and AUC of PBA, PAA and PAGN was about 1.5, 2.3, and 1.6 fold higher when the dose was increased by 1.5 fold from 4 ml to 6 ml (Table 17). On the other hand, the assessment of dose-proportionality at doses higher than 6 ml is limited by a significant difference in the sample size between dose groups as data is available from 5 patients for 9 ml dose group. The urinary excretion of PAGN over 72 hours was about 60% and 49% of the administered dose for 4 ml and 6 ml dose groups, respectively.

In UCD patients, the urinary excretion of PAGN tended to be higher e.g. about 70% of the dose at steady-state than in healthy subjects.
The apparent higher urinary excretion of PAGN may be due to the difference in glutamine concentration between healthy subjects and UCD patients. The elevated plasma glutamine level was observed in patients with elevated blood ammonia level[8][9] than in healthy subjects whose physiological pathways for excretion of waste nitrogen function normally. The observed mean

[8] Maestri et al. (1992) Plasma glutamine concentrations: A guide in the management of urea cycle disorders, J. Pediatr, 121: 259

[9] Ammonia also circulates in the body as free ammonia or within glutamine which functions as a temporary "repository" for ammonia. Consequently, in a urea cycle defect not only does free ammonia rise (hyperammonemia) but glutamine is also elevated.

(SD) glutamine concentration was 541 (822), 608 (69), 607 (97) and 485 (213) µmol/L in healthy subjects, and subjects with hepatic impairment in Child-Pugh A, B, C class, respectively.

Table 17. Mean (SD) parameters after multiple doses (TID for 3 days) in healthy subjects

		4 ml (n=66)	6 ml (n=69)	9 ml (n=5)
PBA equivalent dose (g)		4.4	6.6	9.9
Daily Dose (g)		13.2	19.8	29.7
PBA				
Cmax (µg/ml)		66.3 (26.3)	99.9 (35.3)	46.8 (10.5)
Tmax		2.58 (1.08, 6.22)	6.08 (1.12, 8.00)	3.08 (3.08, 6.08)
AUC_{0-23} (µg·h/ml)[1]		930 (225) (n=15)	1399 (458) (n=40)	941 (210)
PAA				
Cmax (µg/ml)		28.2 (12.5)	65.3 (46.3)	74.9 (19.5)
Tmax		4.08 (2.08, 6.13)	6.08 (0.583, 8.08)	6.08 (2.13, 6.10)
AUC_{0-23} (µg·h/ml) [1]		942 (381) (n=25)	2064 (1322) (n=60)	3684 (1722)
PAGN				
Cmax (µg/ml)		46.8 (10.5)	74.9 (19.5)	115 (26.1)
Tmax		4.08 (2.08, 6.13)	6.08 (2.58, 8.12)	6.08 (4.08, 6.08)
AUC_{0-23} (µg·h/ml) [1]		941 (210) (n=65)	1642 (429) (n=68)	2298 (331)
Urinary excretion				
PAA	Ae (0-72) (**mg**)	12.0 (9.24)	25.3 (18.8)	38.0 (17.8)
	fe (%)	0.0365 (0.0281)	0.0512 (0.0380)	0.0513 (0.0241)
PAGN	Ae (0-72) (g)	38.146 (5.716)	46.839 (10.959)	49.292 (9.607)
	fe (%)	59.8 (8.97)	49.0 (11.5)	34.4 (6.70)

[1] Mean AUC_{0-23} (µg·h/ml) was estimated with concomitant TID dosing (HPN-100-010). The dose was administered with a meal at 0, 5, and 10 hr after the first dose. The PK samples were collected at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23 hours post-dose. Because the sampling frequency is not consistent among each dosing period, the calculated AUC_{0-23} is likely under/overestimated and should be referred only in the context of comparison under this study condition.

2.3 Intrinsic Factors

2.3.1 What is the effect of age on PK of PAA and what is the impact of any differences in exposure on safety responses?

Modeling and simulations suggest that PAA Cmax would be below 500 µg/ml in most pediatric patients at the highest dose and it would be comparable between Buphenyl and HPN-100 treatments (Table 18). Please see the Pharmacometrics Review for more details.

Table 18. PAA Exposure from Infant to Adults using a BSA Based Dosing Regimen:

Labeled High Dose (13g/m^2) and a Low Dose (4.98g/m^2)

	HPN-100 (4.98 g/m2/day)									NaPBA (4.98 g/m2/day)								
	Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)			Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)		
	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%
0-2	1.67	1.32	2.01	29	15	79	233	156	412	1.67	1.31	2.01	35	16	132	250	160	505
3-5	2.94	2.41	3.46	27	15	75	221	149	382	2.93	2.4	3.45	34	16	129	244	157	493
6-11	4.61	3.61	5.90	25	13	69	203	137	344	4.6	3.606	5.88	33	16	125	237	152	476
12-18	7.35	6.16	8.08	22	12	59	181	124	301	7.34	6.142	8.07	32	15	119	225	146	451
Adult	8.84	8.45	9.23	22	12	57	175	115	286	8.83	8.43	9.23	34	16	123	238	146	484
	HPN-100 (13 g/m2/day)									NaPBA (13 g/m2/day)								
	Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)			Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)		
	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%
0-2	4.36	3.45	5.25	163	66	707	1335	679	4852	4.35	3.42	5.232	194	74	921	1534	720	5725
3-5	12.04	9.42	15.398	126	54	489	1038	553	3275	12.02	9.41	15.36	175	68	821	1384	660	4977
6-11	17.62	16.07	17.62	89	39	342	723	392	2005	17.6	16.04	17.6	138	53	615	1047	504	3404
12-18	7.66	6.28	9.033	146	61	597	1201	623	4048	7.63	6.27	9.01	186	71	867	1469	691	5418
Adult	17.62	17.62	17.62	59	28	180	483	284	1034	17.6	17.6	17.6	103	42	459	755	387	2206

Source: hype-pcs-100, Table 4.3:5, Page 35.

Please see Tables 4.2.1 and 4.2.2. in Appendix 4.2. for individual PK for PBA and PAA by non-compartmental analysis in pediatric patients aged 6-17 years.

In this development program, the highest observed PAA plasma concentration in UCD patient was 480 µg/ml was observed in one year old patient with ASS after administration of HPN-100 at 12.5 g/m^2 given in four divided doses (HPN-100-012). On the other hand, 529 µg/ml was the highest observed plasma concentration in 2 month-old patient with ASS after administration at daily dose of 8 g/m^2 Buphenyl given in four divided doses. Plasma concentrations after switching to HPN-100 could not be measured until at 24 hours for this 2 month-old patient. (Tables 19, 20)

Table 19. Plasma PAA levels (µg/ml) and plasma PAA/PAGN ratio in patients younger than 1 year old with PAA level higher than 400 µg/ml

Subject	05-1209 (2 month old, ASS) (QID)				05-1210 (1 year old, ASS) (QID)			
	Buphenyl	Ratio	HPN-100	Ratio	Buphenyl	Ratio	HPN-100	Ratio
Dose	500 mg/kg (9.4 g/m^2)				583 mg/kg (14.3 g/m^2)			
PBA equivalent dose (g/m^2)	8.27		8.18		12.57		13.1	
0 h	NS	-	NS	-	264.7	2.3	378.8	2.6
8 h	529.98	5.5	NS	-	286	3.2	480	3.5
12 h	520.2	5.7	NS	-	148	2.2	353.8	2.6
24 h	279.95	3.2	164.1	2.1	137	2.1	289.9	2.4

NS: no sample

Reviewer's comments: *Because of the infrequent PK sampling, the observed peak plasma concentration could be underestimated. The daily dose for these two patients was higher than the mean dose in patients < 6 years old i.e. 7.1 g/m^2 (median 7.7 g/m^2). The sustained high plasma concentration of PAA in these patients is likely attributed to the high dose for their intrinsic conjugation capability for PAA.*

Plasma concentrations of PAA in two other patients younger than 2 year old were lower than 100 µg/ml after daily dose of 6.5 g/m^2 HPN-100.

Table 20. Plasma PAA levels (µg/ml) in patients younger than 1 year old

Subject	11-1211 (11 mo, ASL) (in five doses)		16-1215 (1 year old, ARG) (TID)	
	Buphenyl	HPN-100	Buphenyl	HPN-100
PBA equivalent dose (g/m^2)	5.93	6.24	6.89	6.6
0 h	NS	BLQ	BLQ	1.4
8 h	14.1	7.7	76.8	99.3
12 h	NS	NS	4.5	41.4
24 h	BLQ	BLQ	BLQ	2.1

NS: no sample

2.3.2.5 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Ravicti and its metabolites was not studied.

2.3.2.6 Hepatic Impairment

The effects of hepatic impairment on the PK of PBA, PAA and PAGN were studied after administration of HPN-100 as a single dose, and twice daily for seven consecutive days to subjects with hepatic impairment with cirrhosis and to a control group.

In adult patients with liver cirrhosis (Child-Pugh groups A, B, and C) receiving 100 mg/kg HPN-100 BID dosing for seven days, the mean peak (C_{max}) PAA levels in the Child-Pugh A, B, and C cirrhotic patients ranged from 30.8–53.1 µg/mL, and the maximum peak PAA level observed for any cirrhotic patient was 208.8 µg/mL in the Child-Pugh C group (Table 21).

After single dose administration, the mean urinary excretion of PAGN was comparable regardless of degree of hepatic impairment. Patients with hepatic impairment Child-Pugh C had greater amounts of PBA and PAA excreted in the urine compared to the other groups; however, PBA and PAA in all patients accounted for < 1% of PBA administered.

Table 21. Geometric mean PK parameters (CV%) after the first dose and repeated dosing of 100 mg/kg for 7 days (BID)

	Healthy subjects (n=8)		Child-Pugh A (n=8)		Child-Pugh B (n=8)		Child-Pugh C (n=8)	
Day	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
PBA								
Cmax (µg/ml)	22.87 (72)	26.24 (47.5)	32.19 (49.9)	37.15 (59.6)	48.78 (73.39)	35.50 (62.67)	46.82 (60.28)	39.29 (48.50)
AUC_{0-12} (µg·h/ml)[1]	74.05 (65)	103.64 (42.1)	98.27 (63.5)	112.08 (54.2)	184.73 (59.09)	144.22 (73.13)	187.89 (63.71)	171.90 (43.16)
PAA								
Cmax (µg/ml)	10.03 (66.97	21.92 (62.88)	10.21 (62.25)	29.07 (44.21)	14.78 (74.53)	25.46 (64.26)	16.03 (72.29)	33.28 (121.51)
AUC_{0-12} (µg·h/ml)[1]	34.07 (80.59	99.16 (88.59)	39.64 (78.73)	117.89 (76.82	73.44 (85.58)	138.95 (99.48)	86.36 (92.85)	184.26 (170.56)
PAGN								
Cmax (µg/ml)	32.59 (24.50)	44.33 (32.57)	27.34 (57.03)	36.81 (24.77)	30.66 (41.05)	35.87 (39.90)	31.81 (26.36)	39.85 (35.44)
AUC_{0-12} (µg·h/ml)[1]	212.17 (26.55)	332.60 (25.79	181.50 (54.13)	241.23 (37.85)	204.56 (37.55)	272.53 (60.66)	222.88 (33.73)	310.70 (50.84)
Urinary excretion of PAGN after a single dose								
Molar % (SD) of dose excreted over 48 h	42.2 (11.4)		47.1 (10.4)		44.9 (9.7)		48.5 (29.4)	
range	32.6–66.7		25.4–55.1		30.4–60.6		17.0–100.2	

Reviewer's comments: The dosing frequency studied in Study UP 1204-002 i.e. BID is different from the proposed dosing frequency i.e. TID. After multiple dose administration, mean molar % of dose urinary excretion of PAGN was 68.6, 79.6, 58.2 and 85% in healthy subjects, patients with hepatic impairment of class Child-Pugh A, B, and C, respectively. While the greater degree of accumulation of plasma PAA was observed in patients with hepatic impairment (Table 22), the nitrogen scavenger effect based on urinary excretion of PAGN was not reduced in patients with hepatic impairment.

Table 22. Geometric mean ratios (cirrhotic subjects versus healthy volunteers): AUC_{0-t} and C_{max} of PAA on day 15

Analyte	Subject group	GM ratio	90% CI	P value for group effect
PAA	**AUC_{0-t}**			0.64
	Child-Pugh A	1.22	0.48–3.06	
	Child-Pugh B	1.53	0.61–3.85	
	Child-Pugh C	1.94	0.77–4.88	
PAA	**C_{max}**			0.72
	Child-Pugh A	1.33	0.70–2.52	
	Child-Pugh B	1.16	0.61–2.20	
	Child-Pugh C	1.52	0.80–2.88	

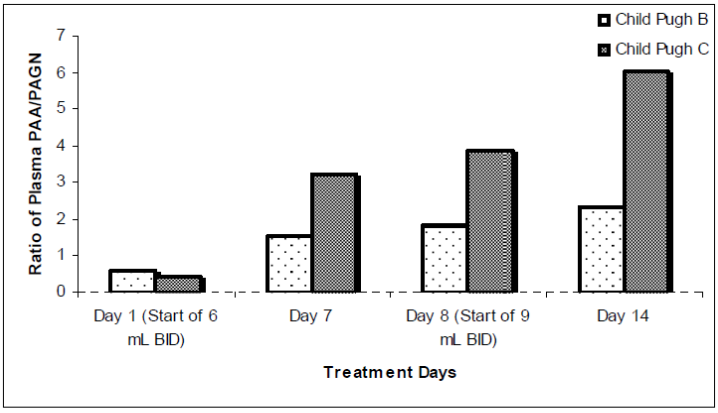
Source: Tables 14.2.1.26 and 14.2.1.27

The sponsor also provided PK in patients with clinically decompensated cirrhosis (Child-Pugh B and C) with episodic HE (HPN-100-008). Mean doses of HPN-100 administered in Study HPN-100-008 were 13.2 and 19.8 g. During 6 mL BID dosing, peak PAA levels ranged from 13.5 to 358.0 µg/mL, with a mean C_{max} PAA of 143.51 µg/mL. For patients administered 9 mL BID dosing, peak PAA levels ranged from 56.9 to 654.6 µg/mL, with a mean C_{max} PAA of 291.90 µg/mL.

Reviewer's comments: While the dosage regimen and the target patient population is different from the current proposal i.e. [redacted] (b) (4), the total daily dose used in Study HPN-100-008 is comparable to the proposed upper limit of the dose for UCD patients i.e. 17 g/day. The systemic exposure to PAA in this study may reflect the potential worst scenario for UCD patients who have severe hepatic impairment and were administered with high doses.

The saturation in the conversion of PAA to PAGN was suggested by an increased ratio of PAA/PAGN after multiple doses in these Child-Pugh B and C patients who received HPN-100 in high doses (Figure 13).

Figure 13. HPN-100-008 Part A: Ratio of Plasma PAA/PAGN by Child-Pugh Class



Source: HPN-100-008 Part A: Listings 20 and 26. BID = twice daily; PAA = phenylacetate; PAGN = phenylacetylglutamine.
Note: The ratio reflects the mean of all available plasma PAA:PAGN ratios at all time points on a given day for all patients who had visits on that day.

2.3.2.7 How does gender affect the PK?

Gender-based effects were noted for all metabolites, with females having higher plasma concentrations, in general, compared to males. Mean DN-C_{max} for PBA was approximately 24% higher for females (treatments combined). In the 4 mL TID group, mean DNAUC$_{0-23}$ for PBA did not differ significantly; however, it was approximately 36% higher in females in the 6 mL TID group. Mean DN-C_{max} of PAA was approximately 51% higher in females in the 4 mL TID group and approximately 120% higher in the 6 mL TID group. Mean DN-AUC$_{0-23}$ for PAA was approximately 108% higher in females (treatments combined). For PAGN, mean DN-C_{max} was approximately 17% higher and mean DNAUC$_{0-23}$ approximately 21% higher in females in the 6 mL group. In addition, the amount of PAGN excreted in urine was approximately 14% lower in females than in males (Table 23). The analyses did not account for differences in gender related to body size. The similar gender effect was also noted for Buphenyl (Buphenyl Labeling).

Table 23. Mean ratio of the dose-normalized systemic exposure by gender

Analyte	Parameter[a]	Units	Least-Squares Means[b]				Test/Reference Ratio (%)[c]	90% Confidence Interval (%)[d]
			N	Female (Test)	N	Male (Reference)		
PBA	DN-C_{max}	µg/mL/mg	55	17.2	71	13.9	124	(107.34, 142.43)
PAA	DN-AUC_{0-23}	µg·h/mL/mg	39	329	37	159	208	(169.16, 255.07)
PAGN	DN-Ae	1	55	7703	72	8955	86.0	(79.41, 93.20)

Source: HPN-100-010: Table 11-9 (Table 14.2.3-1)

2.3.2.8. What was the dose for different UCD subtype?

Urea Cycle Disorder is caused by genetic mutations on enzymes that are involved in urea cycle to eliminate nitrogen from body. The diagnosis for majority not all of patients was done by genotyping and for some biochemical analysis was performed for diagnosis. In clinical trials, there was unbalanced distribution of subtype of UCD by age. For example, while OTC is predominant in patients older than 6 years, ASS and ASL were predominant in children younger than 6 years old (12/15) (Table 24). In clinical practice, a severity of disease which may be related to the on-set time of the disease and subtype of UCD is taken into account when the dose of Buphenyl was determined by physicians.

Reviewer's comments: *Currently Buphenyl is indicated only for patients with OTC, ASS and CPS1 deficiency but not for ASL, ARG and HHH deficiency. The distribution of total daily dose was similar regardless of the age at UCD onset. The BSA normalized dose tended to be lower for patients with ASL than for patients with OTC or ASS within the same age group in the study. Due to the small number of patients for subtypes other than OTC, a definitive conclusion can not be drawn on the dose for each UCD subtype. In addition, the residual enzyme or transporter activities resulting from specific genotypes within a UCD subtype can be more critical than the UCD subtype in determining the dose.*

Table 24. Mean total daily dose (g/m^2; min, max) by UCD subtype

	Age			
Study	HPN-100-012	HPN-100-005	UP-1204-003	HPN-100-006
Subtype	> 28 day, < 6 yr	> 6 yr,< 17 yr	> 18 yr	> 18 yr
OTC	8.78 (6.9-11.5) (n=3)	10 (6.9-14.4) (n=9)	7 (4.9-9.9) (n=8)	7.6 (0.7-15.4) (n=40)
ASL	6.84 (1.5-10.1) (n=8)	6.7 (n=1)		
ASS	11.6 (9.3-14.1) (n=3)	11.3 (n=1)	8.2 (n=1)	5.7 (2.6-7.9) (n=3)
ARG	7.17 (n=1)			
CPS I				10.9 (n=1)
HHH			6.14 (n=1)	

Source: modified from Table AH3. 1.4 from the amendment dated 8/27/12

2.4 Extrinsic Factors

2.4.1 What other factors can influence the efficacy of the drug?

Pharmacotherapy for UCD is accompanied by strict dietary control for protein intake. Hyperammonemia can be precipitated by other factors such as a change in protein intake, infection and dehydration.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

In vitro studies suggest that HPN-100 may reduce the metabolism of concomitant medications that are substrates of CYP2C9, CYP3A4/5 and CYP2C19. No in vivo studies were conducted to confirm the prediction. It should be noted that the dose and consequently the systemic exposure to PBA is highly variable due to individualized therapy. Therefore, the potential of in vivo drug interaction predicted based on the mean plasma concentration resulted from a wide range of doses may not be applicable to all individuals. Nevertheless, further evaluation of in vivo drug interaction potential is warranted.

2.4.2.2 Is the drug a substrate of CYP enzymes?

No. HPN-100 is mainly hydrolyzed by lipases in the intestine and esterases in plasma. HPN-100 also metabolized in human liver and intestinal microsomes. The hydrolysis of HPN-100 in human liver microsomes was completed abolished by an esterase inhibitor suggesting that esterases are mainly responsible for HPN-100 hydrolysis. Major metabolites of HPN-100, PBA are converted to PAA via beta-oxidation in mitochondria. Therefore, a contribution of CYP enzymes in metabolism of HPN-100 and its metabolites is insignificant.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Effects of PBA and PAA on the CYP enzymes were studied using cultured human hepatocytes for the induction of CYP1A2 and CYP3A4 and using human liver microsomes for the inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. The sponsor stated that the potential effects of HPN-100 on induction of CYP enzymes could not be studied due to its limited solubility while the inhibitory effects of HPN-100 on CYP enzymes were studied.

CYP induction

In vitro studies suggest that it is unlikely that PBA and PAA induce CYP1A2 and CYP3A4 in vivo. The levels of induction of CYP1A2 and CYP3A4/5 after treatment with up to 8.6 mM PBA or up to 20.7 mM PAA were low compared to those of the positive controls (omeprazole or rifampicin, respectively) (Table 25). There was minimal induction (<1.6-fold) of CYP1A2 by either PBA or PAA in cultured human hepatocytes. A control inducer omeprazole at 100 mM induced CYP1A2 activity by 4-9 fold.

Table 25.

Effect of PBA and PAA treatment on CYP1A2 induction				
Hepatocyte donor	**PBA (mM)***	**Fold induction**	**Relative potency (%)**	**Omeprazole (fold induction)**
Hu0999 8.	6	1.1	1.8	8.7
Hu4156 2.	87	1.2	4.3	4.6
Hu4199 2.	87	1.2	2.1	8.8
Hepatocyte donor	**PAA (mM)***	**Fold induction**	**Relative potency (%)**	**Omeprazole (fold induction)**
Hu0999 20	.7	1.3	5.8	6.3
Hu4156 20	.7	1.2	5.8	4.5
Hu4199 20	.7	1.5	6.6	9.0

* Concentration at which maximum fold induction and relative potency occurred

There was minimal induction of CYP3A4/5 by PBA in cultured human hepatocytes from 2 of the 3 donors under the conditions of this study. In the third donor there was >2-fold induction of CYP3A4/5 by PBA (at concentrations of 2.87 and 8.6 mM). However, the induction of CYP3A4/5 by PBA in this donor was not concentration-dependent and the extent of induction was about 50% lower compared to the positive control (rifampicin).

There was minimal induction (<1.8-fold) of CYP3A4/5 by PAA in cultured human hepatocytes under the conditions of this study. The effects were not concentration-dependent in every case and there was inter-individual variability in response (Table 25).

Table 26. Effect of PBA and PAA treatment on CYP3A4/5 induction

Hepatocyte donor	**PBA (mM)***	**Fold induction**	**Relative potency (%)**	**Rifampicin (fold induction)**
Hu0999 2.	87	1.3	5.8	5.6
Hu4156 8.	6	1.2	2.1	9.1
Hu0793 2.	87	2.3	30.8	5.1
Hepatocyte donor	**PAA (mM)***	**Fold induction**	**Relative potency (%)**	**Rifampicin (fold induction)**
Hu0999 6.	9	1.6	11.1	6.5
Hu4156 20	.7	1.7	18.2	5.1
Hu0793 20	.7	1.4	13.1	4.3

* Concentration at which maximum fold induction and relative potency occurred

Reviewer's comments: *The plasma concentration of intact HPN-100 was not measurable in UCD patients.*

CYP inhibition

The potential inhibitory effects of HPN-100, PBA and PAA on CYP enzymes were studied in vitro. HPN-100 and PBA, both at a final concentration of 5 mM, and PAA, at a final concentration of 20.7 mM were incubated with pooled human liver microsomes and NADPH at 37ºC (30°C for CYP1A2 assay) for either 0 or 30 minutes, prior to the addition of one of a range of substrates, each a probe for one specific or two closely related CYP enzymes. In vitro HPN-100 is not a reversible inhibitor of human CYP enzymes. Neither HPN-100, PBA nor PAA is a time-dependent inhibitor of human CYP *in vitro*.

On the other hand, in vitro studies suggest that PBA is a reversible inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 while PBA (5 mM (0.821 mg/ml)) did not inhibit CYP1A2, CYP2C8, CYP2C19 or CYP3A4/5 (midazolam 1'-hydroxylase) (Table 26).
. The inhibition constant, K_i calculated for CYP2C9 and CYP2D6 was 1.3 mM and 1.5 mM, respectively (approximately 0.2 mg/ml for both) and calculation of [I]/K_i ratios were greater than 0.1 suggesting a 'possible' *in vivo* interaction of PBA with CYP2C9 and CYP2D6 (Table 27).

For the inhibition of CYP3A4/5, IC_{50} was calculated for PBA instead of K_i because of allosteric kinetics characteristics of the reversible inhibition of CYP3A4/5 (testosterone 6-hydroxylase activity). Calculation of [I]/IC_{50} ratio was greater than 0.1 at all testosterone concentrations suggesting a 'possible' *in vivo* interaction of PBA with CYP3A.

PAA inhibited CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 at 20.7 mM (Table 27). Based on the initial study result, Ki was further calculated for a representative CYP enzyme, i.e. CYP2C9. The inhibitor constant, K_i calculated for CYP2C9 was 15.1 mM (approximately 2.056 mg/ml) and calculation of [I]/K_i ratio was < 0.1 based on mean peak PAA concentration in UCD patients (Table28). The [I]/K_i ratio was 0.185 in Cirrhotic-HE patients at 9 ml BID.

***Reviewer's comments**: It is unclear why CYP2C9 was chosen for further investigation while higher degree of inhibition was observed for other enzymes such as CYP1A2 and CYP3A4.*

Table 27. In vitro CYP inhibition study

CYP	Activity	% Inhibition							
		Selective Inhibitor†	HPN-100 (5 mM, 2.65 mg/ml)		PBA (5 mM, 0.821 mg/ml)		Selective Inhibitor‡	PAA (20.7 mM, 2.818 mg/ml)	
			Pre-incubation time (min)		Pre-incubation time (min)			Pre-incubation time (min)	
			0	30	0	30		0	30
CYP1A2	7-Ethoxyresorufin *O*-deethylase	87	5	8	6	2	87	58	47
CYP2C8	Taxol 6α-hydroxylase	35	11	10	24	27	39	50	49
CYP2C9	Diclofenac 4'-hydroxylase	96	35	19	68	72	97	47	44
CYP2C19	*S*-Mephenytoin 4'-hydroxylase	79	8	7	26	19	72	37	37
CYP2D6	Bufuralol 1'-hydroxylase	61	1	4	64	63	73	49	57
CYP3A4/5	Testosterone 6β-hydroxylase	98	15	6	80	85	96	60	63
CYP3A4/5	Midazolam 1'-hydroxylase	97	19	24	2	-13	97	63	65

- Preceding a number indicates negative inhibition
† For HPN-100 and PBA incubations
‡ For PAA incubations

Table 28. [I]/K_i and [I]/IC_{50} ratios for CYP2C9, CYP2D6 and CYP3A4/5 in different patient populations - PBA

	PBA	[I]/Ki	[I]/Ki	[I]/IC_{50}[3]
	Mean peak concentration (mg/ml)	CYP2C9 (Ki= 0.212 mg/ml)	CYP2D6 (Ki=0.243 mg/ml)	CYP3A4/5 IC_{50} (0.294-0.535 mg/ml)
UCD pediatric[1]	0.0956	0.451	0.393	0.325-0.179
UCD adult[2]	0.0701	0.331	0.288	0.238-0.131
Healthy volunteer	0.037	0.175	0.152	0.126-0.069
Cirrhotic –HE 9 ml BID	0.1412	0.666	0.581	0.480-0.264

Modified from Table 12A, B, C in CFU0005
[1] Study HPN-100-002
[2] Study UP 1204-003
[3]The inhibitory effect of PBA on CYP3A4/5 showed an allosteric inhibition; therefore, a calculation of Ki was not possible. Instead IC50 values were calculated for the inhibition of CYP3A4/5 by PBA.

Table 28. [I]/Ki ratios for CYP2C9 in different patient populations - PAA

	PAA	[I]/Ki
	Mean peak concentration (μg/ml)	CYP2C9 (Ki= 2.056 mg/ml)
UCD pediatric[1]	90.5	0.044
UCD adult[2]	40.5	0.0197
Healthy volunteer (MD)	25.5	0.0072
Cirrhotic –HE 9 ml BID	381.35 (1.9-652.3)	0.185 (0.0009-0.317)

Reviewer's comments: The wide range of doses, the likelihood of in vivo drug interaction in the individual patient may vary.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The interaction study with p-gp was not studied for HPN-100 and its major metabolites.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The product label for Buphenyl states following:
"Probenecid is known to inhibit the renal transport of many organic compounds, including hippuric acid, and may affect renal excretion of the conjugated product of BUPHENYL as well as its metabolite"

No studies were conducted to investigate whether PBA, PAA or PAGN is a substrate of organic anion transporter (OAT).

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

In Study HPN-100-006, most patients reported taking at least one concomitant medication with NaPBA and HPN-100 treatment (93.3% and 97.7%, respectively). The most commonly reported classes of medications taken by ≥ 20% of patients were other psychostimulants and nootropics (~ 65 %), calcium (~25.0%), and multivitamins (~ 20.0%). The most commonly reported concomitant medications taken by ≥ 20% of patients with NaPBA and HPN-100 treatments, respectively, were citrulline (62.2% and 63.6%), and multivitamins (20.0% and 20.5%).
Depending on the UCD subtype, appropriate amino acid supplement such as citrulline or arginine supplements will be likely co-administered.

Reviewer's comments:
It should be noted that about 60% patients in Study HPN-100-006 was taking citrulline since majority of patients had OTC deficiency which can not produce citrulline. Nonetheless in patients who have citrullinemia due to defects in distal enzymes (ASS1, ASL, ARG) in the urea cycle after the formation of citrulline, concomitant citrulline is not expected.

For diagnosis of subtype of UCD, plasma concentration of citrulline is used to discriminate between the proximal and distal urea cycle defects, as citrulline is the product of the proximal enzymes (OTC and CPS1) and a substrate for the distal enzymes (ASS1, ASL, ARG).

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions?

The observed discrepancy between undetectable plasma level of HPN-100 in UCD patients and detectable plasma HPN-100 in healthy subjects was not sufficiently explained.

The data is not available if intact HPN-100 is detectable in plasma in UCD patients younger than 6 years. HPN-100 was not used in neonates who may have different lipases in the intestine from adults and older children. The efficiency of hydrolysis of HPN-100 in the intestine may be different.

The data is not available to answer whether mono- or di-ester intermediates of HPN-100 are present in humans. This is not a critical issue for approval of the product. However, based on the observed carcinogenesis in animals with HPN-100, information may be needed for any additional metabolites formed from HPN-100 that are not formed from Buphenyl.

2.5 General Biopharmaceutics

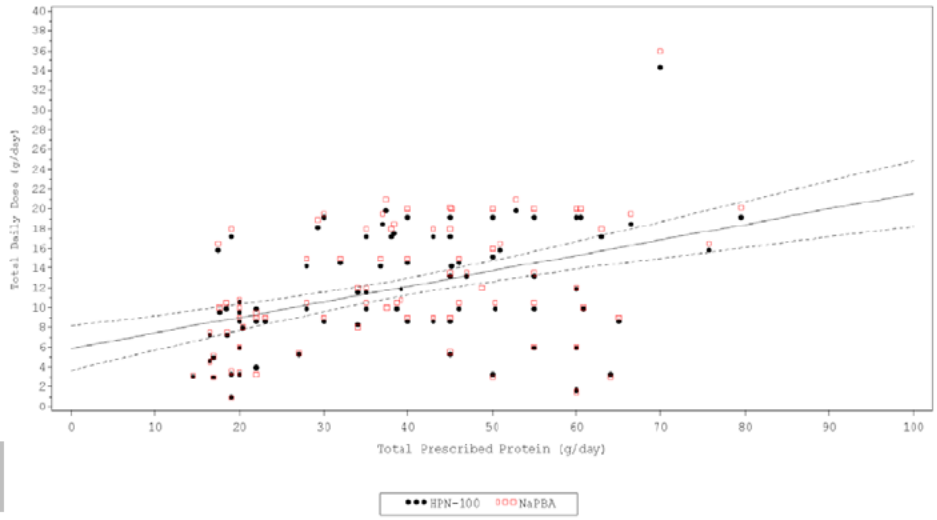
2.5.3 What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

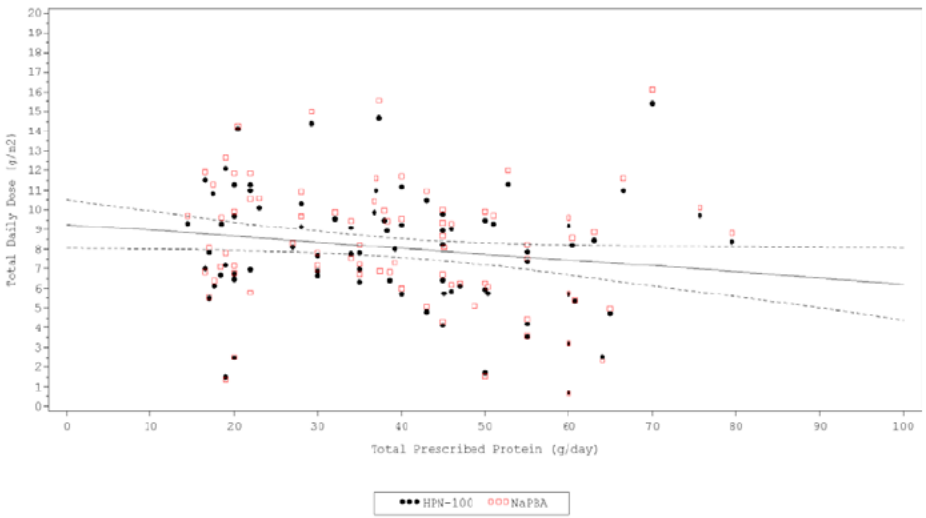
The effect of food was not formally evaluated during this program. The sponsor concluded a lack of food effects based on Study UP 1204-002. In Study UP 1204-002, fasting was required until 4 hours after administration of HPN-100 on Day 1 while on Days 8-15 a meal was allowed after administration HPN-100 without a specified time for breakfast. In a later communication, the time for a standardized breakfast was indicated as 10 am while the dose

was given at 7-8 am in the morning. Therefore the PK characterized after the morning dose administered 2-3 hours prior to a meal is not considered collected under fed condition.

HPN-100 was administered with meals in all clinical studies in UCD patients. HPN-100 should be taken with meals to control the postprandial increase in blood ammonia. In addition, most of patients are under diet management; therefore, a lack of typical food effect study is not considered critical.
In addition, the daily protein intake is a factor to be considered in dose determination.
There was no significant correlation observed between total daily dose (g or g/m2) and total prescribed protein (Figure 14). There was a tendency of a decrease in BSA based dose as the total daily dose increases. It may be in part due to the different severity of disease. A higher prescribed protein intake seems to reflect less severe disease status which may require lower doses.

Figure 14. Total daily dose by total prescribed protein





Source: Figure AH2.6.8.

2.6 Analytical Section

2.6.1 How the active moieties are identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

In support of bioanalytical assay, the sponsor submitted following bioanalytical method validation reports.

Plasma bioanalytical method validation reports include the following:

- QPS Report 148-0403: LC-MS/MS assay validation of 4-phenylbutyric acid, phenylbutyrylglycine, phenylbutyrylglutamine, phenylacetic acid, N-phenylacetylglycine, and phenylacetylglutamine in human plasma
- QPS Report 148-0405: LC-MS/MS assay validation of GT4P in human plasma

Urine bioanalytical method validation reports include the following:

- QPS Report 148-0404: LC-MS/MS assay validation of 4-phenylbutyric acid, phenylbutyrylglycine, phenylbutyrylglutamine, phenylacetic acid, N-phenylacetylglycine, and phenylacetylglutamine in human urine

Glycerol phenylbutyrate (a.k.a. GPB, GT4P, HPN-100) and its major metabolites, PBA, PAA and PAGN were measured in the plasma by adequately validated LC/MS/MS. Phenylacetate is an active moiety of GPB.

In Study UP 1204-001, UP 1204-002 and UP 1204-003, metabolites phenylbutyrylglycine (PBG), phenylbutyrylglutamine (PBGN), and N-phenylacetylglycine (PAG) were measured in plasma and urine. Nonetheless, the concentrations were mostly below detection limit in plasma. These metabolites were not measured in subsequent studies in UCD patients.

PAGN in urine was also measured by adequately validated LC/MS/MS. The bioanalytical assay validation for 4-phenylbutyric acid (PBA), phenylacetic acid (PAA), and phenylacetylglutamine (PAGN) was performed using charcoal-stripped sodium heparin human plasma blank to remove PAGN which is an endogenous substance in blank plasma. To make proportional standard and QC solutions the plasma was charcoal stripped to remove PAGN.

The bioanalytical assay validation for HPN-100 (GPB, GT4P) was conducted in presence of acetonitrile to stabilize GPB in human plasma.

Therefore two plasma samples were prepared at the study site; one for HPN-100 and another for its metabolites.

Reviewer's comments: The addition of acetonitrile at the study site was attributed to the measurable HPN-100 plasma level in healthy subjects while it was not documented either in the protocol or in-run bioanalytical study report for Study HPN-100-005.

2.6.2 Which metabolites have been selected for analysis and why?

HPN-100 is a pro-drug of PBA which is further converted to PAA, an active moiety. PAGN is a final product to be excreted in urine to scavenge elevated blood ammonia.

2.6.3 How was blood ammonia measured?

Blood ammonia was measured using several different assay kits at local laboratories. Ammonia measurements in blood are known to vary with storage and handling and are, therefore, typically stored on ice and analyzed promptly. In order to minimize the possibility of inaccurate ammonia values in the pivotal study (HPN-100-006), ammonia measurements from each subject were performed by the CLIA-approved laboratory at each site rather than at a central laboratory.

Blood ammonia was measured either by colorimetric or enzymatic method using commercially available assay systems available to each study site. **Eleven assay kits** were used for the pivotal phase 3 trial, HPN-100-006. All of the IVD kits used are commercially available with components of the methods (analyzers, reagent kits, and calibration kits) having been cleared by the FDA through 510(k) pre-market authorization. The majority of blood ammonia samples were assayed by one type of assay system. Of note each ammonia assay kit provides its own normal ammonia level (Table 29, 30).

Reviewer's comments: Because there was no cross-assay validation information among assay kits, a comparison of blood ammonia level measured by different assay kits is not reliable. Nevertheless, a comparison within a subject whose ammonia level was measured using the same assay kit at the same laboratory is reasonably acceptable for the purpose of comparison of maintenance of ammonia level after switchover between two treatments.

Table 29. Ammonia assay systems used in HPN-100-006

Assay Type	Number of patients	Assay system	Site No.
Colorimetric	28 (27 included in ITT)	VITROS Chemistry Products AMON Slide	1,2,3,5,7,12,15,17
Enzymatic	18 (17 included in ITT)	Ammonia-Dimension-RXL	4
		Beckman-Coulter Ammonia	8
		Dimension VISTA	10
		Dimension Flex	13
		Beckman Coulter Synchron	16, 22
		Ammonia Ultra	18
		Cobas NH3L (Roche)	19
		ADVIA chemistry (Simens)	20
		Quest	21
		SYNCHRON® system	6

Table 30. Plasma Ammonia Assay Methods for Study HPN-100-006

Assay Method	Investigator	# of Subjects	Reaction Principle	Linear Assay Range	Reference Normal Range (specified for assay)	Specimen Rejection Criteria
Colorimetric (indirect)	Lee (1)	7	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	9-26 µmol/L	Hemolysis Serum samples
Colorimetric (indirect)	Berry	1	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	10-35 µmol/L	Hemolysis Not collected on ice
Colorimetric (indirect)	Rhead (3)	2	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	11-35 µmol/L	Hemolysis Clotted samples Serum samples
Enzymatic (direct)	Lichter (4)	1	Enzymatic with GLDH	0-1000 µmol/L	<51 µmol/L	Not received on ice Not centrifuged within 20 minutes Quantity not sufficient Not analyzed within 2 hours
Colorimetric (indirect)	Diaz (5)	9	Conversion of NH3 + bromphenol blue→blue dye	1-500 µmol/L	9-29 µmol/L	Serum samples
Enzymatic (direct)	Vockley (6)	1	Enzymatic with GLDH	9-1000 µmol/L	9-33 µmol/L	Not analyzed within 30 minutes Sample must be removed from cells immed after centrifugation Sample must stay capped and chilled
Colorimetric (indirect)	Feigenbaum / Schulze (7)	2 (1 included in ITT population)	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	<35 µmol/L	Hemolysis Clotted Not received on ice Needs anaerobic collection in plastic syringe Send to lab within 15 minutes of collection
Enzymatic (direct)	McCandless (10)	1	Glutamate dehydrogenase w/NADPH	25-1000 µmol/L	<110 µmol/L	Hemolysis Not received on ice Not centrifuged within 20 minutes
Enzymatic (direct)	Smith (11)	1	Enzymatic with GLDH	10-700 µmol/L	Females: 11-51 µmol/L Males: 16-60 µmol/L	Hemolysis Lipemia Serum samples Sample must stay capped and chilled Must be analyzed within 20-30 minutes
Colorimetric (indirect)	Longo (12)	3	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	8-27 µmol/L	Hemolysis Not received on ice or frozen Not centrifuged within 15 minutes Serum or blood Specimens containing oxalate or citrate
Enzymatic (direct)	Berquist (13)	3	Glutamate Dehydrogenase (GLDH)	10-1000 µmol/L	<30 µmol/L	Hemolysis Lipemia Not on ice or frozen Not received within 20 minutes Capillary specimens (heel/finger sticks)
Colorimetric (indirect)	Gallagher (15)	2	Conversion of NH3 + bromphenol blue→ blue dye	9-500 µmol/L	9-30 µmol/L	Not received on ice Not centrifuged within 15 minutes
Enzymatic (direct)	Harding (16)	2	Glutamate Dehydrogenase (GLDH)	16-1700 µg/dL (9.4-997.80 µmol/L)	16-60 µg/dL (9-35 µmol/L)	Hemolysis Lipemia
Colorimetric (indirect)	Bartholomew (17)	2	Conversion of NH3 + bromphenol blue→blue dye	9-500 µmol/L	10-64 µmol/L	Hemolysis Not received on ice Not centrifuged within 15 minutes Not received in a lithium heparin tube Capillary specimens (heel/finger sticks)

Assay Method	Investigator	# of Subjects	Reaction Principle	Linear Assay Range	Reference Normal Range (specified for assay)	Specimen Rejection Criteria
Enzymatic (direct)	Kronn (18)	1	Enzymatic with GLDH	9-1700 µg/dL (4.7-997.80 µmol/L)	18-72 µmol/L (31-123 µg/dL)	Hemolysis Not on ice or frozen Sample must be filled
Enzymatic (direct)	Zori (19)	1	Glutamate Dehydrogenase (GLDH)	10-700 µmol/L	Females: 11-51 µmol/L Males: 16-60 µmol/L	Hemolysis EDTA tube Ice free Lipemia
Enzymatic (direct)	Bartley (20)	4 (3 included in ITT population)	Glutamate Dehydrogenase (GLDH)	6-767 µmol/L	11-35 µmol/L	Hemolysis Lipemia Not sent on ice Not received within 30 minutes
Enzymatic (direct)	21 Al-Ibrahim (21)	1	Enzymatic with Glutamate Dehydrogenase (GLDH)	11-604 µmol/L	<51 µmol/L	Hemolysis Lipemia Not on ice or frozen Not received within 20 minutes
Enzymatic (direct)	22 Korson (22)	2	Enzymatic with Glutamate Dehydrogenase (GLDH)	16-1700 µg/dL (9.4-997.80 µmol/L)	16-60 µg/dL (9-35 µmol/L)	Not on ice or frozen Not analyzed within 30 minutes

Normalization of blood ammonia

To account the differences in assays, the sponsor corrected the blood ammonia level by the ratio of upper limit of normal ammonia range for each assay kit to a upper limit of the standard reference range i.e. 35 µmol/L as below.

- S=x* (Us/Ux)
  - S: Normalized value
  - X: Ammonia readout
  - Us: Upper limit of the standard reference range which is defined as 5-35 µmol/L
  - Ux: Upper limit of a laboratory reference range specified for each assay

Upper limit for laboratory reference range varies for each assay and ranges mostly 30-60 µmol/L. According to the sponsor's normalization approach, the readout of 35 µmol/L would have been normalized to 45 if Ux is 29 µmol/L and to 17 µmol/L if Ux is 64 µmol/L, respectively. The normalization does not change the determination of whether the ammonia level is greater than the upper limit of normal range or not according to the normal range specified for each assay.

2.6.4 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

The accuracy and precision for each analyte was acceptable. Please see Tables 31-34.

Table 31: Plasma Bioanalytical Method Validation Summary

Attribute	Analyte			
	GPB	**PBA**	**PAA**	**PAGN**
Linear Range	5–100 ng/mL	1–100 µg/mL	1–100 µg/mL	1–100 µg/mL
LLOQ	5 ng/mL	1 µg/mL	1 µg/mL	1 µg/mL
ULOQ	100 ng/mL	100 µg/mL	100 µg/mL	100 µg/mL
Selectivity, Precision (% CV), accuracy (% difference)	5 ng/mL: % CV = 7.0 % difference = 8.0	1 µg/mL: % CV = 11.7 % difference = −4.5	1 µg/mL: % CV = 5.2 % difference = −7.1	1 µg/mL: % CV = 3.0 % difference = 3.4
QC Concentration	5, 10, 40, 90 ng/mL[d]	1, 3, 40, 90 µg/mL	1, 3, 40, 90 µg/mL	1, 3, 40, 90 µg/mL
Intra-Day Precision (% CV)	(4.2, 10.0)	(2.9, 12.2)	(2.2, 10.1)	(3.2, 11.7)
Inter-Day Precision (% CV)	(5.7, 9.1)	(5.0, 9.3)	(3.3, 6.8)	(5.8, 7.2)
Intra-Day Accuracy (% difference)	(−6.7, 8.4)	(−11.7, 10.9)	(−3.3, 14.3)	(−4.8, 10.6)
Inter-Day Accuracy (% difference)	(−2.8, 5.9)	(−8.7, 5.4)	(−0.4, 12.0)	(−2.1, 6.7)
Stability				
Master Stock Solution Stability in Solvent	149 d at −20°C in acetonitrile 7 h at room temperature in acetonitrile	345 d at −20 °C in methanol 18 h at room temperature in methanol	194 d at −20 °C in methanol 20.5 h at room temperature in methanol	555 d at −20 °C in methanol 20.5 h at room temperature in methanol
Freeze and Thaw Stability	10 cycles at −70 °C	10 cycles at −70°C	10 cycles at −70°C	10 cycles at −70°C
Dilution Integrity	2000 ng/mL diluted 100×	200 µg/mL diluted 20×	200 µg/mL diluted 20×	200 µg/mL diluted 20×
Storage Stability	433 d at −70 °C (plasma:acetonitrile, [1:2, v/v]) 5 h at room temperature (plasma:acetonitrile, [50:50, v/v])	554 d at −70 °C (plasma) 20 h at 4°C (plasma)	554 d at −70 °C (plasma) 20 h at 4°C (plasma)	554 d at −70 °C (plasma) 20 h at 4°C (plasma)
Autosampler Stability of Processed Samples	140 h at room temperature	325 h at room temperature	325 h at room temperature	325 h at room temperature

CV = coefficient of variation; GPB (GT4P) = glycerol phenylbutyrate (formerly glyceryl tri-[4 phenylbutyrate]); LLOQ = lower limit of quantitation; PAA = phenylacetic acid; PAG = phenylacetylglycine; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; PBG = phenylbutyrylglycine; PBGN = phenylbutyrylglutamine; QC = quality control; ULOQ = upper limit of quantitation.

Table 32: Urine Bioanalytical Method Validation Summary

Attribute	Analyte		
	PBA	**PAA**	**PAGN**
Linear Range	1–100 µg/mL	1–100 µg/mL	100–10000 µg/mL
LLOQ	1 µg/mL	1 µg/mL	100 µg/mL
ULOQ	100 µg/mL	100 µg/mL	10000 µg/mL
Selectivity, precision (% CV), accuracy (% difference) at LLOQ	1 µg/mL: % CV = 4.7 % difference = −5.0	1 µg/mL: % CV = 1.7 % difference = −10.3	100 µg/mL: % CV = 6.6 % difference = 0.7
QC Concentrations	1, 3, 30, 90 µg/mL	1, 3, 30, 90 µg/mL	100, 300, 3000, 9000 µg/mL
Intra-Day Precision (% CV)	(1.5, 6.1)	(0.9, 5.5)	(2.3, 14.7)
Inter-Day Precision (% CV)	(2.8, 7.0)	(2.1, 4.7)	(5.4, 11.8)
Intra-Day Accuracy (% difference)	(−11.0, 0.6)	(−10.9, −2.3)	(−7.4, 6.3)
Inter-Day Accuracy (% difference)	(−5.6, −1.9)	(−7.4, −3.4)	(−4.0, 1.0)
Stability			
Master Stock Solution Stability in Solvent	345 d at −20 °C in methanol 18 h at room temperature in methanol	194 d at −20 °C in methanol 20.5 h at room temperature in methanol	343 d at −20 °C in methanol 20.5 h at room temperature in methanol
Freeze and Thaw Stability	10 cycles at −70 °C	10 cycles at −70 °C	10 cycles at −70 °C
Dilution Integrity	200 µg/mL diluted 20×	200 µg/mL diluted 20×	20000 µg/mL diluted 20×
Storage Stability in Urine	460 d at −70 °C 21 h at room temperature	460 d at −70 °C 21 h at room temperature	460 d at −70 °C 21 h at room temperature
Autosampler Stability of Processed Samples	261 h at room temperature	261 h at room temperature	225 h at room temperature

Table 33: Plasma Bioanalytical Method Validation Summary

Attribute	Analyte		
	PAG	**PBG**	**PBGN**
Linear Range	1–100 µg/mL	1–100 µg/mL	1–100 µg/mL
LLOQ	1 µg/mL	1 µg/mL	1 µg/mL
ULOQ	100 µg/mL	100 µg/mL	100 µg/mL
Selectivity, Precision (% CV), accuracy (% difference)	1 µg/mL: % CV = 9.7 % difference = 1.8	1 µg/mL: % CV = 5.3 % difference = −5.7	1 µg/mL: % CV = 10.3 % difference = −0.7
QC Concentration	1, 3, 40, 90 µg/mL	1, 3, 40, 90 µg/mL	1, 3, 40, 90 µg/mL
Intra-Day Precision (% CV)	(4.2, 12.3)	(2.8, 12.2)	(1.7, 12.4)
Inter-Day Precision (% CV)	(6.4, 10.8)	(5.3, 7.6)	(5.4, 8.0)
Intra-Day Accuracy (% difference)	(−8.6, 10.9)	(−9.0, 11.5)	(−3.7, 15.7)
Inter-Day Accuracy (% difference)	(−3.7, 6.4)	(−6.2, 5.1)	(0.0, 10.8)
Stability			
Master Stock Solution Stability in Solvent	406 d at −20 °C in methanol 20.5 h at room temperature in methanol	556 d at −20 °C in methanol 18 h at room temperature in methanol	556 d at −20 °C in methanol 18 h at room temperature in methanol
Freeze and Thaw Stability	10 cycles at −70 °C	10 cycles at −70 °C	10 cycles at −70 °C
Dilution Integrity	200 µg/mL diluted 20×	200 µg/mL diluted 20×	200 µg/mL diluted 20×
Storage Stability	554 d at −70 °C (plasma) 20 h at 4°C (plasma)	554 d at −70 °C (plasma) 20 h at 4°C (plasma)	554 d at −70 °C (plasma) 20 h at 4°C (plasma)
Autosampler Stability of Processed Samples	325 h at room temperature	325 h at room temperature	325 h at room temperature

CV = coefficient of variation; GPB (GT4P) = glycerol phenylbutyrate (formerly glyceryl tri-[4 phenylbutyrate]); LLOQ = lower limit of quantitation; PAA = phenylacetic acid; PAG = phenylacetylglycine; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; PBG = phenylbutyrylglycine; PBGN = phenylbutyrylglutamine; QC = quality control; ULOQ = upper limit of quantitation.

Table 34: Urine Bioanalytical Method Validation Summary

Attribute	Analyte		
	PAG	**PBG**	**PBGN**
Linear Range	1–100 µg/mL	1–100 µg/mL	1–100 µg/mL
LLOQ	1 µg/mL	1 µg/mL	1 µg/mL
ULOQ	100 µg/mL	100 µg/mL	100 µg/mL
Selectivity precision (% CV), accuracy (% difference) at LLOQ	1 µg/mL: % CV = 8.2 % difference = 4.8	1 µg/mL: % CV = 6.6 % difference = −3.2	1 µg/mL: % CV = 5.0 % difference = 5.8
QC Concentrations	1, 3, 30, 90 µg/mL	1, 3, 30, 90 µg/mL	1, 3, 30, 90 µg/mL
Intra-Day Precision (% CV)	(1.1, 10.7)	(1.4, 14.9)	(2.2, 12.2)
Inter-Day Precision (% CV)	(5.8, 8.2)	(6.7, 10.2)	(6.3, 11.0)
Intra-Day Accuracy (% difference)	(−7.4, 7.0)	(−9.8, 8.1)	(−8.1, 9.5)
Inter-Day Accuracy (% difference)	(−2.5, −1.4)	(−4.7, 1.2)	(−5.2, −1.2)
Stability			
Master Stock Solution Stability in Solvent	406 d at −20 °C in methanol 20.5 h at room temperature in methanol	556 d at −20 °C in methanol 18 h at room temperature in methanol	556 d at −20 °C in methanol 18 h at room temperature in methanol
Freeze and Thaw Stability	10 cycles at −70 °C	10 cycles at −70 °C	10 cycles at −70 °C
Dilution Integrity	200 µg/mL diluted 20×	200 µg/mL diluted 20×	200 µg/mL diluted 20×
Storage Stability in Urine	460 d at −70 °C 21 h at room temperature	460 d at −70 °C 21 h at room temperature	464 d at −70 °C 21 h at room temperature
Autosampler Stability of Processed Samples	261 h at room temperature	261 h at room temperature	261 h at room temperature

CV = coefficient of variation; GPB (GT4P) = glycerol phenylbutyrate (formerly glyceryl tri-[4 phenylbutyrate]); LLOQ = lower limit of quantitation; PAA = phenylacetic acid; PAG = phenylacetylglycine; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; PBG = phenylbutyrylglycine; PBGN = phenylbutyrylglutamine; QC = quality control; ULOQ = upper limit of quantitation

3. Major Labeling Recommendations

1) We recommend following revisions to the subsection for the effects on the QT interval in the section 12.2.
The effect of multiple doses of Ravicti 13.2 g/day and 19.8 g/day on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm crossover study in 40 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) for Ravicti was below 10 ms. However, assay sensitivity was not established in this study. Therefore, a small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out. The 19.8-g/day dose utilized in this study is the highest intended clinical dose.

2) We recommend that the correction factor for Ravicti dose from Buphenyl dose be included in the label.

3) We recommend that a subsection of "Hepatic Impairment" be created under section 12.3 to include details on the study design and the results.

4) Detailed labeling recommendations other than followings are deferred until the labeling negotiation.

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1. Pharmacometric Review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is there an exposure-response relationship between PAA and safety events?

A relationship between PAA C_{max} and nervous system adverse events was observed in healthy volunteers (Figure 3), but not urea cycle disease (UCD) patients (Figure 2). Potential reasons for the discrepancy between healthy volunteers and patients include the following:

- UCD patients were well-controlled on a stable dose of BUPHENYL upon entering the trial. Presumably, this dose was titrated based on safety as well as ammonia levels. Therefore, for each individual patient, the PAA levels were tolerable. This is supported by the relatively lower overall incidence of nervous system adverse events in UCD patients compared to healthy volunteers.
- UCD patients are more tolerant to nervous system side effects. Some of the manifestations of hyperammonia are similar to those that can be expected at high levels of PAA. Therefore, these patients may have become more tolerant to these adverse reactions over the course of their disease.
- On the other hand, healthy subjects are not accustomed to the side effects of hyperammonia and may be more sensitive or responsive to the effects of PAA levels

For a relationship between PAA levels and nervous system disorders to be observed, one might need to study individual dose titration over a range of doses in an individual. This might be achieved in *de novo* patients, but the development program only included a limited number of these individuals.

Figure 1: Relationship Between PAA C_{max} (µg/mL) and Incidence of Nervous System Adverse Events (All Grade) in Healthy Volunteers

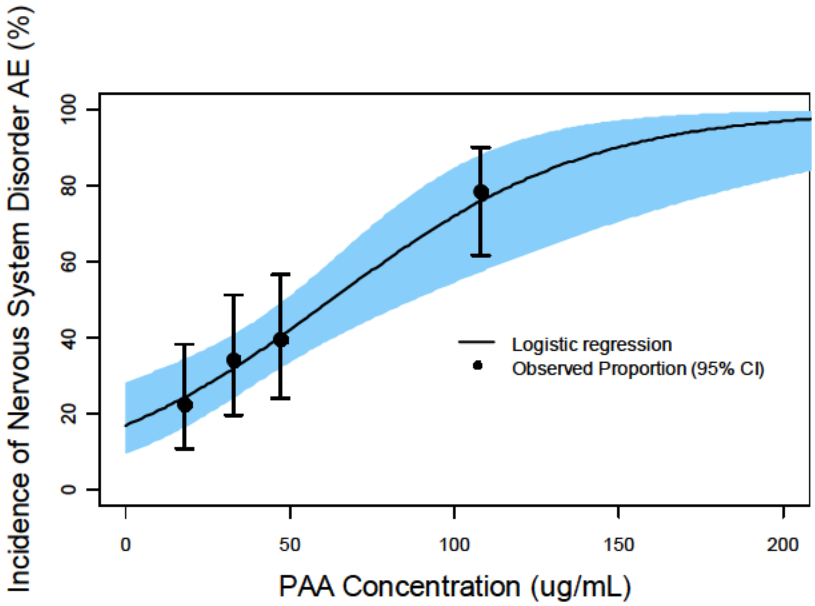
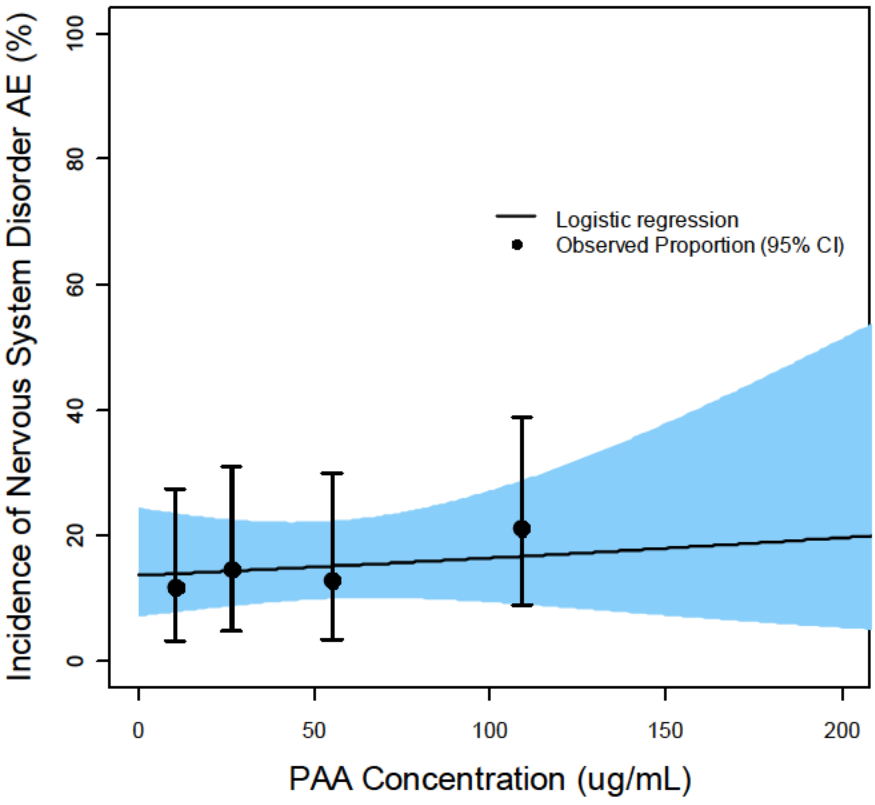


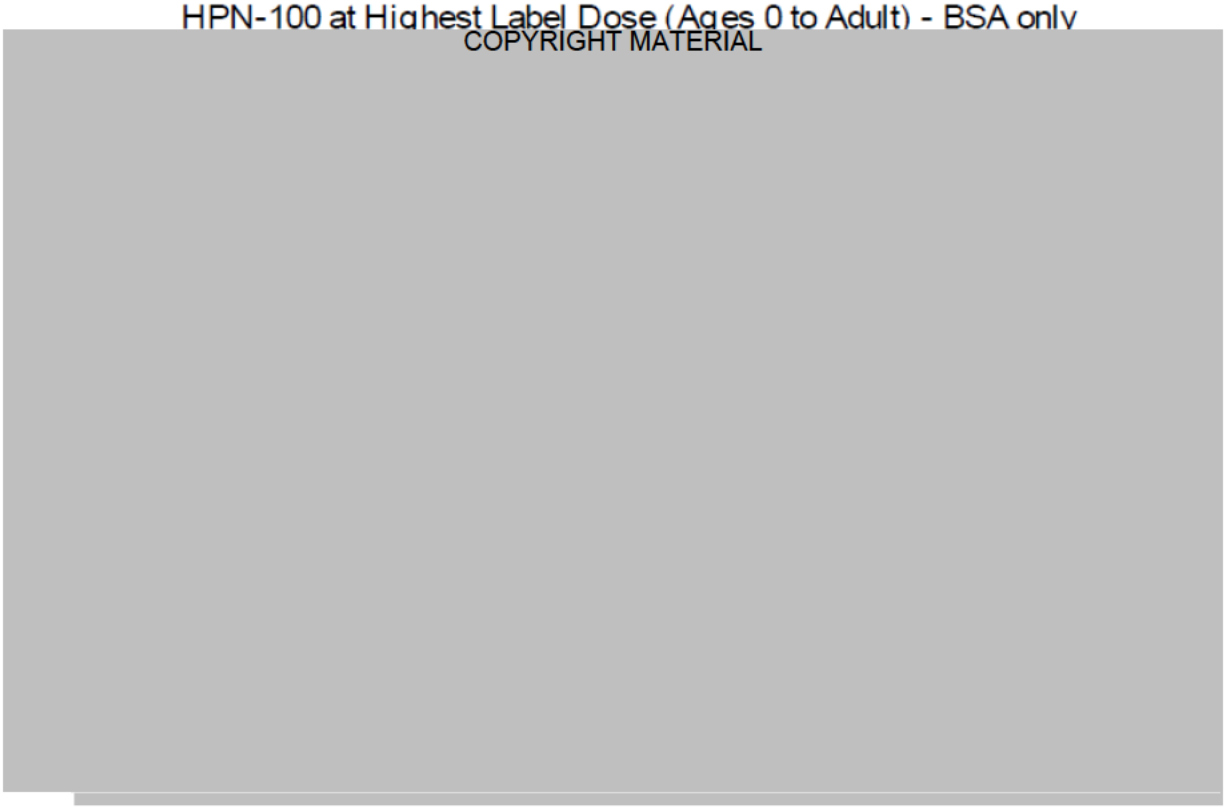
Figure 2: Lack of Relationship Between PAA C_{max} (µg/mL) and Incidence of Nervous System Adverse Events in UCD Patients



Is the proposed dose range of HPN-100 for adult and pediatric patients appropriate?

Yes, the proposed dose range of HPN-100 for adult and pediatric patients appears reasonable. Even at the highest proposed dose of HPN-100, PAA levels after HPN-100 dosing are predicted to be similar to an already approved product, BUPHENYL (NaPBA) (Figure 3). Therefore, HPN-100 does not appear to provide an added risk compared to BUPHENYL. PAA levels in the youngest children, however, are expected to be higher than in adolescents or adults. Given the relatively limited data in infants, additional safety information is this population is warranted.

Figure 3: Total Predicted Daily PBA Dose and PAA Exposure (C_{max} and AUC) from Infant to Adults using a BSA Based Dosing Regimen: Highest Labeled Dose The dashed line in the middle plots corresponds to the PAA level at which nervous system disorders were observed in a literature study [Thibault et al., Cancer Research 1994; 54: (1690-1694)]



Source: hype-pcs-100, Figure 4.3:4, Page 33.

Recommendations

The Sponsor's proposed dosing range of HPN-100 is appropriate.

Label Statements

The Sponsor's population pharmacokinetic modeling does not adequately support the following proposed label statements:

(b) (4)

Population pharmacokinetic modeling and dosing simulations found BSA to be the most significant covariate explaining the variability of metabolite clearance. Metabolite clearance, in particular PAA, was proportional to body surface area (BSA) and explained the differences in PAA levels between adult and pediatric patients. The projected median and 95th percentile values with Ravicti dosing simulations at low and high end of the recommended dose range are summarized in Table 3.

Table 2: Projected median and 95th percentile values with Ravicti dosing simulations

Age Group	Ravicti 4.98 g/m^{2}day				Ravicti 13 g/m^{2}day			
	C_{max}		AUC		C_{max}		AUC	
	Median	95%	Median	95%	Median	95%	Median	95%
0-2	29	79	233	412	163	707	1335	4852
3-5	27	75	221	382	126	489	1038	3275
6-11	25	69	203	344	89	342	723	2005
12-18	22	59	181	301	146	597	1201	4048

Pertinent regulatory background

Hyperion submitted NDA 203284 on December 23, 2011 for Ravicti™ (glycerol phenylbutyrate or HPN-100) to support a proposed indication as an adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders. The clinical efficacy of HPN-100 is primarily based on a non-inferiority trial to BUPHENYL, the design of which was agreed with the FDA in the context of a Special Protocol Assessment. BUPHENYL (sodium phenylbutyrate) is an approved product which consists of the same active moiety (phenylbutyrate) and Ravicti™. Evidence of effectiveness is primarily derived from a single, randomized, double-blind, active-controlled, crossover trial which demonstrated non-inferiority of HPN-100 to BUPHENYL in the primary endpoint of blood ammonia control, assessed as 24-hour area under the concentration versus time curve.

Results of Sponsor's Analysis

Population Pharmacokinetic Modeling

A population pharmacokinetic analysis was performed to describe the disposition of BUPHENYL and HPN-100. Specifically, the model was used to predict plasma PAA concentrations in pediatric and adult UCD patients. Literature reports suggested a PAA level above 499 µg/mL was associated with neurologic adverse events. Therefore, the goal of the simulations was to compare PAA exposure at the proposed HPN-100 doses to this cutoff value.

Data

The development of the original population pharmacokinetic model was based on data from switch-over studies in which UCD patients received both BUPHENYL and HPN-100. The dataset included 53 adult UCD patients who contributed 1,100 and 1,042 data points (PBA, PAA

and PAGN) for HPN-100 and BUPHENYL, respectively and 11 pediatric UCD patients aged 6 to 17 years who contributed 214 and 184 data points for HPN-100 and BUPHENYL, respectively. A summary of the studies is described in Table 3.

Table 3: Summary of Studies Used in Original Population Pharmacokinetic Analysis

Study	Design	Population	Phase	N	Treatments	Treatment Regimen
UP 1204-003	Open-label, switch-over, dose escalation study	Adult UCD patients	2	9	Buphenyl for 7 days followed by dose escalation period for HPN-100 to an equimole dose of PBA for 7 days	**Arm 1**: Buphenyl after 7 days **Arm 2**: HPN-100 dose escalation followed by 7-days dosing of HPN-100 at equimole dose
HPN-100-005	Open-label, switch-over, fixed sequence study of the safety and tolerability of HPN-100 compared to NaPBA in children with UCD	Children aged 6-17 years with UCD	2	11	NaPBA for 7 days followed by HPN-100 for 7 days	NaPBA for 7 days followed by HPN-100 alone for 7 days
HPN-100-006	Randomized, double-blind, cross-over, active-controlled study of the efficacy and safety of HPN-100	Adult UCD patients	3	44	NaPBA + HPN-100 placebo for 14 days then HPN-100 + NaPBA placebo for 14 days or HPN-100 + NaPBA placebo for 14 days then NaPBA + HPN-100 placebo for 14 days	**Arm 1**: NaPBA + HPN-100 placebo for 14 days followed by HPN-100 + NaPBA placebo for 14 days **Arm 2**: HPN-100 + NaPBA placebo for 14 days followed by NaPBA + HPN-100 placebo for 14 days alone for 7 days

Source: hype-cs-004, Table 3.3:1, Page 24.

The dataset was subsequently augmented with pharmacokinetic data from HPN-100-012, a switch-over study in pediatric patients aged 29 days to 17 years. The 26 patients in this study contributed 335 and 296 data points for HPN-100 and BUPHENYL, respectively.

Structural Model

The general structure of the pharmacokinetic model describing PBA, PAA and PAGN kinetics is illustrated in

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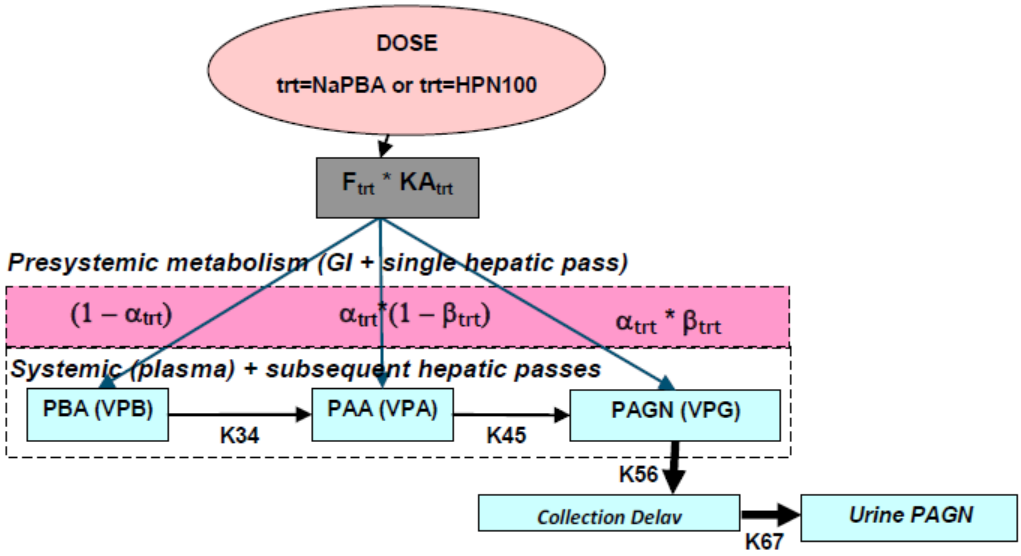
Figure 4. The absorption model was developed to account for the fact that PBA is absorbed more slowly following administration of HPN-100 than BUPHENYL and incorporates the hypothesis that lower plasma levels of PBA following administration of HPN-100 is due to a fractionally greater amount of PBA being presystemically converted. In other words, some of the PBA derived from HPN-100 (and BUPHENYL) dose has already been converted to PAA and PAGN before any of these analytes enter the bloodstream. In this model, bioavailiability (F_{trt}) and absorption rate are provided separately for each treatment (HPN-100 or BUPHENYL). For simplicity, F_{trt} was fixed to values derived from noncompartment analysis. The α parameter reflects the distribution of PBA to plasma and presystemic compartments and β reflects the proportion of PBA that is converted presystemically to PAA and PAGN. Separate parameters were estimated for the two treatments. The two treatments used the same concentration-independent rate constants for the conversion of PBA to PAA (K34) and elimination of PAGN (K56). A saturable metabolism model with Michaelis-Menten parameters was used to describe the elimination of PAA to PAGN. A delay rate constant was used to describe the delay between appearance of PAGN in the urine and bladder emptying.

Figure 4: Structural Pharmacokinetic Model



Source: hype-cs-004, Figure 4.2:3, Page 29

Covariate Model

Covariates were tested on clearance and volume of distribution parameters. Demographic covariates included BSA, weight and age. Disease-specific covariates included plasma glutamine levels, dietary protein intake and age of UCD diagnosis. The final model included BSA as a covariate on all clearance and volume of distribution terms, as well as the presystemic conversion terms (α and β)

Final Model Results

Parameter estimates of the final model are provided in Table 4 and Table 5.

Table 4: Presystemic Parameters of Final Model

		HPN-100		NaPBA	
Formulation Dependent Parameters	**Units**	**Estimate**	**BSV**	**Estimate**	**BSV**
Absorption rate constant (Kax)	1/h	0.331	55	1.40	71
Extent of bioavailability (ADULT) - FIXED TO PK report findings [8]	%	69	17	71	18
Extent of bioavailability (PEDIATRIC) - FIXED TO PK report findings [7]	%	66	16	69	16
Presystemic distribution of PBA (alpha x BSA/1.73)		0.35	--	0.11	--
Distribution of PBA to PAA and PAGN presystemically (beta x BSA/1.73)		4.39	--	7890	--
Clinical meaning of estimated parameters					
Absorption half-life	**0.693/Kax (h)**	2.10		0.500	
PBA percent metabolized presystemically	**alpha/(1+alpha)x100**	26		10	
PAA percent metabolized to PAGN presystemically	**beta/(1+beta)x100**	81		100	

Source: hype-pcs-100, Appendix 9.2, Page 48

Table 5: Parameters of the Final Pharmacokinetic Model

PBA parameters	**Units**	**Estimate**	**BSV%**
PBA Volume of Distribution (VPB/F)	L	12.4 x (BSA/1.73)	71
PBA Clearance to PAA (CLB/F)	L/h	12.7 x (BSA/1.73)	34
PBA systemic conversion to PAA rate (K34)	1/h	1.02	--
PBA Proportional residual error	%	66	--
PBA Additive residual error	uM	6.1	--
PAA Parameters	**Units**	**Estimate**	**BSV%**
PAA Volume of Distribution (VPA/F)	L	30.8 x (BSA/1.73)	62
Vmax for PAA to PAGN (VMPA)	umole/h	5260 x (BSA/1.73)	--
Km for PAA to PAGN (KMPA)	uM	193	--
CL as Vmax/Km (linear portion)	L/h	27	--
PAA Proportional residual error	%	53	--
PAA Additive residual error	uM	7.3	--
PAGN parameters	**Units**	**Estimate**	**BSV%**
PLASMA			
PAGN Volume of Distribution (VPG/F)	L	23.4 x (BSA/1.73)	31
PAGN Clearance (CLG/F)	L/h	10.6 x (BSA/1.73)	21
PAGN elimination rate constant (K56)	1/h	0.45	--
URINE			
Delay compartment rate constant (K67)	1/h	1.02	--
PAGN Plasma Proportional residual error	%	34	--
PAGN Plasma Additive residual error	uM	3.8	--
PAGN Urine Proportional residual error	%	50	--
PAGN Urine Additive residual error	umoles	3.8	--

Source: hype-pcs-100, Appendix 9.2, Page 48

Goodness of fit plots are presented for PAA only (
Figure 5) because this was the analyte of interest. The observed vs. population prediction plot shows a bias, especially at low levels of PAA.

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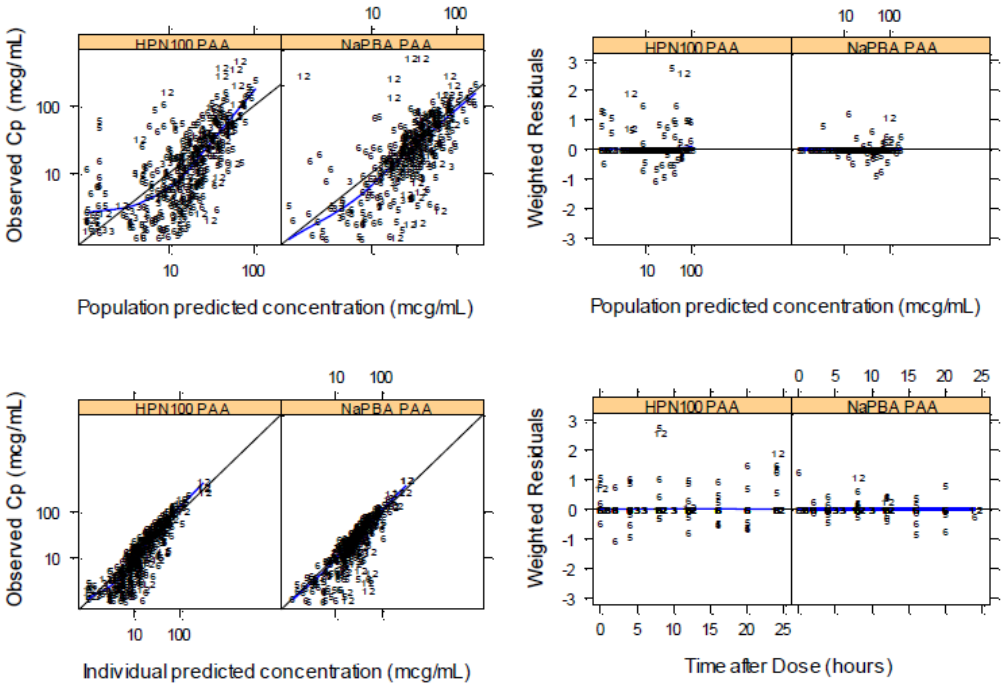
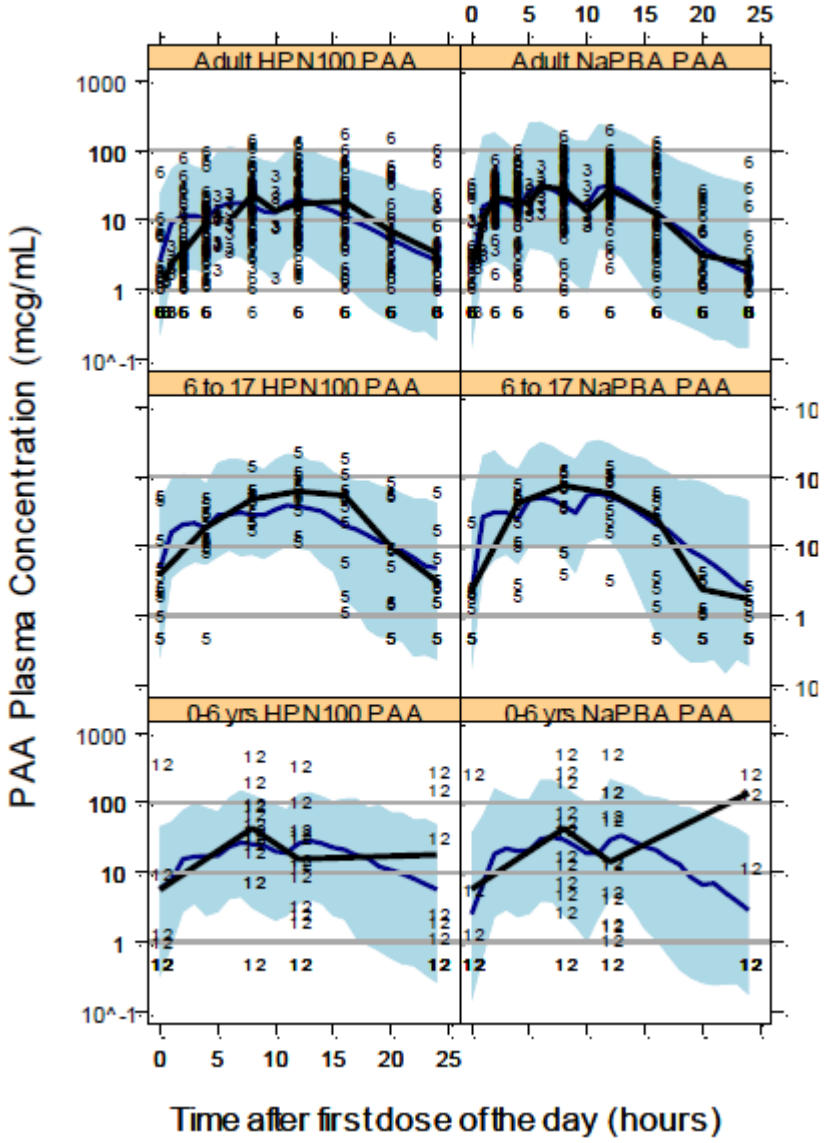
Figure 5: Basic Goodness of Fit Plots for the Final Model



Source: hype-pcs-100, Appendix 9.3, Page 49

The visual predictive check stratified by age group, however, shows that the model was reasonably able to reproduce the observed data. The model is limited by the relatively sparse pediatric data, especially in patients from 0 to 6 years of age.

Figure 6: Visual Predictive Check Stratified by Age Group



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Source: hype-pcs-100, Figure 4.2:2, Page23.

Since the goal of the modeling exercise was to predict PAA levels after HPN-100 dosing, it is important to compare the predictions of the model to actual observations (Table 6 and Table 7.)

Table 6: Comparison of PAA Exposure Calculated from Noncompartmental Analysis and Simulations for HPN-100-005 and HPN 100-006. Note: m31 is the final model and should be used for comparison.

	HPN-100-005						HPN-100-006					
	NaPBA			HPN-100			NaPBA			HPN-100		
	NCA	Sims (m18)	Sims (m31)	NCA	Sims (m18)	Sims (m31)	NCA	Sims (m18)	Sims (m31)	NCA	Sims (m18)	Sims (m31)
C_{max} (mcg/mL)												
Arithmetic Mean	75.1	89.4	130.7	90.5	95.9	87	52.2	69.5	95.4	38.5	48.6	47.3
CV%	34	146	173	69	118	145	80	161	263	103	157	171
Median	73.7	55.6	81.2	69.2	66.4	59.6	52.2	38.9	53.6	25.4	31.7	32.2
AUC (mcg.h/mL)												
Arithmetic Mean	773	692	1045	964	959	768	599	634	753	447	478	425
CV%	73	135	134	64	106	100	92	177	208	130	174	118
Median	767	481	791	858	705	623	409	354	511	242	300	323

NCA = calculated based on noncompartmental analysis [7,8]
Sims = exposure predicted based on dosing simulations using models m18 and m31

Source: hype-pcs-100, Table 4.3:1, Page 27.

Table 7: Comparison of PAA Exposure Calculated from Noncompartmental Analysis and Simulations by Age Group for HPN-100-012

	29 days to < 2 years				2 to < 6 years				< 6 years			
	NaPBA		HPN-100		NaPBA		HPN-100		NaPBA		HPN-100	
	NCA	Sims (m31)	NCA	Sims (m31)	NCA	Sims (m31)	NCA	Sims (m31)	NCA	Sims (m31)	NCA	Sims (m31)
C_{max} (mcg/mL)												
Arithmetic Mean	227	100.6	196	77.8	46.5	92	54.4	64.5	98	94.3	84.7	67.9
CV%	102.9	201	128	145	129.9	225	104.9	163	152.1	218	148.3	158
Median	181.4	48.8	99.3	38.6	30.1	53.1	37.5	44.1	42.6	52.5	40.3	42.7
AUC (mcg.h/mL)												
Arithmetic Mean	4138	617	3322	434	386	614	488	464	1458	615	1096	456
CV%	123.7	145	148	135	183.6	138	132.7	114	211.3	140	214	119
Median	2631	487	930	378	393	431	393	352	211	487	350	378

NC: not calculated; NCA = calculated based on noncompartmental analysis [6]
Sims = exposure predicted based on dosing simulations using model m31

Source: hype-pcs-100, Table 4.3:2, Page 28.

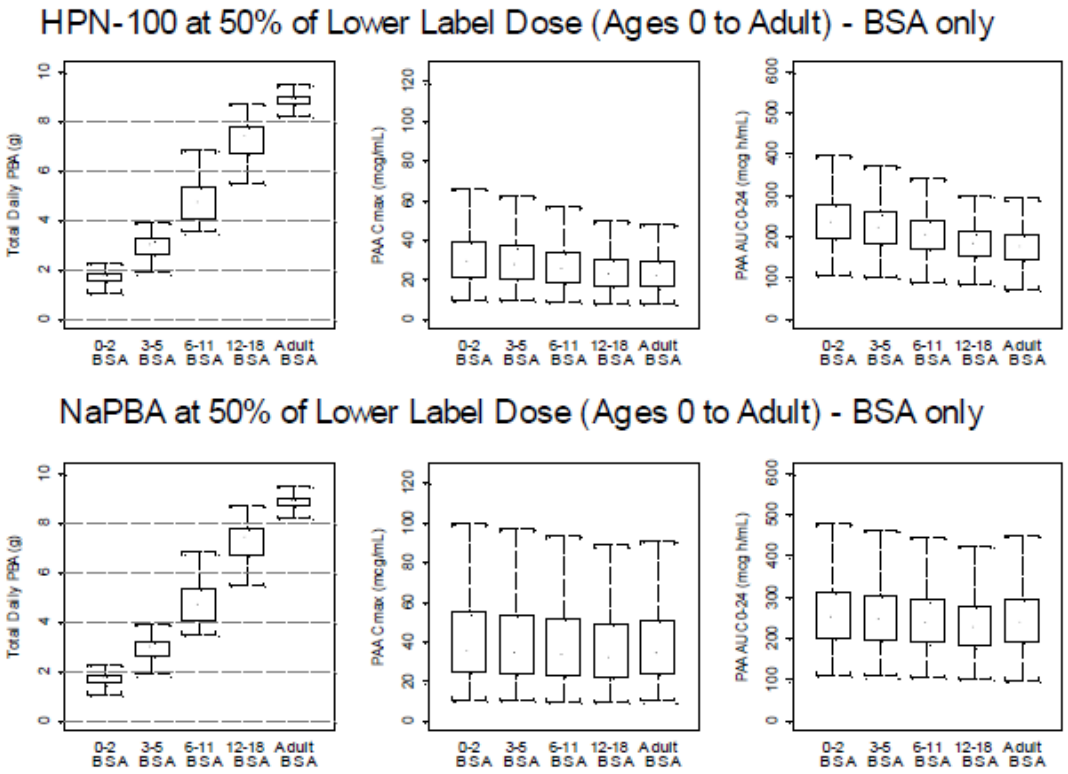
Reviewer's Comments: The Sponsor's model does not perform well in pediatric subjects less than 2 years of age. As seen in Table 7, *PAA levels are underpredicted. The poor performance of the model may reflect the lack of adequate data in this age group. The model also shows a clear bias at low PAA levels in all patients. Furthermore, standard errors of the parameter estimates were not reported. Simulations suggest that maximum PAA levels can be predicted reasonably well in patients greater than two years of age. The model also accounts for some of the large extent of variability observed in the studies. Simulations using this model will be useful to explore the anticipated PAA levels at different doses in adult and pediatric UCD patients but should be interpreted with caution. Results of the simulations should not be included in labeling.*

Simulations

Simulations were performed using the PBA equivalent of the highest labeled BUPHENYL dose (13 g /m^2/day) and 50% of the lower labeled BUPHENYL dose (4.98 g/m^2/day), which is similar to the lower end of the proposed HPN-100 dosing range. The results are presented in Figure 3 and Figure 7. Tabular listing of the simulated data is presented in Table 8. The results indicate that:

- PAA levels are expected to increase as age decreases
- PAA levels are similar following BUPHENYL and HPN-100 treatment
- BSA dosing appears to produce less variability compared to body weight based dosing for patients less than 20 kg but older than 1 year

Figure 7: Predicted PAA Exposure from Infant to Adults using a BSA Based Dosing Regimen: 50% of the Lower Labeled Dose



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Source: hype-pcs-100, Figure 4.3:5, Page 34.

Table 8: Tabular Listings of Simulations Results from Figure 3 and Figure 7

	HPN-100 (4.98 g/m2/day)									NaPBA (4.98 g/m2/day)								
	Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)			Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)		
	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%
0-2	1.67	1.32	2.01	29	15	79	233	156	412	1.67	1.31	2.01	35	16	132	250	160	505
3-5	2.94	2.41	3.46	27	15	75	221	149	382	2.93	2.4	3.45	34	16	129	244	157	493
6-11	4.61	3.61	5.90	25	13	69	203	137	344	4.6	3.606	5.88	33	16	125	237	152	476
12-18	7.35	6.16	8.08	22	12	59	181	124	301	7.34	6.142	8.07	32	15	119	225	146	451
Adult	8.84	8.45	9.23	22	12	57	175	115	286	8.83	8.43	9.23	34	16	123	238	146	484
	HPN-100 (13 g/m2/day)									NaPBA (13 g/m2/day)								
	Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)			Total Daily PBA (g)			C_{max} (mcg/mL)			AUC (mcg.h/mL)		
	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%	Median	5%	95%
0-2	4.36	3.45	5.25	163	66	707	1335	679	4852	4.35	3.42	5.232	194	74	921	1534	720	5725
3-5	12.04	9.42	15.398	126	54	489	1038	553	3275	12.02	9.41	15.36	175	68	821	1384	660	4977
6-11	17.62	16.07	17.62	89	39	342	723	392	2005	17.6	16.04	17.6	138	53	615	1047	504	3404
12-18	7.66	6.28	9.033	146	61	597	1201	623	4048	7.63	6.27	9.01	186	71	867	1469	691	5418
Adult	17.62	17.62	17.62	59	28	180	483	284	1034	17.6	17.6	17.6	103	42	459	755	387	2206

Source: hype-pcs-100, Table 4.3:5, Page 35.

Exposure-Response Modeling

Efficacy

The Sponsor performed an analysis to explore the relationship between blood ammonia and exposure. Blood ammonia was represented as $AUC_{0\text{-}24}$ or change in ammonia from time 0 to C_{max}. Exposure variables included dose as total daily dose and dose adjusted for body size as well as PAA AUC. The Sponsor included data from the following switch-over and extension clinical studies: UP 1204-003, HPN-100-005 and HPN-100-005SE, HPN-100-006, HPN-100-007. The results of graphical and correlation analyses did not reveal a consistent or strong relationship between exposure and blood ammonia. The Sponsor notes that the lack of a relationship is most likely due to the fact that the patients enrolled in these studies were already dosed to effect so that their ammonia levels were already within the normal range. Also, other factors contribute to ammonia levels, including residual urea synthetic capacity and dietary nitrogen intake.

Table 9: Pearson's Correlation for Exposure-Response Relationships

Relationship	Group	Pearson's Corr. (r)	Critical Value of Pearson's r*	Statistically Significant?
Ammonia AUC versus total daily PBA	Peds: Both formulation (switch-over)	-0.29	0.360	N
	Peds: HPN-100 (switch-over)	-0.43	0.521	N
	Peds: NaPBA (switch-over)	-0.20	0.521	N
	Adults: Both formulation (switch-over)	0.31	0.173	Y
	Adults: HPN-100 (switch-over)	0.24	0.243	N
	Adults: NaPBA (switch-over)	0.38	0.231	Y
Ammonia AUC versus total daily PBA per BSA	Peds: Both formulation (switch-over)	0.10	0.360	N
	Peds: HPN-100 (switch-over)	0.15	0.521	N
	Peds: NaPBA (switch-over)	0.09	0.521	N
	Adults: Both formulation (switch-over)	0.32	0.173	Y
	Adults: HPN-100 (switch-over)	0.30	0.243	Y
	Adults: NaPBA (switch-over)	0.35	0.231	Y
Pred. ammonia AUC versus total daily PBA per BSA	Peds: Fasting state (extension studies)	-0.16	0.164	Y
	Adults: Fasting state (extension studies)	0.13	0.164	N
Pred. ammonia AUC versus total daily PBA per BSA	Peds: All state (extension studies)	-0.10	0.164	N
	Adults: All state (extension studies)	0.19	0.164	Y
Ammonia AUC (obs. or pred.) versus total daily PBA per BSA	All peds: Extension & switch-over	-0.14	0.301	N
	All adults: Extension & switch-over	0.26	0.173	Y
	All patients: Extension & switch-over	0.18	0.164	Y

p value < 0.05

Source: Ammonia Exposure-Response Report, Appendix 7.1, Page 28.

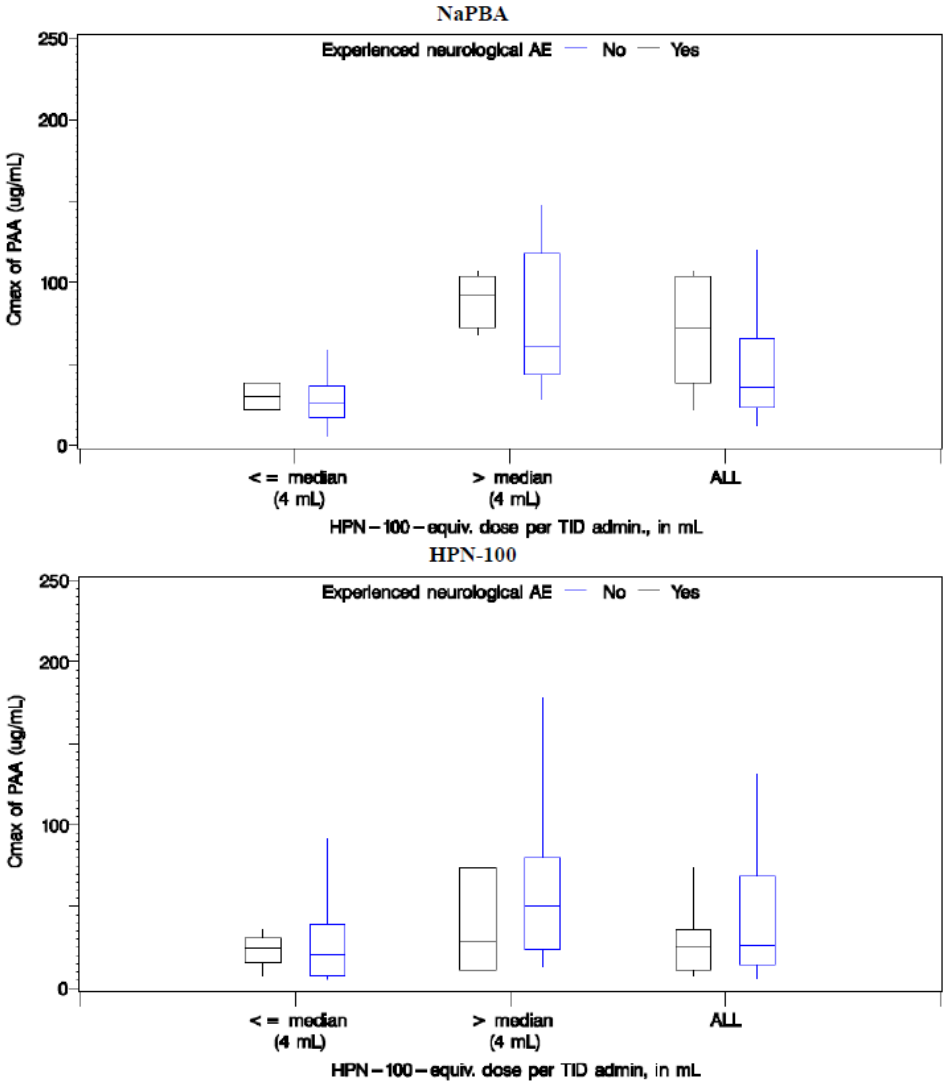
Reviewer's Comment: We agree that it would be difficult to establish a relationship between dose and effect in these studies because patients were already well controlled when they entered the study. One way to understand the dose-response relationship would be to study patients as they are titrated to a dose of BUPHENYL or HPN-100.

Safety

The Sponsor explored the relationship between PAA exposure and neurological treatment-emergent adverse events in UCD patients enrolled in the switch-over studies. Data were summarized for all patients as well as for patients receiving a dose lower or higher than the

median (4mL TID). Within each group, PAA C_{max} values were summarized by neurological adverse event status (Table 10). No relationship was observed.

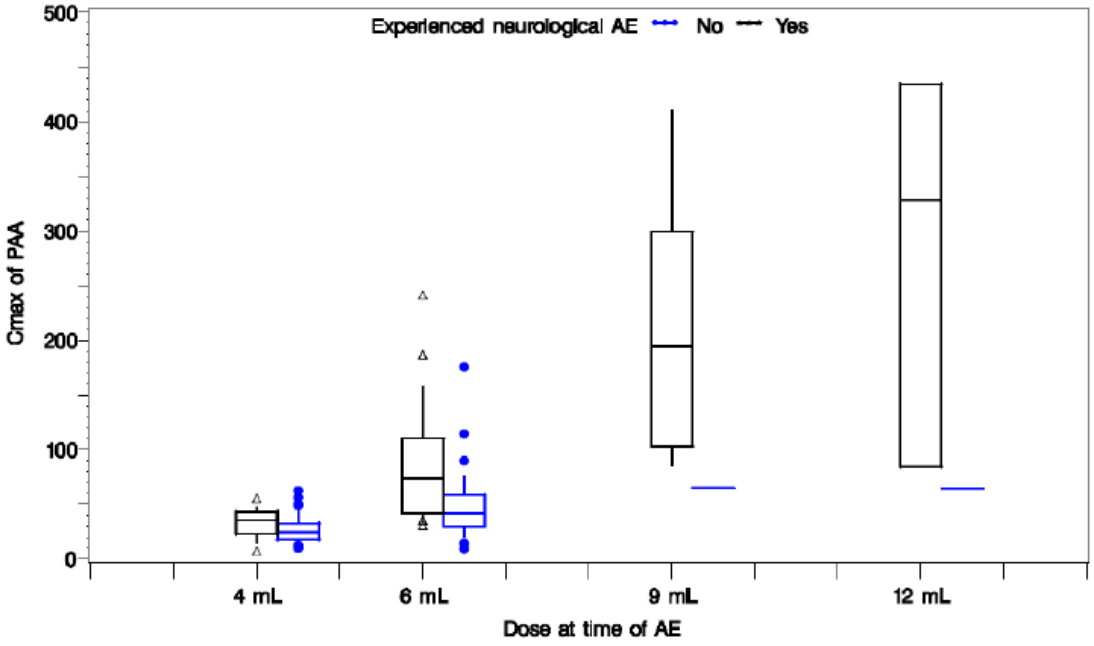
Table 10: PAA C_{max} by Neurological Adverse Event Status in UCD Patients



Source: Summary of Clinical Safety, Figure 2.7.4-3, Page 95

The same analysis was performed in healthy volunteers from study HPN-100-010. Doses of HPN-100 ≥ 6mL TID were associated with a significantly ($p<0.001$) higher incidence of neurological adverse events (Table 11)

Table 11: PAA C_{max} by Neurological Adverse Event Status in Healthy Volunteers



Source: Summary of Clinical Safety, Figure 2.7.4-6, Page 105

Reviewer's Comments: See the Reviewer's analysis in Section 4 of this review.

Reviewer's Analysis

Introduction

The label of the approved product BUPHENYL refers to a study from the literature [Thibault et al., Cancer Research 1994; 54: (1690-1694)] in cancer patients receiving intravenous phenylacetate (250 to 200 mg/kg/day) in which a relationship between PAA concentration and neurotoxicity was observed. The authors of the study reported that adverse events were associated with plasma PAA levels ranging from 499 to 1285 µg/mL. We therefore performed an independent analysis to explore the relationship between PAA levels and neurologic adverse events in the HPN-100 development program.

Objectives

Analysis objectives are:

1. Explore the relationship between PAA concentrations and neurologic adverse events to inform safe dosing

Methods

The relationship between PAA C_{max} and occurrence of a nervous system disorder was explored with the use of logistic regression. A classification and regression tree analysis (CART) was also performed to identify a PAA exposure below which the probability of a nervous system adverse event decreased. Nervous system adverse events of any grade were included in the analysis. Separate analyses were performed for healthy subjects and UCD patients.

Healthy Volunteers

Data from healthy volunteers were obtained from the thorough QT study (HPN-100-010) in which subjects received HPN-100 doses of 13.2 g/d (4 mL TID; n=66), 19.8 g/d (6 mL TID; n=69), 29.7 g/d (9 mL TID; n=9), and 39.6 g/d (12 mL TID; n=4)) for three days. C_{max} was determined on Day 3 of treatment.

UCD Patients

UCD patients from the short-term controlled studies UP-1204-003 (n=11), HPN-100-005 (n=10) and HPN-100-006 (n=43) were included in the analysis. Subjects had two observations periods, one for BUPHENYL and one for HPN-100. For each observation period, the occurrence or absence of a nervous system adverse event was noted. The C_{max} of PAA in each period was also recorded. The modeling analysis did not take into account whether PAA levels were derived from BUPHENYL or HPN-100 dosing.

Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

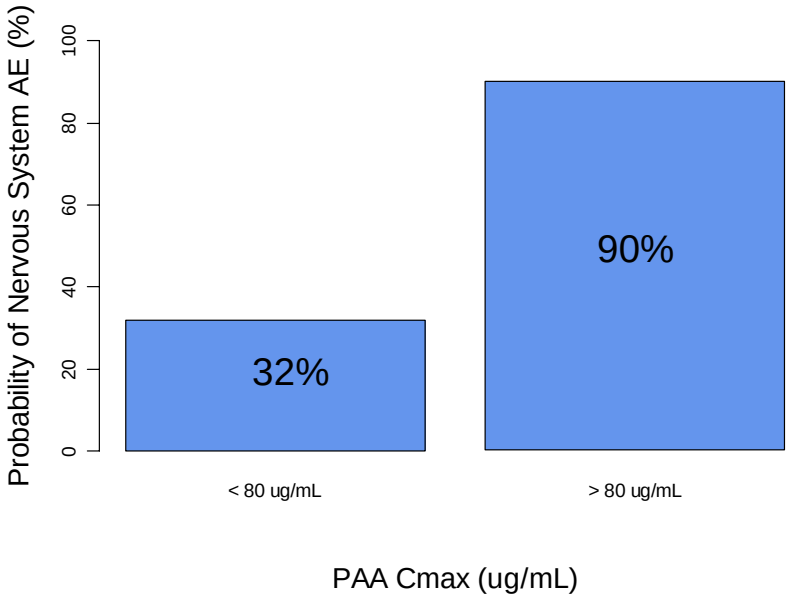
Study Number	Name	Link to EDR
HPN-100-010	PK Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-010/tabulations/sdtm/pp.xpt
HPN-100-010	Dosing Information	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-010/tabulations/sdtm/ex.xpt
HPN-100-010	AE Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/pooled-hi/analysis/legacy/datasets/adae.xpt
HPN-100-006	PK Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-006/tabulations/sdtm/pp.xpt
HPN-100-006	Dosing Information	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-006/tabulations/sdtm/ex.xpt
HPN-100-003	PK Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/up1204-003/tabulations/sdtm/pp.xpt
HPN-100-003	Dosing Information	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/up1204-003/tabulations/sdtm/ex.xpt
HPN-100-005	PK Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-005/tabulations/sdtm/pp.xpt
HPN-100-005	Dosing Information	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/hpn-100-005/tabulations/sdtm/ex.xpt
HPN-100-006, HPN-100-003, HPN-100-005	AE Dataset	//Cdsesub1/evsprod/NDA203284/0000/m5/datasets/pooled-co-safety/analysis/legacy/datasets/adae.xpt

Results

Healthy Volunteers

A significant positive relationship (p=0.00005) was established between PAA C_{max} and the incidence of nervous system adverse events in healthy volunteers (Figure 3). The CART analysis suggests that the incidence of a nervous system adverse event is elevated when the PAA C_{max} exceeds 80 µg/mL (90%) compared to when PAA levels are lower than 80 µg/mL (32%) (Figure 8).

Figure 8: Results of Classification and Regression Tree Analysis in Healthy Volunteers



UCD Patients

A relationship between PAA C_{max} and occurrence of nervous system adverse events was not observed in UCD patients (Figure 2) even though the range of PAA levels in UCD patients was similar to that in healthy volunteers. Potential reasons for the discrepancy between healthy volunteers and patients include the following:

- UCD patients were well-controlled on a stable dose of BUPHENYL upon entering the trial. Presumably, this dose was titrated based on safety as well as ammonia levels. Therefore, for each individual patient, the PAA levels were tolerable. This is supported by the relatively lower overall incidence of nervous system adverse events in UCD patients compared to healthy volunteers.
- UCD patients are more tolerant to nervous system side effects. Some of the manifestations of hyperammonia are similar to those that can be expected at high levels of PAA. Therefore, these patients may have become more tolerant to these adverse reactions over the course of their disease.

For a relationship between PAA levels and nervous system disorders to be observed, one might need to study individual dose titration over a range of doses in an individual This might be achieved in *de novo* patients, but the development program only included a limited number of these individuals.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
make.010.R	Exposure-safety analysis in healthy subjects	Reviews\Ongoing PM Reviews\HPN100_NDA203284_KMK\ER Analyses\Safety
make.010moderate.R	Exposure-safety analysis in healthy subjects (moderate to severe AEs)	Reviews\Ongoing PM Reviews\HPN100_NDA203284_KMK\ER Analyses\Safety
make.patients.R	Exposure-safety analysis in UCD patients	Reviews\Ongoing PM Reviews\HPN100_NDA203284_KMK\ER Analyses\Safety
run31.mod	Final Pop PK model (NONMEM)	Reviews\Ongoing PM Reviews\HPN100_NDA203284_KMK\PPK Analyses\Structure Model
run31.csv	Final Pop PK dataset	Reviews\Ongoing PM Reviews\HPN100_NDA203284_KMK\PPK Analyses\Structure Model

4.2 Demographic and individual PK data in pediatric patients aged 6-17 years

Table 4.2.1. Demographic and blood ammonia during the switch-over from NaPBA toHPN-100 in pediatric patients aged 6-17 years

Patient	Age (years)/ Gender	UCD Subtype	Onset	NaPBA Type	NaPBA Dose (g/d)	NaPBA Dose (g/m^2)	Ammonia AUC		Ammonia Cmax**µmol/L**	
							NaPBA	HPN-100	NaPBA	HPN-100
03-5031	17/F	OTC	Childhood	Tablet	20.0	9.90	735.0	446.4	49.0	43.0
03-5032	16/F	OTC	Childhood	Powder (G Tube)	18.0	12.7	1157.7	503.2	64.0	40.0
03-5033	6/F	OTC	Neonatal	Powder	11.0	10.1	279.7	495.2	34.0	47.0
04-5041	10/F	OTC	Childhood	Powder	12.0	9.45	528.7	487.4	51.2	53.8
04-5042	6/F	OTC	Childhood	Tablet	9.5	10.56	1150.2	1063.6	95.9	73.2
04-5043	7/F	OTC	Childhood	Tablet	10.5	10.94	1279.2	463.1	78.4	25.3
04-5044	6/M	ASS	Neonatal	Powder	9.0	11.84	975.4	842.0	62.9	61.6
05-5051	9/F	OTC	Infantile	Powder	9.0	7.2	914.0	585.4	73.6	44.7
05-5052	12/F	OTC	Infantile	Powder (G Tube)	19.0	15.08	447.9	594.8	25.3	54.3
07-5071	13/F	ASL	Neonatal	Powder	10.5	7.09	886.7	622.2	45.0	37.0
09-5091	10/F	OTC	Infantile	Tablet	8.0	7.55	606.3	538.9	32.9	45.6

Table 4.2.2. Individual plasma concentration of PAA and PBA in pediatric patients aged 6-17 years

Subject	Total dietary protein (g/day)	NaPBA Total daily dose (g/m2)	(g)	PAA NaPBA Cmax (mcg/ml)	PAA NaPBA AUC (mcg*h/ml)	PAA HPN-100 Cmax (mcg/ml)	PAA HPN-100 AUC (mcg*h/ml)	PBA NaPBA Cmax (mcg/ml)	PBA NaPBA AUC (mcg*h/ml)	PBA HPN-100 Cmax (mcg/ml)	PBA HPN-100 AUC (mcg*h/ml)
03-5031	50	9.90	20	85.5	1142	69.2	1040	109	639.4	66	503.9
03-5032	19	12.68	18	148	1740	62.9	858.4	24.9	161.8	113	725.7
03-5033	20	10.09	11	24.3	189.5	115	1313	71.8	315	134	1244
04-5041	34	9.45	12	54.2	488	145	1600	12.6	83.82	61.8	720.2
04-5042	22	10.56	9.5	73.7	767.3	75.3	839.1	84.6	388.4	108	532.1
04-5043	28	10.94	10.5	125	1418	55.4	555.2	62.7	717.6	161	912.9
04-5044	20	11.84	9	118	998.2	109	965.9	14.7	92.51	95.8	475.3
05-5051	30	7.20	9	17.3	116.3	34.8	320.5	3.09	12.34	50	280.9
06-5052	29	15.08	19	119	1173	244	2317	15.5	98.8	127	714.5
07-5071	18	7.09	10.5	4.2	39.15	17.8	129.2	4.19	38.32	27.4	248
09-5091	34	7.55	8	57	430.9	68.2	665.1	7.74	47.68	107	581.1

Table 4.2.3. Individual observed peak concentration[1] after 7 days of dosing in patients aged 2 months to5 years

					Daily dose NaPBA		Ammonia Cmax[1] µmol/L		Ammonia AUC (µmol/L*hours)		**PBA (mcg/ml)**		**PAA (mcg/ml)**	
subject	age (yr)	Sex	UCD	onset	g/m^2	mg/kg	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100
05-1209	2 mo	f	ASS	neonatal	9.39*	500	112.7	24.5	1974	nc	74.7	nc	530	>164
11-1211	11 mo	m	ASL	neonatal	6.73*	297.3	30.3	26.8	517	501	8.52	12.9	14.1	7.73
05-1210	1	m	ASS	neonatal	14.3	583.9	109.2	30.8	1884	399.7	72.2	78.1	286	480
16-1215	1	f	ARG	infantile	7.83	360	67.0	103.0	1419	1199	3.65	44.5	76.8	99.3
04-1207	2	f	ASL	neonatal	5.56	236.2	53.2	32.4	1024	600	5.01	22.5	4.98	37.5
10-1214	2	f	ASL	neonatal	1.4	55.6	44.8	43.3	867	827	blq	11.1	blq	3.48
11-1204	2	f	ASL	neonatal	6.82	271.08	27.5	27.5	572	557	148	47.2	43.6	33.6
04-1202	3	f	OTC	neonatal	8.1	359.15	27.2	20.7	467	403	2.98	51.4	41.7	93.3
05-1213	3	m	ASL	neonatal	8.31	346.15	11.2	21.0	235	nc	269	20.6	18.5	7.43
02-1208	4	f	OTC	infantile	11.9	517.24	112.0	80.0	1712	973	129	15.7	205	207
01-1212	5	m	ASL	neonatal	9.62	373.13	21.2	19.7	265	258	24.9	21.1	57.9	52.4
02-1203	5	m	ASL	neonatal	6.71	241.23	49.0	20.0	604	378	22	41.6	7.52	20.8
11-1201	5	m	ASS	neonatal	11.84	466.32	24.5	29.8	443	543	77.8	76.9	69.6	72.9
11-1206	5	m	ASL	neonatal	10.59	389.61	9.3	13.4	189	258	4.15	39.6	14.4	43.2
16-1205	5	m	OTC	neonatal	7.02	360	92.0	98.0	1537	1513	3.54	32	1.77	27.4

[1] Due to infrequent samplings, underestimated peak concentration can not be ruled out.
*Given in four divided doses

4.3 OCP Filing Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Appendix 4.3 is 3 pages of the Duplicate Clinical Pharmacology and Biopharmaceutics Filing Checklist dated 2/14/12 that can be found in this review

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/s/

INSOOK KIM
12/21/2012

KEVIN M KRUDYS
01/02/2013

NITIN MEHROTRA
01/02/2013

SUE CHIH H LEE
01/02/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Provision of Pharmacovigilance Data

Date:	August 13, 2012
To:	Donna Griebel, MD, Director Division of Gastrointestinal and Inborn Error Products (DGIEP)
Through:	Linda Scarazzini, MD, RPh, Director Division of Pharmacovigilance 1 (DPV 1)
From:	Thang La, PharmD, BCPS Safety Evaluator DPV 1 Ann Mackey, RPh, MPH Safety Evaluator Team Leader, DPV 1 Shewit Bezabeh, MD, MPH Medical Officer, DPV 1
Product Name(s):	Sodium Phenylbutyrate (Buphenyl®)
Subject:	Malignancy
Application Type/Number:	NDA 020572, 020573
Submission Number:	
OSE RCM #:	2012-1662

1 INTRODUCTION

Currently, Sodium Phenylbutyrate (Buphenyl®) is approved for the management of urea cycle disorders. The Division of Gastroenterology and Inborn Errors Products (DGIEP) is reviewing a NDA for HPN-100 or Glycerol Phenylbutyrate (a prodrug) for which the sponsor has conducted carcinogenicity studies in rats and mice. Although the mouse study did not show evidence of increased tumor incidence, the rat study showed a statistically significant increase in pancreatic ancinar cell adenoma and carcinoma, thyroid follicular cell adenoma and carcinoma, adrenal cortical adenoma and carcinoma, uterine polyps and sarcoma, and carcinoma in Zymbal's glands. DGIEP is now requesting DPV to query spontaneous report data and literature for human cases of malignancy reported as a complication of Sodium Phenylbutyrate use.

2 METHODS AND MATERIALS

The Adverse Event Reporting System (AERS) and the literature were searched with the strategy described in Tables I and II.

Table I. AERS Search Strategy	
Date of search	August 3, 2012
Time period of search	No restrictions
Product Terms	Sodium Phenylbu%
MedDRA Search Terms	HLT: Neoplasms malignant site unspecified NEC
Result	No cases retrieved

Table II. Literature Search Strategy	
Date of search	July 30, 2012
Database or system	PubMed
Terms	(sodium phenylbutyrate) AND (malignancies OR malignancy OR lymphoma OR sarcoma OR carcinoma OR adenoma OR safety OR carcinogenicity OR adverse events OR adverse event)
Species	Humans
Article Types	Clinical Trial OR Randomized Controlled Trial OR Review OR Case Reports
Result	No relevant articles

3 DATA AND DISCUSSSION

A search of the AERS database and the NIH PubMed did not identify any reports of malignancy as a possible adverse event with Sodium Phenylbutyrate use. An absence of reports does not imply an absence of adverse events. However, not all malignancies can be reliably detected using uncontrolled AERS data. As a general rule, adverse events with a frequent occurrence or a long latency tend to have multiple confounders and thus are better evaluated using controlled prospective studies. And for sodium phenylbutyrate in particular, any future AERS data (if

available) may also be confounded by indication since the drug has been used as an alternative or investigational treatment for some forms of malignancy.[a, b]

[a] Gore SD et al. Impact of prolonged infusions of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syndromes and acute myeloid leukemia. Clin Cancer Res. 2002 Apr;8(4):963-70.

[b] Phillips JA, Griffin BE. Pilot study of sodium phenylbutyrate as adjuvant in cyclophosphamide-resistant endemic Burkitt's lymphoma. Trans R Soc Trop Med Hyg. 2007 Dec;101(12):1265-9. Epub 2007 Oct 29.

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/s/

THANG X LA
08/14/2012

ANN MACKEY
08/14/2012

SHEWIT BEZABEH
08/14/2012

LINDA J SCARAZZINI
08/15/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203-284	**Brand Name**	Ravicti
OCP Division (I, II, III, IV, V)	DCP III	**Generic Name**	Glycerol phenylbutyrate
Medical Division	DGIEP	**Drug Class**	Ammonia scavenger
OCP Reviewer	Insook Kim, Ph.D.	**Indication(s)**	Adjunctive therapy for chronic management of adult and pediatric patients > 6 years of age with urea cycle disorders involving deficiencies of enzymes in urea cycle
OCP Team Leader	Sue-Chih Lee, Ph.D.	**Dosage Form**	Suspension
Pharmacometrics Reviewer	Kevin Krudys, Ph.D.	**Dosing Regimen**	Starting dose (b) (4) In three divided doses with meals Not to exceed: 17.5 mL (19 g)
Date of Submission	12/23/2011	**Route of Administration**	Oral administration using oral syringe
Estimated Due Date of OCP Review	9/18/2012	**Sponsor**	Ucyclyd Pharma, Inc.
Medical Division Due Date	9/25/2012	**Priority Classification**	Standard
PDUFA Due Date	10/23/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		**QPS Report 148-0403 QPS Report 148-0405 QPS Report 148-0404: Blood ammonia**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:		**4**		• **Lowe2009: effects of pancreatic lipase** • **PAJ005: metabolism of PBA using cryopreserved hepatocytes** • **A5195: in vitro hydrolysis of HPN-100 and impurity standards of (b) (4) in sumulated intestinal fluid** • **A3091-11: in vitro studies of enzymatic hydrolysis**
Blood/plasma ratio:				

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Plasma protein binding:		**1**		• **CFU0003: protein binding**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		• **UP 1204-001: Relative BA study between HPN-100 and NaPBA**
multiple dose:	**X**			**HPN-100-010**
Patients-				
single dose:				
multiple dose:	**x**			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**x**	**1**		**HPN-100-010**
Drug-drug interaction studies -	**x**			
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:		**2**		• **CFU0004: Induction of CYP1A2 and CYP3A4 by PBA and PAA** • **CFU0005: Inhibition of CYP enzymes by HPN-100 and PBA**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**x**	**2**		• **UP 1204-002: hepatic impairment study** • **HPN-100-008 (Part A): run-in to the study for HE**
PD -	**x**			• **HPN-100-010:Effect of HPN-100 on ECG**
Phase 2:	**x**	**2**		• **UP 1204-003: phase 2, open-label, fixed-sequence** • **HPN-100-005: phase 2, open-label, fixed-sequence in pediatric patients (6-17 years old)**
Phase 3:	**x**	**3**		• **HPN-100-006: double-blind, crossover phase 3 study** • **HPN-100-007: open-label phase 3** • **RDCRN5101: UCD Consortium Longitudinal Study**
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**2**		
Phase 3 clinical trial:	**x**	**1**		
Population Analyses -				
Data rich:	**x**	**1**		**HYPE-CS-004**
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		**Buphenyl® as a reference product**
Bioequivalence studies -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		**UP 1204-002**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			**phase 2 study in pediatric to provide dosing information**
Literature References				
Total Number of Studies		**21**		**One study may have multiple objectives**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Did not meet bioequivalence criteria
2	Has the applicant provided metabolism and drug-drug interaction information?	x			In vitro only
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Insook Kim, Ph.D.	2/13/2012
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	2/13/2012
Team Leader/Supervisor	Date

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/s/

INSOOK KIM
02/14/2012

SUE CHIH H LEE
02/14/2012