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Phase 2 Comparison of A Novel Ammonia Scavenging Agent With Sodium Phenylbutyrate In Patients With Urea Cycle Disorders: Safety, Pharmacokinetics And Ammonia Control

Brendan Lee, MD PhD^{1,2}, William Rhead, MD³, George A. Diaz, MD PhD⁴, Bruce F. Scharschmidt, MD⁵, Asad Mian, MD¹, Oleg Shchelochkov, MD¹, JF Marier, PhD, FCP⁶, Martin Beliveau, PhD⁶, Joseph Mauney⁷, Klara Dickinson⁵, Antonia Martinez⁵, Sharron Gargosky⁵, Masoud Mokhtarani, MD⁵, and Susan A. Berry, MD⁸

¹ Baylor College of Medicine, One Baylor Plaza Rm R814, Houston, TX, United States

² Howard Hughes Medical Institute, TX, United States

³ Pediatrics, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI, United States

⁴ Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY, United States

⁵ Hyperion Therapeutics, Inc., 601 Gateway Blvd., Ste. 200, South San Francisco, CA, United States

⁶ Pharsight Corp., Montreal, 2000 Peel St., Suite 570, Quebec, Canada

⁷ Chiltern, 2520 Independence Blvd., Ste. 202, Wilmington NC, United States

⁸ Division of Genetics and Metabolism, University of Minnesota, 420 Delaware Str., SE, Minneapolis, MN, United States

Abstract

Glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) is being studied as an alternative to sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders (UCDs). This phase 2 study explored the hypothesis that GPB offers similar safety and ammonia control as NaPBA, which is currently approved as adjunctive therapy in the chronic management of UCDs, and examined correlates of 24-hour blood ammonia.

Methods—An open-label, fixed sequence switch-over study was conducted in adult UCD patients taking maintenance NaPBA. Blood ammonia and blood and urine metabolites were compared after

Corresponding Author: Brendan Lee, M.D., Ph.D., Investigator, Howard Hughes Medical Institute, Professor, Department of Molecular and Human Genetics; Baylor College of Medicine, One Baylor Plaza Rm R814; Houston, TX 77030, Phone 713-798-8835; Fax 713-798-5168, blee@bcm.tmc.edu.

Conflict of Interest Statement: K. Dickinson, M. Mokhtarani, A. Martinez, S. Gargosky and B.F. Scharschmidt are/were employees of Hyperion at the time of the study. JF Marier and M. Beliveau are employees of Pharsight Corp., which was paid by Hyperion to perform the PK analyses. J. Mauney is an employee of Chiltern, which was paid by Hyperion to perform the biostatistical analyses. None of the other authors have a financial interest in Hyperion, although payments were made by Hyperion to Baylor College of Medicine (B. Lee, PI), Mt. Sinai (G. Diaz, PI), Medical College of Wisconsin (W. Rhead, PI) and the Univ. of Minnesota (S. Berry, PI) for services provided in the conduct of the study.

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7 days (steady state) of TID dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid (PBA).

Results—Ten subjects completed the study. Adverse events were comparable for the two drugs; two subjects experienced hyperammonemic events on NaPBA while none occurred on GPB. Ammonia values on GPB were ~30% lower than on NaPBA (time normalized AUC = 26.2 vs. 38.4 $\mu\text{mol/L}$; Cmax = 56.3 vs. 79.1 $\mu\text{mol/L}$; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time normalized AUC) by *post hoc* analysis. Systemic exposure (AUC₀₋₂₄) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739 $\mu\text{g}\cdot\text{h/mL}$), whereas exposure to phenylacetic acid (PAA) (575 vs. 596 $\mu\text{g}\cdot\text{h/mL}$) and phenylacetylglutamine (PAGN) (1098 vs. 1133 $\mu\text{g}\cdot\text{h/mL}$) were similar. Urinary PAGN excretion accounted for ~54% of PBA administered for both NaPBA and GPB; other metabolites accounted for < 1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN ($r=-0.82$; $p<0.0001$) but weakly or not at all with blood metabolite levels.

Conclusions—Safety and ammonia control with GPB appear at least equal to NaPBA. Urinary PAGN, which is stoichiometrically related to nitrogen scavenging, may be a useful biomarker for both dose selection and adjustment for optimal control of venous ammonia.

Keywords

ammonia; clinical trial; phenylacetylglutamine; phenylbutyrate; urea cycle disorders

INTRODUCTION

Urea Cycle Disorders (UCDs) comprise several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia [1–3]. UCDs result in the accumulation of toxic levels of ammonia in the blood and brain of affected patients and can present in the neonatal period or later in life depending on the severity and type of defect. UCD incidence is estimated to be ~1:8200 live births. [1]. Hyperammonemia is the major cause of morbidity and mortality in UCD patients, and outcome during hyperammonemic crises correlates with blood ammonia levels [4]. Control of blood ammonia levels is the main objective of both acute and chronic management of UCD patients.

Sodium phenylbutyrate (NaPBA), (US trade name: BUPHENYL[®], EU: AMMONAPS[®]) is approved for the chronic adjunctive treatment of certain UCDs and lowers ammonia by enhancing excretion of waste nitrogen. It is a pro-drug that undergoes rapid beta-oxidation to phenylacetate, (PAA), a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine (PAGN) which is then excreted in the urine. PAGN, like urea, contains 2 molecules of nitrogen and therefore represents an alternate to urea for excretion of waste nitrogen [5]. The maximum approved dose of 20 NaPBA grams per day (40 tablets per day) contains approximately 2363 mg of sodium, and current “Dietary Guidelines for Americans 2005” recommends a sodium intake of 2300 mg/day for the general population and 1500 mg/day for individuals with hypertension and selected groups at risk for hypertension [6]. Some UCD patients may be at increased risk for hypertension, and a sodium-free oral treatment option would be especially beneficial for these patients (7, 8).

Glycerol phenylbutyrate (GPB) is an investigational agent being studied as an alternative therapy to NaPBA in UCD patients. It consists of a glycerol backbone with 3 molecules of PBA joined via ester linkage and is a pale yellow nearly odorless and tasteless oil. 17.4 mL of GPB [~1 tsp TID] delivers an amount of PBA equivalent to 20 grams of NaPBA [40 tablets]). The safety and pharmacokinetic (PK) characteristics of GPB have been evaluated in pre-clinical models and in two prior clinical studies, including a randomized, crossover, open-label study in 24 healthy male subjects administered a single oral dose of NaPBA and GPB

(equivalent to 3 g/m² of PBA), and an open label study in 32 adults, including 8 healthy adults and 24 adults with Child-Pugh grade A, B, or C cirrhosis (8 each), each of whom received a single 100 mg/kg dose of GPB followed by 1 week of BID dosing at 100 mg/kg per dose [9]. Collectively, these prior studies suggest that GPB exhibits satisfactory safety, achieves steady state within 4 days or less, and exhibits slow release characteristics. The present phase 2 study, the first in UCD patients, was designed to compare safety, PK and ammonia control of GPB with NaPBA.

MATERIALS AND METHODS

Study Design and Treatments

This was a phase 2, open-label, fixed sequence, switch-over study in patients being treated with NaPBA for a UCD (confirmed via enzymatic, biochemical or genetic testing). Subjects 18 years old or older who had been treated with NaPBA for ≥ 2 weeks were eligible. Liver transplant, hypersensitivity to PBA, PAA or PAGN, clinically significant laboratory abnormalities or ECG findings, or any condition such as infection or medications that could affect ammonia levels were major exclusion criteria.

After enrollment, subjects received NaPBA for at least 7 days, TID with meals at the dose level prescribed by the investigator. On the last day of NaPBA treatment they were admitted to an inpatient research unit for 24-hour PK and ammonia monitoring. Depending on dose, subjects were then either switched directly to 100% GPB, or GPB was introduced in step-wise weekly increments equivalent to ≤ 50 mg/kg/day of NaPBA, with the remainder of the PBA equivalent dose administered as corresponding weekly decrements in the dose of NaPBA. Initiation or increases in GPB dosing were done under observation in an appropriately monitored setting, and subjects were discharged after they were deemed clinically stable and after at least 48 hours of observation. After at least 7 days on 100% GPB administered TID at a dose equivalent to their prescribed dose of NaPBA in terms of PBA delivered, subjects were re-admitted to the research unit for 24-hour PK and ammonia assessment, after which they were switched back to NaPBA. Subjects remained on their prescribed amount of dietary protein throughout the study, received dietary counseling, were instructed to record their diet for at least 3 days prior to each visit and were queried at the end of the study with respect to their preference for NaPBA or GPB.

Compliance was assessed by monitoring drug accountability records and inspection of the returned bottles and vials. Safety was assessed through standard safety laboratory tests, physical exams, serial triplicate ECG, and collection of adverse events. Efficacy was assessed by serial measurement of venous ammonia. An independent Data and Safety Monitoring Board (DSMB) was chartered to oversee the conduct of the study and an interim analysis of safety, ammonia, and PK data was planned after 3 subjects completed the study.

Pharmacokinetic and Ammonia Sampling

Blood samples for analysis of intact GPB, for NaPBA and GPB metabolites including PBA, PAA, PAGN, phenylacetyl glycine (PAG), phenylbutyryl glycine (PBG) and phenylbutyryl glutamine (PBGN), as well as for venous ammonia were collected on the last day of dosing with either NaPBA or GPB at the following time points: at pre-first dose and at 30 minutes and 1, 2, 4, 5, 6, 8, 10, 12, and 24 hours post-first dose. Urine was collected and analyzed for these same drug metabolites and collected in aliquots of 0–6 hours (beginning with the time of the first dose of the day), 6–12 hours and 12–24 hours.

Pharmacokinetic, Pharmacodynamic and Statistical Analyses

PK parameters for PBA, PAA, and PAGN in plasma, PAGN in urine, as well as pharmacodynamic parameters for venous ammonia were calculated with non-compartmental methods using a validated version of WinNonlin Enterprise (Version 5.2). Individual plasma concentrations, urinary amounts and volumes were summarized with descriptive statistics (e.g. number of patients [n], mean, standard deviation [SD], median, minimum, and maximum). The following plasma PK parameters were calculated for PBA, PAA and PAGN using actual time-concentration profiles for each subject: Area under the concentration versus time curve from time 0 (pre-dose) to 24 hours, calculated using the linear trapezoid rule (AUC_{0-24}), maximum plasma concentration at steady state ($C_{max_{ss}}$), minimum plasma concentration at steady state ($C_{min_{ss}}$), time maximum plasma concentration at steady state ($T_{max_{ss}}$), and apparent clearance at steady state (CL_{ss}/F) (calculated as $Dose/AUC_{0-24}$). The terminal elimination half-life of PBA and PAA could not be calculated due to the limited number of samples available after the last dose of GPB and NaPBA. The amount of PAGN excreted in urine over 24 h was calculated from urinary concentration (by multiplying the urinary volume with urinary concentrations). The time-normalized area under the curve (TNAUC) and $C_{max_{ss}}$ were calculated for venous ammonia, a pharmacodynamic marker. TNAUC was calculated as the AUC divided by the time spanned by the actual sampling period.

Ammonia TNAUC and urinary excretion of PAGN were assessed using an ANOVA model with 90% CI for the difference in the means. The 90% CI were constructed from the analysis of variance in the logarithmic scale and back-transformed to the original scale. Intra-patient coefficient of variability for PK and PD parameters were derived from the ANOVA model. Statistical analyses were performed using the LinMix module in WinNonlin Enterprise (Version 5.2). Correlates of blood ammonia were determined using Spearman rank-order correlations. Measurement of total urinary nitrogen (TUN) was performed by Elementar Rapid NIII Analyzer (Mayo Medical Laboratories, Rochester, MN) applying Dumas method of combustion [10] on frozen 24-hr urine samples obtained after 7 days of treatment with NaPBA and GPB.

RESULTS

Patient Demographics and Disposition

A total of 13 subjects with a mean age of 37 (range 21–73) enrolled in the study and 10 subjects (4 males and 6 females) completed all the protocol defined study procedures (Table 1). One subject had an episode of hyperammonemia before switching to GPB. This subject was withdrawn from the study until stable and later re-entered and ultimately completed the study. One subject withdrew consent before transitioning to GPB and 2 other subjects were discontinued at the discretion of the investigators before receiving either study drug. One subject each had argininosuccinate synthetase (ASS), and ornithine translocase (HHH) deficiency; the remaining subjects had ornithine transcarbamylase (OTC) deficiencies. Three subjects had neonatal or infantile onset and all others had either childhood or adult onset UCD. Among the 10 subjects who completed the study, NaPBA had been prescribed for an average (SD) of 9.04 (7.96) years at an average (SD) dose of 191 (44.6) mg/kg/day, equivalent to 7.54 g/m² (1.65) (range = 4.47 to 9.10 g/m², two subjects were taking 20 g/day). Eight of the 10 subjects who completed the study were being prescribed NaPBA at doses below the recommended range of 9.9–13 g/m² (BUPHENYL PI). All but one subject switched from 100% NaPBA to 100% GPB in a single step, and one subject received ~25% less GPB than the PBA molar equivalent of NaPBA due to dose calculation error. Compliance with treatment was excellent; ~99% of all scheduled doses of either NaPBA or GPB were in fact taken based on monitoring of vials and bottles.

Safety and Tolerability

A total of 21 AEs were reported for 7 subjects during 100% NaPBA dosing as compared with 15 AEs for 5 subjects during 100% GPB dosing. Most AEs were categorized as mild (19/21 AEs during 100% NaPBA treatment and 13/15 AEs during 100% GPB treatment) (Table 2). During 100% NaPBA treatment, one AE (mental status change) was considered moderate. During 100% GPB treatment, one subject with history of irritable bowel disease reported an AE (abdominal distension) that was considered severe and one AE (flatulence) that was considered moderate; both resolved without specific treatment. Two subjects experienced SAEs of hyperammonemia while receiving NaPBA, one occurred before the subject began receiving GPB and one occurred 21 days after the subject had completed dosing with GPB and had switched back to NaPBA. Both were categorized as severe. There were no episodes of hyperammonemia on GPB.

Pharmacokinetic and Pharmacodynamic Analyses

All 10 patients who completed the study were considered evaluable for the PK analyses. Plasma PK parameters of PBA, PAA and PAGN and urinary PK parameters of PAGN are summarized in (Table 3) and the 24-hour concentration profiles are depicted in (Figure 1). Systemic exposure (AUC_{0-24}) to PBA following GPB administration was 27% lower than that observed with NaPBA (540 vs. 739 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively) whereas exposure levels of PAA (575 vs. 596 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively) and PAGN (1098 vs. 1133 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively) were similar. PAG, PBG, and PBGN were not detectable in plasma for either drug.

The total amount of PAGN excreted in urine over 24 h following GPB treatment was slightly lower than that observed for NaPBA, but PAGN accounted for 54% of PBA delivered by both drugs (Table 3). Peak urinary PAGN excretion for NaPBA occurred from 6–12 hours after the first dose of the day as compared with 12–24 hours for glycerol phenylbutyrate. Urinary PBA, PAA, PAG, PBG and PBGN each accounted for less than 1% of PBA administered. Total 24-hour creatinine excretion after treatment with NaPBA or glycerol phenylbutyrate was similar with means (SD) of 1.08 (0.43) grams and 1.03 (0.38) grams, respectively. The mean (SD) total urinary nitrogen after treatment with NaPBA and GPB was similar, 9.6 (3.9) g and 9.0 (3.0) g, respectively.

Mean (SD) glutamine levels ($\mu\text{mol}/\text{dL}$) in the 8 patients for whom measurements on both drugs were available were somewhat higher on NaPBA as compared with GPB (739 (294) vs 653 (313); mean decrease = -86.6 (122); ($p > 0.05$).

Blood ammonia values among all patients varied widely on both NaPBA (range 2 – 150 $\mu\text{mol}/\text{L}$; $n = 101$ values total) and on GPB (range 2 – 106 $\mu\text{mol}/\text{L}$, $n = 99$ total values) and also varied widely for any given patient on a single day (2.4- to 54-fold variation on NaPBA; average = 10.4-fold; 2.4 to 12.3-fold variation on GPB; average = 5.4-fold). Mean ammonia values were lower on GPB than on NaPBA when assessed as TNAUC (32% lower: 26.2 vs. 38.4 $\mu\text{mol}/\text{L}$, respectively) and $C_{\text{max,ss}}$ (29% lower: 56.3 vs. 79.1 $\mu\text{mol}/\text{L}$, respectively) (Table 3). Mean ammonia TNAUC values for individual subjects are depicted in (Figure 4); 27.0% of the ammonia values obtained while on GPB were above the upper limit of normal for ammonia at their respective study site (upper limit of normal ranged from 26–35 $\mu\text{mol}/\text{L}$ at the four sites), as compared with 39.6% while on NaPBA (Figure 3). These differences were attributable to lower ‘overnight’ ammonia levels (12–24 hours) and did not reach statistical significance (Figure 2). A *post hoc analysis* indicated non-inferiority of GPB in controlling ammonia compared to NaPBA with respect to TNAUC using standard non-inferiority methodology and the conventional 1.25 upper boundary for the 95% CI. The ratio of the least square geometric means (GPB/NaPBA) was 0.71 with a 95% CI of 0.44 to 1.14.

Correlates of Blood Ammonia

Blood ammonia assessed as TNAUC correlated strongly and inversely with 24-hour urinary PAGN ($r = -0.80$; $p < 0.0001$) following administration of both NaPBA and GPB (Table 4; Figure 4); correlation with urinary PAGN output from 12–24 hours was also significant ($r = -0.75$; $p = 0.001$). Blood ammonia did not correlate with AUC_{0-24} for either plasma PBA or PAA levels in blood for either drug and correlated weakly with plasma PAGN ($r = -0.52$; $p = 0.04$) (Table 4). Urinary PAGN excretion ($r = 0.71$; $p = 0.001$) and venous ammonia ($r = -0.55$; $p = 0.02$) were also significantly correlated with the dose administered.

DISCUSSION

GPB was well tolerated and no clinically important safety issues were identified. Hyperammonemic events requiring hospitalization and recorded as serious adverse events occurred in 2 subjects receiving NaPBA and were determined by the investigators to be due to non-compliance with medication.

The PK characteristics of NaPBA and GPB in plasma were generally similar, with the exception of PBA. The lower plasma levels of PBA in subjects on GPB treatment as compared to NaPBA may reflect differences in the fractional conversion of PBA to PAA and PAGN for the two drugs prior to reaching the systemic circulation. This would be consistent with the ~60% slower absorption of PBA when delivered as GPB vs. NaPBA, presumably because PBA is gradually released from GPB by pancreatic lipases as it passes through the gastrointestinal tract, which would allow more time for intrahepatic/first pass conversion. PAG, PBG and PBGN were not measurable in blood.

PAGN was the major urinary metabolite, with negligible amounts of PAA, PBA, PAG, PBG and PBGN (<1% of PBA dose for each) excreted in urine. 24-hour PAGN output was similar after NaPBA and GPB administration and accounted for ~54% of the administered PBA dose for both drugs.

Blood ammonia levels (TNAUC) were lower on GPB as compared with NaPBA. Although these differences did not achieve statistical significance, a *post hoc* analysis indicated non-inferiority of GPB as compared with NaPBA with respect to venous ammonia assessed as TNAUC, a preliminary finding that needs to be confirmed in a larger number of patients. This difference in ammonia was largely attributable to lower values between 12 and 24 hours, a finding consistent with the delayed peak in urinary PAGN output following glycerol phenylbutyrate (12–24 hours) as compared with NaPBA (6–12 hours), which presumably reflects the delayed release characteristics of GPB. As for ammonia, glutamine levels, which have been shown to correlate with clinical symptoms [3], also tended to be higher on NaPBA than on GPB, although this difference did not reach statistical significance. Collectively, these preliminary findings suggest that GPB is at least equivalent to NaPBA with respect to clearance of waste nitrogen and control of blood ammonia.

Blood ammonia values varied widely both between patients and for the same patient on a given day. The average of all ammonia values on NaPBA exceeded mean upper limit of normal for the study site laboratories and correlated inversely with NaPBA dose. A correlation with dose would not be expected in optimally managed patients if the target of management is normal ammonia values. It is interesting in this regard that 8 of 10 patients were being prescribed lower NaPBA doses than currently recommended in the approved product labeling. Increasing dose in these subjects to within the labeled range (BUPHENYL package insert) might improve ammonia control and, considering the high proportion of UCD patients with self-reported neurological disability, potentially improve neurological outcome [3].

Because of its clinical importance, additional correlates of ammonia control were sought with particular attention to clinically useful biomarkers. As compared with plasma PBA, PAA, or PAGN assessed at 24-hour AUC, with which ammonia showed absent or weak correlation, blood ammonia measured as TNAUC correlated strongly and inversely with UPAGN (Table 4). This is consistent with the fact that urinary PAGN output is stoichiometrically related to waste nitrogen excretion and suggests that urinary PAGN may be useful in dose selection and adjustment. In his pioneering studies, Brusilow outlined the theoretical basis for the relationship between dietary protein intake and PAGN excretion [5]. He pointed out that 18 grams of PAA, if completely converted to PAGN, should mediate excretion of 3.23 grams of waste nitrogen, an amount sufficient to completely replace urea nitrogen as a vehicle for waste nitrogen excretion in subjects receiving a low protein diet (Brusilow 1996) [1]. In support of this prediction, Brusilow, in two separate studies, administered NaPBA or sodium phenylacetate to a 7½ year old male with carbamyl phosphate synthetase deficiency and a 38 year old male with ornithine transcarbamylase deficiency and reported that 80–90% and 92%, respectively, of the PAA administered was excreted as urinary PAGN [5,11]. Furthermore, the FDA-approved label for NaPBA, currently marketed as BUPHENYL® (sodium phenylbutyrate), states that “A majority of the administered compound (approximately 80–100%) was excreted by the kidneys within 24 hours as the conjugation product, phenylacetylglutamine.....[corresponding to].... 0.12–0.15 grams of phenylacetylglutamine nitrogen...”.[12]

In the current study ~54% of administered PBA was excreted as PAGN following the administration of either NaPBA or GPB. This lower fractional conversion to PAGN corresponds to a lower ‘coverage’ of dietary protein per gram of NaPBA. Specifically, 1 gram of PBA would be expected to mediate excretion of waste nitrogen derived from ~2.4 g of dietary protein if completely converted to PAGN, but only ~1.4g of dietary protein at 60% conversion, assuming that nitrogen comprises ~16% of dietary protein and that ~47% of dietary protein is excreted as waste nitrogen (Brusilow 1991) [5]. It is known that secondary metabolites can be excreted after NaPBA treatment including glucuronides and phenylbutyrate beta-oxidation side products [13]. The results further suggest that urinary PAGN output may be useful for dose adjustment. Individual ammonia values varied on average more than 7-fold over 24 hours, even in the context of a controlled clinical study, and 24 hour monitoring of ammonia (TNAUC) as performed in the present study are clinically impractical. Urine collections, by contrast, are routinely performed. Across both treatment periods, 24-hour PAGN excretion was less than 10 grams, which corresponds to a NaPBA dose of ~12 grams assuming 54% conversion, 9 times. In 7 of these instances (77.8%), ammonia TN-AUC exceeded 30 µmol/L (approximate average upper limit of normal among the study sites).

While these preliminary observations need to be validated in a larger group of patients, they suggest that a urinary PAGN output of 10 grams may be one parameter to consider in achieving optimal ammonia control in adult patients. The findings that PAGN output from 12–24 hours also correlated with ammonia and that urinary creatinine output tended to be constant in a given subject further suggest that either shorter collections and/or the ratio of urinary creatinine to PAGN concentration may prove clinically useful and deserves further exploration.

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Urea Cycle Disorders Rare Disease Clinical Research Consortium O'Malley Foundation Fellowship and a National Urea Cycle Disorders Foundation Fellowship.

List of Abbreviations

ASS	arginosuccinate synthetase deficiency
AUC ₀₋₂₄	24 hour area under the curve
glycerol phenylbutyrate	generic name for glyceryl tri (4-phenylbutyrate)
GPB	glycerol phenylbutyrate
HHH	ornithine translocase deficiency
NaPBA	sodium phenylbutyrate
PAA	phenylacetic acid
PAG	phenylacetyl glycine
PAGN	phenylacetylglutamine
PBA	phenylbutyric acid
PBG	phenylbutyryl glycine
PBGN	phenylbutyryl glutamine
PK	pharmacokinetic
TNAUC	time normalized area under the curve
UCD	urea cycle disorder
ULN	upper limit of normal

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Panel A **Panel B**

Panel C

Figure 1. PBA, PAA and PAGN Plasma Concentration Profiles Following One Week of Sodium Phenylbutyrate or Glycerol Phenylbutyrate Treatment

Plasma phenylbutyric acid (PBA; Panel A), phenylacetic acid (PAA; Panel B) and phenylacetylglutamine (PAGN Panel C) were measured for 24 hours following one week of dosing with either sodium phenylbutyrate (NaPBA) or glycerol phenylbutyrate (GPB) and are displayed as mean $\pm$ SD. Times 0 and 24 hours correspond to just prior to dosing and breakfast.

Figure 2. Venous Ammonia Concentration Profiles Following One Week of NaPBA or Glycerol Phenylbutyrate Treatment

Venous ammonia was measured for 24 hours following one week of dosing with either sodium phenylbutyrate (NaPBA) or glycerol phenylbutyrate (GPB) and is displayed as mean $\pm$ SD. Times 0 and 24 hours correspond to just prior to dosing and breakfast.

Figure 3. Venous Ammonia Concentrations In Individual Subjects Following One Week of Sodium Phenylbutyrate or Glycerol Phenylbutyrate Treatment

Venous ammonia in individual subjects following one week of dosing with either sodium phenylbutyrate (NaPBA; left) or glycerol phenylbutyrate (GPB; right). The values shown represent time-normalized area under the curve and are displayed as mean $\pm$ SD. Times 0 and 24 hours correspond to just prior to dosing and breakfast.

Figure 4. Relationship between blood ammonia and urinary output of phenylacetylglutamine (PAGN). Blood ammonia assessed as time-normalized area under the curve (Y-axis) correlated inversely ($r = -0.80$; $p < 0.001$) with urinary PAGN output (X-axis). One subject was excluded from this post hoc analysis since TNAUC was calculable for only 6 hours during treatment with GPB

Table 1

Patients Demographics

	Patients Completing The Study (N=10)
Gender [n (%)]	
Male	4 (40.0)
Female	6 (60.0)
Age (years) at Screening	
Mean (SD)	38.2 (17.85)
Height (cm)	
Mean (SD)	165.6 (7.88)
Weight (kg)	
Mean (SD)	80.41 (31.647)
UCD Diagnosis [n (%)]	
OTC Deficiency ¹	8 (80.0)
ASS Deficiency ²	1 (10.0)
HHH Syndrome ³	1 (10.0)
UCD Onset [n (%)]	
Neonatal (0 – <=30 days)	1 (10.0)
Infantile (>30 days – <=2 years)	2 (20.0)
Childhood or adult onset (>2 years)	7 (70.0)
Duration of NaPBA Treatment (years)	
Mean (SD)	9.04 (7.966)
Median	8.50
Min, Max	0.0, 25.0
Type of NaPBA [n (%)]	
Powder	3 (30.0)
Tablets	7 (70.0)
NaPBA daily dose (mg/kg/day)	
Mean (SD)	190.79 (44.641)
Median	187.50
Min, Max	144.0, 298.0
Average Protein intake during study (mg/kg/day)	
Mean (SD)	0.55 (0.146)
Median	0.60
Min, Max	0.3, 0.8
Percentage of patients treated with L-Citrolline	6 (60%)

¹ Ornithine transcarbamylase deficiency² arginosuccinate synthetase deficiency³ Ornithine translocase deficiency

Table 2Summary of Treatment–Emergent Adverse Events ¹

Adverse Event Term	NaPBA N=13		Glycerol Phenylbutyrate N=10	
	All	Related	All	Related
Any AE (number of subjects)	21 (7)	6 (5)	15 (5)	11 (5)
Gastrointestinal Disorders	7 (3)	2 (2)	5 (2)	5 (2)
Nausea	2	0	0	0
Dyspepsia	1	1	0	0
Abdominal Pain	2	0	0	0
Gastro-oesophageal Reflux Disease	1	1	0	0
Abdominal Distension	0	0	1	1
Abnormal Faeces	0	0	1	1
Constipation	0	0	1	1
Diarrhoea	1	0	0	0
Dry Mouth	0	0	1	1
Flatulence	0	0	1	1
Metabolism and Nutrition Disorders	3 (2)	1 (1)	3 (3)	3 (3)
Increased Appetite	1	1	3	3
Hyperammonaemia	1	0	0	0
Dehydration	1	0	0	0
Nervous System Disorders	6 (3)	2 (2)	0	0
Clonus	1	0	0	0
Dizziness	1	1	0	0
Dysgeusia	1	1	0	0
Encephalopathy	1	0	0	0
Nystagmus	1	0	0	0
Tremor	1	0	0	0
General Disorders and Administration Site Conditions	1 (1)	1 (1)	1 (1)	1 (1)
Chills	1	1	0	0
Hunger	0	0	1	1
Infections and Infestations	0	0	1 (1)	0
Herpes Simplex	0	0	1	0
Psychiatric Disorders	2 (2)	0	0	0
Food Aversion	1	0	0	0
Mental Status Change	1	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	4 (2)	1 (1)
Pharyngolaryngeal pain	0	0	2	1
Cough	0	0	1	0
Rhinorrhoeas	0	0	1	0
Skin and Subcutaneous Tissue Disorders	1 (1)	0	0	0

Adverse Event Term	NaPBA N=13		Glycerol Phenylbutyrate N=10	
	All	Related	All	Related
Skin Odour Abnormal	1	0	0	0
Investigations	0	0	1 (1)	1 (1)
Weight Increased	0	0	1	1
Musculoskeletal and Connective Tissue Disorders	1 (1)	0	0	0
Back Pain	1	0	0	0

Source: UP 1204-003 Summary Tables 14.3.1 and 14.3.3

¹ Table reflects number of events and events reported during 7 days of NaPBA (sodium phenylbutyrate) prior to transition to glycerol phenylbutyrate, and 7 days of sole glycerol phenylbutyrate treatment after completion of transition from NaPBA treatment.

Table 3

PK Parameters and Ammonia Following NaPBA and Glycerol Phenylbutyrate Administration

PK/PD Parameters	Arithmetic Mean (CV%)	
	Glycerol Phenylbutyrate (n=10)	NaPBA (n=10)
PBA in Plasma		
AUC ₀₋₂₄ (µg•h/mL)	540 (60.2) *	740 (49.1) *
Cmax _{ss} (µg/mL)	70.1 (64.7)	141 (44.3)
Cmin _{ss} (µg/mL)	2.87 (265)	0.588 (255)
PAA in Plasma		
AUC ₀₋₂₄ (µg•h/mL)	575 (169) *	596 (124) *
Cmax _{ss} (µg/mL)	40.5 (147)	53.0 (94.7)
Cmin _{ss} (µg/mL)	7.06 (310)	3.56 (194)
PAGN in Plasma		
AUC ₀₋₂₄ (µg•h/mL)	1098 (44.2) *	1133 (31.0) ***
Cmax _{ss} (µg/mL)	71.9 (55.9)	83.3 (25.8)
Cmin _{ss} (µg/mL)	12.1 (134)	16.8 (86.3)
PAGN in Urine		
Total excreted 0–24 hr (µg) ***	10 784 747 (25.9)	12 153 473 (48.2)
0–6 hr (µg)	2381371 (61.3)	2452838 (41.6)
6–12 hr (µg)	3027310 (44.9)	4859121 (54.7)
12–24 hr (µg) ***	5433033 (50.4)	4645447 (59.8)
Recovery of PBA as PAGN (%)	54 (15)	54 (16)
Total Urinary Nitrogen in 24 hr		
Mean (SD) g	9.0 (3.0) **	9.6 (3.9) **
Ammonia		
TNAUC (µmol/L)	26.2 (38.9)	38.4 (51.0)
Cmax _{ss} (µmol/L)	56.3 (49.5)	79.1 (50.6)
% normal ammonia values ⁺	59.5 (34.04)	73.1 (27.04)
Mean Ammonia Ratio (glycerol phenylbutyrate/NaPBA)		
	0.71	
95% CI of ratio	0.44–1.14	

AUC₀₋₂₄: Area under the concentration from time 0 (pre-dose) to 24 hours, Cmax_{ss}: Maximum plasma concentration at steady state, Cmin_{ss}: Minimum plasma concentration at steady state, TNAUC: Time-normalized area under the curve.

*
n=8,

**
n=7,

n=9

⁺ % normal ammonia values are presented as mean (SD)

Table 4

Correlation Between Ammonia and Plasma PAA, PBA and PAGN, and Urinary PAGN (UPAGN) ^{1, 2}

	Plasma PAA	Plasma PBA	Plasma PAGN	UPAGN	Dose	U-PAGN 12-24
N	15	15	16	18	18	16
R	-0.23	0.08	-0.52	-0.80	-0.55	-0.75
p	NS	NS	0.04	<0.0001	0.02	<0.001

¹ Ammonia was measured as time-normalized area under the curve (TNAUC)

² Spearman Rank-Order Correlation

Data from both NaPBA and glycerol phenylbutyrate were included in the analysis

Data from one subject with more than 50% missing data on glycerol phenylbutyrate were excluded.

NS = not significant at $\alpha=0.05$.