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Ammonia Control in Children Ages 2 Months through 5 Years with Urea Cycle Disorders: Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate

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Abstract

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Objectives—To examine ammonia levels, pharmacokinetics (PK), and safety of glycerol phenylbutyrate (GPB, HPN-100) and sodium phenylbutyrate (NaPBA) in young children with urea cycle disorders (UCDs).

Study design—This open label switch-over study enrolled patients ages 29 days to under 6 years taking NaPBA. Patients underwent 24-hr blood and urine sampling on NaPBA and again on a PBA-equimolar dose of GPB and completed questionnaires regarding signs and symptoms associated with NaPBA and/or their UCD.

Results—15 patients (8 ASL, 3 ASS, 3 OTC, 1 ARG) ages 2 months through 5 years enrolled in and completed the study. Daily ammonia exposure (24-hour AUC) was lower on GPB and met predefined non-inferiority criteria (ratio of means 0.79; 95% CI 0.593–1.055; $p = 0.03$ Wilcoxon; 0.07 t -test). Six patients experienced mild AEs on GPB; there were no SAEs or significant lab changes. Liver tests and ASA levels among patients with ASL were unchanged or improved on GPB. Eleven of 15 patients reported 35 symptoms on Day 1; 23 of these 35 symptoms improved or resolved on GPB. Mean systemic exposure to PBA, PAA and PAGN were similar and PAA exposure tended to be higher in the youngest children on both drugs. Urinary PAGN concentration was greater on morning voids and varied less over 24 hours on GPB versus NaPBA.

Conclusions—GPB results in more evenly distributed urinary output of PAGN over 24 hours, was associated with fewer symptoms and offers ammonia control comparable with that observed with NaPBA in young children with UCDs.

Keywords

clinical trial; pharmacokinetics; phenylacetic acid; phenylacetylglutamine; urinary PAGN

Urea cycle disorders (UCDs) comprise several inherited enzyme and transporter deficiencies that impair urea cycle function and result in accumulation of toxic levels of ammonia in the blood and brain, with the most severely affected patients typically presenting early in life ^{1–3}. Control of hyperammonemia is a central objective of treatment, and most patients with UCD, in particular severely affected children with early onset disease, require strict dietary protein restriction ^{4, 5}.

Patients with UCD whose symptoms are not controlled by dietary protein restriction and/or dietary supplements often receive sodium phenylbutyrate (NaPBA), which is approved in the US and Europe for the chronic treatment of UCDs involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (ASS). NaPBA lowers ammonia by enhancing excretion of waste nitrogen in the form of phenylacetylglutamine (PAGN), a urea surrogate that provides an alternate pathway for waste nitrogen excretion ^{4, 6, 7}.

GPB, an investigational agent being developed for treatment of UCDs, has the same mechanism of action as NaPBA ^{8, 9, 10}. However, unlike NaPBA, which is a salt, it is a short-chain triglyceride consisting of glycerol joined by ester linkage to three molecules of PBA, which is released following GPB hydrolysis by pancreatic lipases. It contains no sodium and offers palatability advantages over NaPBA ^{8, 9, 10}.

Although NaPBA has been utilized for UCD treatment for over three decades ¹¹, there are little systematically collected data pertaining either to daily ammonia exposure or the pharmacokinetics of NaPBA in very young patients with UCD ¹⁰. The clinical development of GPB afforded an opportunity to study these issues in young children with UCDs.

METHODS

This study consisted of two parts: a 10-day switch-over period followed by a long-term GPB treatment phase for up to 12 months. This report describes the results of the switch-over part only. This trial was registered with ClinicalTrials.gov (NCT01347073). Eligible patients included children aged 29 days to < 6 years with a confirmed or clinically suspected UCD who had been receiving a stable dose of NaPBA powder for at least 5 days. The protocol was designed to capture information important for evaluating safety, pharmacokinetic (PK), and efficacy while recognizing sampling limitations in young children. Data points of interest were obtained retrospectively for up to 12 months prior to enrollment and prospectively during the study. These included relevant common signs and symptoms associated with UCD or NaPBA treatment.

Pharmacokinetic and Ammonia Sampling During the Switchover

On Day 1, patients were observed for at least 24 hours in a monitored clinical setting while receiving NaPBA and underwent 24-hr blood sampling at 0 (trough), 8, 12 (peak) and 24 hr (trough) time points. On Day 2, patients were switched to a dose of GPB that delivered the same amount of PBA and were discharged once the investigator deemed them to be clinically controlled. After receiving all of their PBA as GPB for 10 $\pm$ 4 days, patients again underwent the same 24-hr blood sampling in a monitored clinical setting, after which interested patients and families were permitted to continue in the long-term follow-up GPB treatment phase. On both Days 1 and 10, time 0 corresponded to pre-dose and pre-breakfast (fasting for at least 4 hours) and subsequent times reflected time post-first dose. Plasma amino acids were collected at time 0 on Days 1 and 10. Because timed urine samples would have required internal or external catheterization and was not ethically feasible, spot urine samples were collected at time 0, 12 and 24 hours on Days 1 and 10.

Diet

The diet chosen for each patient depended on developmental needs, age, and residual enzyme activity. The amount of protein, type of protein, type and amount of dietary supplements as well as total calories consumed on Days 1 and 10 were to be identical and determined at screening to avoid confounding interpretation of the ammonia results.

Biochemical Analyses

NaPBA and GPB metabolites including PBA, PAA, and PAGN were measured by validated liquid chromatography tandem mass spectrometry methods at Quest Pharma Services as previously described ^{8,9, 10}. Venous ammonia was measured by the accredited hospital laboratory at each site and normalized to a standard range of 9–35 μ mol/L. Plasma amino acids were measured by Baylor Medical Genetics Laboratories.

Pharmacokinetic Analyses, Efficacy Endpoints, and Statistical Analyses

Plasma PK measure of PBA, PAA, and PAGN and urine PAGN were calculated using noncompartmental methods with WinNonlin® Enterprise (Version 5.2) as previously described^{8, 9, 10}.

The primary efficacy measure was 24-hour ammonia AUC (NH₃_{24-hour AUC}), calculated based on the sequence of ammonia concentrations outlined above. The primary efficacy endpoint was predefined as comparison of NH₃_{24-hour AUC} on the last day of NaPBA treatment vs. last day of GPB treatment. Secondary efficacy endpoints included the maximum ammonia concentrations and percentage of abnormal ammonia values on Days 1 and 10. All subjects who received any amount of both study medications were included in the intention-to-treat (ITT) population, which was the primary population for analysis of efficacy and pharmacokinetic parameters.

Non-inferiority of GPB to NaPBA with respect to ammonia was prospectively defined. An analysis of variance (ANOVA) model for the natural log-transformed NH₃_{24-hour AUC} was constructed with factors for treatment as a fixed effect and subject as a random effect. The 90% and 95% confidence interval (CI) for the difference between GPB and NaPBA means (GPB minus NaPBA) on the natural log scale was constructed using the least square means from the ANOVA model. The difference and lower and upper confidence intervals of NH₃_{24-hour AUC} values were exponentiated to express the results as geometric means, ratio of geometric means, and corresponding CI on the original scale. Non-inferiority was to be achieved if the upper bound of the 95% CI was less than or equal to 1.25.

Safety Oversight

An independent data and safety monitoring board (DSMB) was chartered to oversee the safety of the study patients. The DSMB reviewed safety data and was notified if the sponsor became aware of a serious adverse event (SAE) or if a patient met any of the pre-defined stopping rules.

RESULTS

Fifteen patients enrolled in and completed the switch-over, including 4 aged 29 days to < 2 years and 11 aged 2 to < 6 years (Table I). Three patients had a G-tube used for NaPBA administration on Day 1; however, no patients used a G-tube for administration of GPB on Day 10. Ten of the 15 enrolled patients had at least one hyperammonemic crisis in the 12 months prior to the study (range = 0 – 7 per patient).

Efficacy

GPB was non-inferior to NaPBA in controlling blood ammonia (Table II). The ratio of the geometric means of NH₃_{24-hour AUC} on Day 10 to Day 1 was 0.79, and the upper 95% CI for NH₃_{24-hour AUC} was below the predefined non inferiority upper margin of 1.25 (Table II). Mean ammonia levels were non-significantly lower on Day 10 (GPB) than on Day 1 (NaPBA) at all time points (Figure, A), as were mean daily average ammonia and peak ammonia levels and the proportion of abnormal ammonia values both overall and at each

time point (Table II). Mean ammonia levels during GPB treatment were similar in the younger as compared with older patients (daily average = 28 and 24 $\mu\text{mol/L}$ for ages 29 days to < 2 years and 2 to < 6 years, respectively). The median $\text{NH}_3_{24\text{-hour}}$ AUC on Days 10 and 1 among the 3 patients who took GPB orally and NaPBA by G-tube were 399.73 and 572.35 $\mu\text{mol/L}\cdot\text{hours}$, respectively.

Pharmacokinetics

Because of difficulty with blood draws in these young patients, PK parameters could not be calculated for one patient each during dosing with NaPBA and GPB. Plasma and urine metabolites concentrations and systemic exposures are depicted in Figure, B. Systemic PBA, PAA and PAGN plasma exposure did not differ significantly between the two drugs (Figure, B). PBA or PAA was undetectable in many samples, primarily those taken fasting; up to 75% for PBA and 46% for PAA after NaPBA treatment with fewer concentrations below the limit of quantitation after GPB treatment. PAGN was measurable in nearly all samples. The fluctuation index, calculated as a percentage based on the difference between maximum and minimum plasma concentration ($(C_{\text{max}} - C_{\text{min}})/C_{\text{min}} \times 100$), was high for all three metabolites, but generally somewhat less on GPB for PBA and PAGN with mean fluctuation index for PBA = 1781% on GPB and 5102% on NaPBA; for PAA = 2141% on GPB and 1289% on NaPBA; and for PAGN = 907% on GPB and 1459% on NaPBA.

Systemic PBA exposure did not differ significantly between younger and older children. However, PAA and to a lesser extent PAGN exposure, were generally higher among pediatric patients under 2 years of age than among patients ages 2 to < 6 years. However, the PK data among the four patients under age 2 showed considerable variability. Data from two patients showed similar patterns to the older children, whereas, the other two patients under two years of age exhibited the highest PAA values observed during the study. The highest PAA value was seen in a two-month-old female with ASS receiving NaPBA at a dose equivalent to 2.7 g (8.28 g/m^2) of PBA ($\text{AUC}^{0-24} = 11130 \mu\text{g}\cdot\text{hr/mL}$ and $C_{\text{max}} = 530 \mu\text{g/mL}$). A one-year-old male with ASS receiving GPB at a dose equivalent to 7.3 g (13.11 g/m^2) of PBA (equivalent of the maximum labeled dose for NaPBA) also showed a high PAA values ($\text{AUC}^{0-24} = 4783 \mu\text{g}\cdot\text{hr/mL}$ and $C_{\text{max}} = 286 \mu\text{g/mL}$).

Urinary PAGN output, assessed as urinary PAGN concentration in $\mu\text{g/mL}$ was significantly greater in the morning spot urines (0 and 24 hours) and generally similar at the 12 hour time points during dosing with GPB as compared with NaPBA (Figure, B). Similar differences were observed for the ratio of concentrations of urinary PAGN to creatinine, which should correct for differences in urine volume, (data not shown). As compared with NaPBA, 24-hour urinary PAGN concentration exhibited less variability during GPB dosing (Figure, B).

Safety

The DSMB met to review subject safety as outlined in the charter and did not request any changes in study conduct. Six patients (40%) experienced AEs during the 10 days of GPB treatment; all were mild in severity. Only one AE was reported for more than 1 patient (vomiting in 2 patients who had been taking NaPBA via gastrostomy tube (G tube) but took GPB orally); 1 patient each reported lymphadenopathy, flatulence, cardiac murmur, and

popular rash. There were no SAEs and no discontinuations due to AEs. Because patients took NaPBA on Day 1 only and because pre-existing symptoms such as nausea and vomiting while taking NaPBA were recorded as pre-existing conditions rather than as AEs unless they worsened, no AEs were recorded on Study Day 1 while taking NaPBA.

Symptoms Related to UCD and Treatment

On Day 1, as part of the collection of data points of interest, 12 of 15 patients reported a total of 38 symptoms associated with NaPBA or their UCD, the most common of which were body odor (6 patients) followed by recurrent abdominal pain, vomiting after taking drug and refusal to eat due to smell or taste of the drug (3 patients each). Most symptoms either improved or resolved on Day 10 (Table III). Improvement was reported for body odor and recurrent vomiting (5 patients each), vomiting after taking drug, abdominal pain, recurrent nausea and refusal to eat (3 patients each), and 1 patient each experienced improvement in the remaining symptoms (Table III). One patient who received NaPBA through a G-tube and who received GPB orally reported a new onset of occasional vomiting upon or after taking GPB.

Amino Acids

Amino acid results were similar on Days 1 and 10 and no statistically significant differences were found. Median glutamine levels were non-significantly lower on Day 10 than Day 1 (677 vs. 731 $\mu\text{mol/L}$, median change from baseline of $-48 \mu\text{mol/L}$). Median levels of branched chain amino acids were similar or non-significantly higher on Day 10 vs. Day 1 (valine = 91 vs. 97.5 $\mu\text{mol/L}$; leucine = 44 vs. 41 $\mu\text{mol/L}$; isoleucine = 20.5 vs. 16.5 $\mu\text{mol/L}$), as were median levels of alanine (318 vs. 291 $\mu\text{mol/L}$) and glycine (300 vs. 281 $\mu\text{mol/L}$).

Laboratory Findings Including Liver Biochemical Tests

There were no changes in hematologic or serum chemistry measures during dosing with GPB as compared with NaPBA. Elevations of alkaline phosphatase, ALT, and aspartate aminotransferase (AST) were detected most commonly among the ASL and ASS subgroups at baseline, among whom these liver tests tended to be similar or lower on Day 10 than at baseline. Mean alkaline phosphatase values decreased during the study (401.8 to 282.2 IU/L; change from baseline of -135.2 IU/L), as did alanine aminotransferase (ALT) values (101.1 IU/L to 64.5 IU/L; change from baseline of -21.6 IU/L). Elevated arginosuccinic acid (ASA) levels were restricted to patients with ASL subtype, among whom 6 of 7 patients with values available at both baseline and Day 10 had lower ASA values on Day 10 than at baseline. Of interest, the patient with ASL with the highest ASA level at baseline (777 $\mu\text{mol/L}$) and the greatest drop in ASA level at Day 10 (585 $\mu\text{mol/L}$; decrease of $-192 \mu\text{mol/L}$) also had the highest levels of alkaline phosphatase and ammonia AUC levels at baseline (2180 U/L and 1024 $\mu\text{g}\cdot\text{h/mL}$) and the greatest decrease in both alkaline phosphatase and ammonia AUC by Day 10 (670 IU, 601 $\mu\text{g}\cdot\text{h/mL}$).

DISCUSSION

The study population is representative of patients with UCD under the age of 6 years, both with respect to the distribution of UCD subtypes and history of prior hyperammonemic crises. Patients with ASL, ASS and ARG deficiency collectively accounted for 12 of the 15 patients, likely reflecting the fact that these are the subtypes generally identified by newborn screening ^{1, 2}.

GPB met the predefined non-inferiority criteria with respect to ammonia control as compared with NaPBA. Indeed, 24-hour ammonia exposure was lower as assessed by area under the curve, a difference that achieved statistical significance by Wilcoxon rank-sum test ($p = 0.033$) but not by paired t-test ($p\text{-value} = 0.075$). Mean ammonia levels were non-significantly lower on GPB at all time points, as were mean daily average ammonia and peak ammonia levels. Mean ammonia levels during GPB treatment were similar in younger children ages 29 days to < 2 years as in children ages 2 to < 6 years. The comparative ammonia findings during GPB and NaPBA treatment were also similar to those previously reported in older children with UCDs ages 6–17, in which daily ammonia exposure on GPB tended to be lower than on NaPBA, a finding which achieved significance in the per-protocol population ¹⁰. The use of a G-tube did not seem to affect systemic exposure and switching from G-tube administration of NaPBA to oral administration of GPB was done in all three patients safely.

The lower ammonia levels on GPB likely reflects the slower absorption of PBA when given orally as GPB as compared with NaPBA, presumably because GPB, a short chain triglyceride, requires digestion by pancreatic lipases whereas NaPBA, a salt, does not ^{8, 9, 10}. The slower absorption of PBA during treatment with GPB was reflected by less variability in urinary PAGN concentrations as well as the ratio of the concentrations of urinary PAGN to urinary creatinine. However, unlike prior studies where total urinary output of PAGN was very similar for the two drugs, the statistically significantly higher concentrations of PAGN in the spot urine samples collected in the morning after dosing with GPB, as well as the significantly higher ratios of urinary PAGN to urinary creatinine in the morning voids, which should correct for potential differences in urine volume between Days 1 and 10, suggest that urinary PAGN output, and hence PBA absorption, may actually be greater during dosing with GPB as compared with NaPBA.

Systemic exposure during dosing with GPB vs. NaPBA resulted in similar plasma exposure to PBA, PAA and PAGN. The high fluctuation indices for PAA, PBA and PAGN can be explained by inter-patient variability as well as the wide range of GPB doses, which corresponded to the PBA equivalent of their prescribed doses of NaPBA ranging from 0.7 g to 8 g. The fluctuation in plasma metabolite levels further suggests that urinary concentration of PAGN, or urinary PAGN to creatinine concentration ratio may be more useful than plasma levels for compliance and therapeutic monitoring in young patients with UCD.

PAA assessment is of particular interest as plasma PAA levels ranging from 499 – 1285 µg/mL have been reported to be associated with reversible toxicities including headache,

somnolence, nausea, and vomiting when PAA is administered intravenously to cancer patients^{13, 14}. The finding of generally higher PAA levels in the youngest patients under the age of 2 appear consistent with prior population PK analyses and dosing simulations, which indicate that the rate of PAA metabolism varies directly with body size¹². Although analyses to date have demonstrated no relationship between PAA levels and adverse events for either GPB or NaPBA in patients with UCD¹⁵, the higher PAA levels in the youngest patients, including one value during NaPBA dosing in the range reportedly associated with adverse events in patients with cancer, suggest that PAA monitoring may be worthwhile during dosing with either NaPBA or GPB.

GPB was associated with no changes in routine laboratory tests, although liver biochemical tests tended to improve during GPB treatment in the subgroup with ASL deficiency. Although the number of patients with ASL (8) is small and the findings therefore need to be interpreted cautiously, the lower levels of ASA and alkaline phosphatase among some patients in this subgroup suggest that the improvement in alkaline phosphatase may be attributable to lesser production and intrahepatic accumulation of ASA during GPB as compared with NaPBA treatment.

Finally, GPB treatment was not associated with clinically significant adverse events in these young patients with UCD. Indeed, the patient and parent questionnaires in the context of the present open label study suggest the patients exhibited fewer adverse effects associated with UCD and/or its treatment while on GPB as compared with NaPBA.

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List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ARG	arginase deficiency
ASA	arginosuccinic acid
ASL	argininosuccinate lyase deficiency
ASS	argininosuccinate synthetase deficiency
AUC₀₋₂₄	24 hour area under the curve
CV%	coefficient of variation
DSMB	Data Safety and Monitoring Board
GPB	glycerol phenylbutyrate (generic name for glyceryl tri (4-phenylbutyrate), also referred to as HPN-100)

ITT	intention to treat
NaPBA	sodium phenylbutyrate
NH₃ 24-hour AUC	ammonia 24-hour area under the curve
OTC	ornithine transcarbamylase deficiency
PAA	phenylacetic acid
PAGN	phenylacetylglutamine
PBA	phenylbutyric acid
PK	pharmacokinetic
UCD	urea cycle disorder
ULN	upper limit of normal
U-PAGN	urinary PAGN

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Appendix

D.C., K.D., M.M., T.M., and B.S. were employees of Hyperion Therapeutics at the time of the study. None of the other authors have a financial interest in Hyperion Therapeutics, although payments were made by Hyperion to Maine Medical Center (W.S.), Mt. Sinai School of Medicine (G.D.), University of Minnesota (S.B.), Oregon Health Sciences University (C.H.), Children's National Medical Center (U.L.-K.), and Case Western Reserve University (S.M.) for services provided in the conduct of the study. Hyperion Therapeutics sponsored the study and, as required by GCP (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>) and in consultation with the investigators and with the US Food and Drug Administration, was involved in all phases including: writing the first draft of the manuscript (B.S.), study design, collection analysis and interpretation of data and the decision on whether and where to submit the manuscript. Each of the coauthors has reviewed the manuscript and takes full responsibility for its content. Additional support was provided by Clinical and Translational Science Awards/General Clinical Research Center grants (Baylor College of Medicine, M01RR00188; Case Western Reserve University, UL1RR024989; Clinical and Translational Science Institute at Children's National Medical Center NIH/NCRR, UL1RR31988; Mount Sinai School of Medicine, UL1RR29887; Oregon Health & Science University, UL1RR24140; University of Minnesota, UL1RR33183; the Urea Cycle Disorders Consortium-NIH U54RR019453), and grants from the O'Malley Foundation.

Trial registered with ClinicalTrials.gov: NCT01347073

Figure.

Ammonia and metabolite levels during treatment with glycerol phenylbutyrate (GPB) and sodium phenylbutyrate (NaPBA). A, Mean $\pm$ SD ammonia levels during treatment with GPB or NaPBA at several time points over 24 hours. B, Mean $\pm$ SD plasma levels of phenylbutyric acid (PBA), phenylacetic acid (PAA) and phenylacetyl glutamine (PAGN) as well as urinary concentrations of PAGN. The limit of quantitation, shown by the dashed line, is 1 $\mu\text{g/mL}$. Systemic PBA exposure did not differ significantly between the two drugs (mean (SD) $\text{AUC}_{0-24} = 255$ (54.5) vs. 483 (146.0) $\mu\text{g}\cdot\text{h/mL}$ on GPB and NaPBA,

respectively). Mean systemic PAA and PAGN exposure were also similar for the two drugs (mean (SD) AUC_{0-24} for PAA = 1096 (214.0) vs. 1458 (211.3) $\mu\text{g}\cdot\text{h}/\text{mL}$ for GPB and NaPBA, respectively; mean (SD) AUC_{0-24} for PAGN = 1130 (71.2) vs. 946 (75.5) $\mu\text{g}\cdot\text{h}/\text{mL}$ for GPB and NaPBA, respectively). Urinary PAGN concentration at 0 hr = 11030 (101) on GPB and 5847 (143) on NaPBA; PAGN:creatinine concentration ratio at 0 hr = 18.8 on GPB and 11.9 on NaPBA, p-value = 0.01; urinary PAGN concentration at 24 hr = 16688 (57) on GPB and 9901 (96) on NaPBA; PAGN:creatinine concentration ratio at 24 hr = 23.4 on GPB and 13.2 on NaPBA, p-value = 0.045) and generally similar at the 12 hour time points (urinary PAGN at 12 hr = 14134 (76) on GPB and 13900 (105) on NaPBA; PAGN:creatinine concentration ratio = 41.4 on GPB and 33.3 on NaPBA, p-value = 0.77).

Table 1

Patient Demographics and Baseline Characteristics

Characteristic	All Patients (N=15)
Male / Female	8 / 7
Age at screening (years)	
Mean (SD)	2.87 (1.885)
Median	3.00
Range	0.0–5.0
Subjects ages 29 days to < 2 years; 2 to < 6 years	4; 11
Race, n (%): White; Black or African-American; Other	12; 2; 1
Weight (kg)	
Mean (SD)	15.2 (4.68)
Median	14.5
Range	6.2–23.1
BSA (m ²)	
Mean (SD)	0.63 (0.142)
Median	0.63
Range	0.3–0.9
UCD diagnosis (n): ASL, ASS, OTC, ARG	8; 3; 3; 1
UCD Onset (n): Neonatal (< 30 days); Infantile (> 30 days to < 2 years)	13; 2
Method of diagnosis (n): amino acid analysis; DNA mutational analysis; enzyme analysis; other	9; 4; 1; 1
Duration of NaPBA treatment (months):	
Mean (SD)	19.3 (17.2)
Median	19.0
Range	0.2–62.0
Daily NaPBA dose (g)	
Mean (SD)	5.28 (2.45)
Range	0.8–9.0
Patients with a G-tube, n (%)	3 (20%)
Hyperammonemic crises prior to enrollment: No. Pts (Total)	
ASL	6(9)
ASS	2(3)
OTC	2(9)
ARG	0(0)
Overall	10 (21)

Table 2

Blood Ammonia by Treatment

Parameter	GPB (N=13)	NaPBA (N=15)
NH₃24-hour AUC (μmol/L*hours)		
Mean (SD)	647.63 (379.944)	914.43 (630.206)
Median	543.08	604.96
Min, Max	258.6, 1513.5	189.3, 1974.8
Ratio of geometric means ^b	0.79	
P-values	0.075 ^c , 0.033 ^d	
90% CI ^b	0.625, 1.002	
95% CI ^b	0.593, 1.055	
NH₃ (umol/L)		
Mean daily ammonia	25	37
Mean Cmax ^e	39	53
Proportion of abnormal values		
Time zero	2/14 (14%)	7/15 (47%)
8 hours	1/14 (7%)	4/14 (29%)
12 hours	2/11 (18%)	6/14 (43%)
24 hours	3/14 (21%)	5/15 (33%)
All time points	8/53 (15%)	22/58 (38%)

^a ANOVA with factors for treatment (fixed effect) and patient (random effect)

^b Results on original scale obtained by exponentiating the corresponding log-transformed results of ammonia during treatment with GPB as compared with NaPBA

^c Paired t-test

^d Wilcoxon signed-rank test

^e Cmax = maximal daily ammonia value

Table 3

Signs and Symptoms Associated with UCD or its Treatment

Symptoms	All Subjects (N=15)					
	Baseline	Improved* on day 10	Present at Day 1 and Unchanged	Not Present at Day 1 but present at Day 10	Not Present at either Day 1 nor Day 10	Unable to Assess
Body odor	6	5	1	0	9	0
Burning sensation in mouth/throat	1	1	0	0	9	5
Chronic or recurrent headache	1	1	0	0	7	0
Episodic lethargy or sleepiness	3	2	1	0	12	0
Heartburn	1	1	0	0	7	7
Irritability/agitation/excessive crying	3	0	3	0	12	0
Protein intolerance	4	2	2	0	7	4
Recurrent abdominal pain	3	3	0	0	9	3
Recurrent nausea	3	3	0	0	7	5
Recurrent vomiting	5	5	0	1**	9	7
Refuse to eat due to taste/smell of drug	3	3	0	0	10	0
Vomiting upon or after taking drug	5	3	2	1**	12	0
Total Symptoms	38	29	9	2		

* Improved denotes either complete resolution or decrease in frequency of the symptom

** Reported by a subject receiving NaPBA through a G tube and stated GPB orally for the first time.