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Authors

Diaz, George A
Krivitzky, Lauren S
Mokhtarani, Masoud
et al.

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AMMONIA CONTROL AND NEUROCOGNITIVE OUTCOME AMONG UREA CYCLE DISORDER PATIENTS TREATED WITH GLYCEROL PHENYLBUTYRATE

George A. Diaz, **Lauren S. Krivitzky**, **Masoud Mokhtarani**, **William Rhead**, **James Bartley**, **Annette Feigenbaum**, **Nicola Longo**, **William Berquist**, **Susan A. Berry**, **Renata Gallagher**, **Uta Lichter-Konecki**, **Dennis Bartholomew**, **Cary O. Harding**, **Stephen Cederbaum**, **Shawn E. McCandless**, **Wendy Smith**, **Gerald Vockley**, **Stephen A. Bart**, **Mark S. Korson**, **David Kronn**, **Roberto Zori**, **J. Lawrence Merritt II**, **Sandesh Sreenath-Nagamani**, **Joseph Mauney**, **Cynthia LeMons**, **Klara Dickinson**, **Tristen L. Moors**, **Dion F. Coakley**, **Bruce F. Scharschmidt**, and **Brendan Lee**

Mount Sinai School of Medicine, Department of Genetics and Genomic Sciences, Department of Pediatrics, New York, NY (G.A.D.); Children's Hospital of Philadelphia, Philadelphia, PA (L.S.K.); Hyperion Therapeutics, South San Francisco, CA (M.M., K.D, T.L.M., D.F.C, B.F.S.); The Medical College of Wisconsin, Milwaukee, WI (W.R.); Long Beach Memorial Hospital, Long Beach, CA (J.B.); The Hospital for Sick Children, Toronto, ON, Canada (A.F.); The University of Utah, Salt Lake City, UT (N.L.); Stanford University, Palo Alto, CA (W.B.); University of Minnesota, Minneapolis, MN (S.A.B.); Children's Hospital Colorado, Aurora, CO (R.G.); Children's National Medical Center, Washington, DC (U.L-K.); Nationwide Children's Hospital, Columbus, OH (D.B.); Oregon Health Sciences University, Portland, OR (C.O.H.); University of California, Los Angeles, CA (S.C.);Case Western Reserve University, Cleveland, OH (S.E.M.); Maine Medical Center, Portland, ME (W.S.); Children's Hospital of Pittsburgh, Pittsburgh, PA (G.V.); SNBL, Baltimore, MD (S.A.B.) Tufts Medical Center, Boston, MA (M.S.K.); Westchester Medical Center, Westchester, NY (D.K.); University of Florida, Gainesville, FL (R.Z.);Seattle Children's Hospital, Seattle, WA (J.L.M.);Baylor College of Medicine, Houston, TX (S.S-N., B.L.); Chiltern, Raleigh, NC (J.M.); and the National Urea Cycle Disorders Foundation (C.L.)

Abstract

Background—Glycerol phenylbutyrate is under development for treatment of urea cycle disorders (UCDs), rare inherited metabolic disorders manifested by hyperammonemia and neurological impairment.

Methods—We report the results of a pivotal phase 3, randomized, double-blind, crossover trial comparing ammonia control, assessed as 24-hour area under the curve (NH_3-$AUC_{0\text{-}24hr}$), and pharmacokinetics during treatment with glycerol phenylbutyrate versus sodium phenylbutyrate (NaPBA) in adult UCD patients and the combined results of 4 studies involving short- and long-term glycerol phenylbutyrate treatment of UCD patients ages 6 and above.

Results—Glycerol phenylbutyrate was non-inferior to NaPBA with respect to ammonia control in the pivotal study, with mean (SD) NH_3-$AUC_{0\text{-}24hr}$ of 866 (661) versus 977 (865) μmol·h/L for glycerol phenylbutyrate and NaPBA, respectively. Among 65 adult and pediatric patients completing 3 similarly designed short term comparisons of glycerol phenylbutyrate versus NaPBA, NH_3-$AUC_{0\text{-}24hr}$ was directionally lower on glycerol phenylbutyrate in each study, similar

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 MS225, Houston, TX 77030, Phone: 713-798-8835, Fax: 713-798-5168, blee@bcm.edu.

among all subgroups, and significantly lower ($p<0.05$) in the pooled analysis, as was plasma glutamine. The 24-hour ammonia profiles were consistent with slow release behavior of glycerol phenylbutyrate and better overnight ammonia control. During 12 months of open label glycerol phenylbutyrate treatment, average ammonia was normal in adult and pediatric patients and executive function among pediatric patients, including behavioral regulation, goal setting, planning and self-monitoring, was significantly improved.

Conclusions—Glycerol phenylbutyrate exhibits favorable pharmacokinetics and ammonia control relative to NaPBA in UCD patients, and long-term glycerol phenylbutyrate treatment in pediatric patients was associated with improved executive function (ClinicalTrials.gov NCT00551200, NCT00947544, NCT00992459, NCT00947297).

Keywords

executive function; glutamine; hyperammonemia; neuropsychological function; sodium phenylbutyrate

Urea cycle disorders (UCD) are rare inborn errors of metabolism which result from mutations in the genes encoding for one of six enzymes or two transporters necessary for normal function of the urea cycle and are characterized by hyperammonemia and life-threatening hyperammonemic crises[1,2]. Hyperammonemia-related neurologic injury ranges from lethal cerebral edema to mild or subclinical cognitive impairment among individuals with milder genetic defects[3]. Abnormalities in executive function, manifested by difficulty in goal setting, planning, monitoring progress and purposeful problem solving significantly impair day-to-day function among children with UCDs, even those with milder disease who present beyond the neonatal period[4].

Management of UCD patients typically involves dietary protein restriction, dietary supplements and, when dietary management alone is insufficient, sodium phenylbutyrate (NaPBA), which is the only approved drug (Ucyclyd Pharma, US trade name: BUPHENYL®, EU: AMMONAPS®) for treatment of UCDs[2,5]. Glycerol phenylbutyrate is an investigational agent being developed for UCDs [6,7,8]. Like NaPBA, it contains phenylbutyric acid (PBA), a pro-drug that is converted via β-oxidation to the active moiety, phenylacetic acid (PAA), which conjugates with glutamine to form phenylacetylglutamine (PAGN). PAGN is excreted in the urine and mediates waste nitrogen excretion. Unlike NaPBA, glycerol phenylbutyrate consists of three molecules of PBA joined to glycerol in ester linkage that is hydrolyzed in the small intestine by pancreatic lipases to release PBA, contains no sodium, has minimal taste and no odor, and 17.4 mL contains the same amount of PBA as 40 tablets of NaPBA, the maximal approved daily dose [6,7,8].

The development of glycerol phenylbutyrate for UCD, rare disorders with fewer than 500 patients in the US currently estimated to be treated with NaPBA, has involved a cooperative effort among investigators of the NIH-funded UCD Consortium, the National Urea Cycle Disorders Foundation and Hyperion Therapeutics [2,9,10]. This report describes the results of the pivotal phase 3 study of glycerol phenylbutyrate for UCD, as well as short and long-term ammonia control and neurocognitive outcomes among a total of 91 UCD patients participating in four clinical trials.

METHODS

Trial Design

The pivotal study (HPN-100-006) was conducted under a Special Protocol Agreement with the US Food and Drug Administration and approved by Health Canada. The study was a

randomized, double-blind, double dummy active-controlled, crossover study to test the hypothesis that glycerol phenylbutyrate is non-inferior to NaPBA with respect to blood ammonia control. The protocol-specified sample size of 44 was based on the number required to achieve 90% power to demonstrate non-inferiority, assuming equivalent ammonia control for GPB and NaPBA. Secondary objectives were to assess safety and pharmacokinetics; plasma glutamine was analyzed post-hoc. Adult UCD patients with UCD subtypes including deficiencies of carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC) and arginosuccinic acid synthetase (ASS) on maintenance therapy with NaPBA were enrolled.

Patients were randomized equally in accordance with a computer-generated central randomization schedule to receive placebo glycerol phenylbutyrate plus active NaPBA or placebo NaPBA plus active glycerol phenylbutyrate for 14 days and then crossed over to receive the alternate treatment. All investigators and study personnel, including the site pharmacist, were blinded to the study drug assignment. The dose of glycerol phenylbutyrate was calculated to deliver the same amount of PBA as each patient's baseline NaPBA dose. Therefore, regardless of treatment, patients received the same amount of PBA throughout the study and followed a stable diet in terms of protein and calorie intake. At the end of each treatment period, patients underwent repeated blood sampling over 24 hours in a monitored clinical setting for NH_3 and plasma and urine levels of metabolites, including PBA, PAA, and PAGN. The primary efficacy measure was daily ammonia exposure, assessed as 24-hour area under the curve (NH_3-$AUC_{0\text{-}24hr}$), which was natural log-transformed and analyzed using an analysis of variance. Non-inferiority was to be achieved if the upper 95% confidence interval (CI) for the ratio of the least squares means between glycerol phenylbutyrate and NaPBA was less than or equal to 1.25. The non-inferiority margin of 1.25 is consistent with FDA guidance on bioequivalence studies and corresponds to an absolute difference of approximately 9 umol/L for a patient with an ammonia at the upper limit of normal (35 umol/L), a clinically insignificant change.

Protocols UP 1204-003 and HPN-100-005, the results of which have been previously reported, were open-label, fixed-sequence, NaPBA to glycerol phenylbutyrate switch-over studies in adult (n=10) and pediatric patients (n=11), respectively, on maintenance therapy with NaPBA[6,8]. The duration of dosing for each treatment was 7 days, after which patients underwent 24 hr ammonia and PK sample collection similar to the pivotal study.

Patients completing studies HPN-100-005 and HPN-100-006 were offered enrollment into one of two 12-month glycerol phenylbutyrate treatment protocols (HPN-100-005SE, HPN-100-007), which required monthly visits that included measurement of fasting ammonia. These protocols also allowed for enrollment of adult and pediatric UCD patients, including all UCD subtypes, who had not completed HPN-100-005 or HPN-100-006. The results of these studies are included for the purposes of pooled analyses.

All patients underwent neuropsychological testing at the time of enrollment in HPN-100-005SE or HPN-100-007 and again at study completion. All patients were administered a short form of the WASI® (Wechsler Abbreviated Scale of Intelligence) to estimate intellectual ability. Pediatric patients were also assessed by two parent questionnaires: the CBCL® (Child Behavior Checklist) to evaluate internalizing (e.g., mood/anxiety) and externalizing behaviors and the BRIEF® (Behavior Rating Inventory of Executive Function) to assess day-to-day executive functioning. The BRIEF consists of several subscales which are combined into two functional domains; the Metacognition Index (MI), which measures cognitive control (e.g., working memory, planning, organization, etc) and the Behavioral Regulation Index (BRI) which measures behavioral control (e.g., inhibition, flexibility, emotional control). In addition to WASI, adults were administered the

Lafayette Grooved Pegboard test (fine motor skills), California Verbal Learning Test-Second Edition (verbal memory), and digit span test (focused attention and working memory).

Hyperammonemic crises were prospectively defined in all protocols as requiring at least one ammonia value over 100 μmol/L plus clinical manifestations compatible with hyperammonemia. All protocols were conducted under a US IND and were reviewed and approved by the appropriate Institutional Review Board. A Data Safety Monitoring Board was engaged throughout the studies and reviewed all safety results periodically. All patients or their parents signed a consent or assent form, which had been approved by local Institutional Review Boards, prior to enrollment and initiation of any protocol-specific activities.

RESULTS

Pivotal Study (HPN-100-006)

Forty-six patients enrolled; 45 received at least one dose of study drug and 44 completed the study and constituted the intention to treat (ITT) population (Table 1). Enrollment began in October of 2009 and follow-up of the last patient was completed in September of 2010. Overall treatment compliance was excellent, with 98% and 100% of patients being at least 80% compliant with the NaPBA and glycerol phenylbutyrate treatments, respectively. The predominance of patients with OTC deficiency in the pivotal study, as well as the entire study population, is generally consistent with the predominance of this UCD subtype in the population at large[9,10,14]. Patients had been taking an average of 14.54 g/day of NaPBA for an average of approximately 13 yrs at enrollment.

NH_3 values on both drugs were lowest after overnight fasting and peaked postprandially. The primary endpoint was achieved; the lower and upper 95% confidence intervals for the ratio of NH_3-$AUC_{24\ hr}$ on glycerol phenylbutyrate relative to NaPBA in the ITT population were 0.799 and 1.034, respectively (Table 2). Irrespective of treatment sequence, plasma glutamine values were lower during treatment with glycerol phenylbutyrate as compared with NaPBA (mean (SD) of 761.2 (243.2) vs. 805.5 (246.6) μmol/L; ULN = 746 (p=0.064 by paired t-test and p= 0.048 by Wilcoxon signed-rank test) (Table 2).

Adverse events (AEs) on study were reported by 61% and 51% of patients during glycerol phenylbutyrate and NaPBA treatment, respectively, with most being gastrointestinal and generally mild. Symptoms suggestive of gastrointestinal disorders included diarrhea, flatulence, abdominal discomfort, dyspepsia, nausea, and oral discomfort. No clinically significant lab or ECG changes were observed. One patient experienced a hyperammonemic crisis and one withdrew early because of high NH_3 and headache; both during NaPBA treatment. One patient had an SAE of gastroenteritis on glycerol phenylbutyrate. There were no deaths during the study. As compared with NaPBA treatment, 24-hour AUC and peak plasma metabolite levels in the pivotal study tended to be lower on glycerol phenylbutyrate (PBA = 433 vs. 508 μg·h/mL, PAA = 447 vs. 599 μg·h/mL, PAGN = 1127 vs. 1252 μg·h/mL) and trough values higher (PBA = 1.44 vs. 0.0905 μg/mL; PAA = 2.11 vs. 0.903 μg/mL; PAGN = 15.1 vs. 9.09 μg/mL). Twenty-four hour urinary PAGN output was very similar (69% to 71% of PBA dose excreted as urinary PAGN for glycerol phenylbutyrate and NaPBA, respectively), but with a greater proportion of UPAGN excreted overnight (i.e. from 12–24 hours) on glycerol phenylbutyrate as compared to NaPBA (Table 2).

Pooled Analysis – Short Term Ammonia Control and Glutamine

The individual and pooled analyses of NH_3-$AUC_{0\text{-}24hr}$ of protocols HPN-100-006, UP 1204-003 and HPN-100-005 are summarized in Table 2 and depicted in the left panel of

Figure 1. Each study showed non-inferiority of glycerol phenylbutyrate to NaPBA and directionally lower ammonia values during glycerol phenylbutyrate treatment, a difference which was statistically significant in the pooled analysis ($p<0.05$). The analysis of non-inferiority was consistent among the subpopulations examined, including age (6–17, ≥ 18 years), sex (male, female), UCD type (OTC, non-OTC), and age at onset of UCD symptoms (≤ 2, > 2 years) (Figure 2).

Blood glutamine levels were non-significantly lower on glycerol phenylbutyrate in both Phase 2 studies and were significantly lower on glycerol phenylbutyrate than NaPBA in the pooled analysis with a mean (SD) of 740.7 (262.8) vs. 792.7 (247.3) μmol/L ($p=0.006$ paired t-test; $p=0.004$ Wilcoxon signed-rank test).

In the pooled analysis the most frequently reported AEs with glycerol phenylbutyrate and NaPBA were GI disorders (32.3% and 25.7%) followed by nervous system disorders (12.3% and 15.7%). Common AEs reported by at least 10% of patients during glycerol phenylbutyrate treatment included diarrhea, flatulence and headache, and, with NaPBA treatment, nausea.

Long-Term Treatment

Forty patients who completed HPN-100-006 and 11 who completed HPN-100-005 enrolled in the long-term protocols; 26 additional adult and pediatric patients were also enrolled in the long-term protocol for a total of 77 UCD patients (51 adult and 26 pediatric patients ages 6–17, collectively including ARG, ASL, ASS, CPS, HHH, and OTC, subtypes) (Figure 3). Mean ammonia values during long term treatment with glycerol phenylbutyrate were similar to the mean fasting values (time 0 or 24 h) observed during the short-term controlled studies and well below the upper limit of normal (35 umol/L) for both pediatric and adult patients at each monthly visit, with monthly means approximately half the upper limit of normal and ranging from 6.3 (Month 9) to 29.6 μmol/L (Month 11) (Figure 1).

Common AEs reported in at least 10% of patients during long-term treatment included vomiting, upper respiratory tract infection, nausea, nasopharyngitis, diarrhea, headache, hyperammonemia, decreased appetite, cough, fatigue, dizziness, and oropharyngeal pain. Only two AEs, hyperammonemia and dizziness, were reported that had not previously been reported with short-term treatment.

Fifteen patients reported 24 hyperammonemic crises in the 12 months preceding enrollment during treatment with sodium phenylbutyrate, whereas 12 patients experienced 15 crises while being treated with GPB on study. As compared with the prior hyperammonemic crises, those during glycerol phenylbutyrate treatment tended to be associated with lower ammonia values at admission, at peak, and at discharge (143.86 versus 171.04 μmol/L, 167.57 versus 183.55 μmol/L, and 35.67 versus 42.41 μmol/L, respectively).

All neuropsychological test results remained stable in adults, as did WASI and CBCL scores in pediatric patients. Most BRIEF subscales at baseline among pediatric patients were at or close to a T score of 65, consistent with borderline and/or clinically significant dysfunction[11]. The T scores of 50 with a standard deviation of 10 are considered normative means for all BRIEF clinical scales, and T score of 65 is generally considered clinically significant executive dysfunction[4]. Among 22 pediatric patients who completed the neuropsychological testing after 12 months (Figure 4), all BRIEF domains were significantly improved with means (SD) at the end of the study as compared to baseline for the Behavioral Regulation Index 53.7 (9.8) versus 60.4 (14.0) ($p = 0.028$); Metacognition Index 57.5 (9.8) versus 67.5 (13.7) ($p < 0.001$); and Global Executive Scale 56.5 (9.7) versus 66.2 (14.0) ($p < 0.001$).

DISCUSSION

The 91 UCD patients enrolled in the trials reported here collectively correspond to approximately 20% of all UCD patients in the US who are currently estimated to be treated with NaPBA. In the pivotal study, glycerol phenylbutyrate met its predefined endpoint of non-inferiority to NaPBA with respect to ammonia control, assessed as NH_3-$AUC_{24\ hr}$. Consistent with the results of each of the prior two phase 2 studies, NH_3-$AUC_{24\ hr}$ was directionally lower during treatment with glycerol phenylbutyrate and the 24-hour profiles for both blood ammonia concentration and U-PAGN excretion were consistent with slow release behavior of glycerol phenylbutyrate[6,8].

Similarities in study design (e.g., study population, efficacy measures, analytical approach) and dosing (PBA mole-equivalent doses of NaPBA and HPN-100) among protocols UP 1204-003, HPN-100-005, and HPN-100-006 allowed for pooling of data from these studies. In the pooled analysis, NH_3-$AUC_{24\ hr}$ was significantly lower during treatment with glycerol phenylbutyrate, a difference that was entirely attributable to better control during late afternoon and overnight hours, when UCD patients might be expected to be particularly vulnerable. These findings were consistent among all pre-defined subgroups. Furthermore, mean blood ammonia levels remained within the normal range for up to 12 months in both adult and pediatric patients.

Glutamine also tended to be lower on glycerol phenylbutyrate as compared with NaPBA by post hoc analyses in each study individually and was significantly lower in the pooled analysis. Glutamine not only represents a precursor for PAGN formation, but it correlates with ammonia control, is often used as a dosing biomarker, and its intracellular accumulation in glial cells is believed to be one of the factors responsible for cerebral edema, a potentially lethal UCD complication[12,13,14].

These encouraging biochemical findings in short terms studies were corroborated by the findings in the long term follow-up studies, which included approximately 40% fewer hyperammonemic crises and improvement in executive functioning among pediatric patients, for whom mean fasting ammonia averaged approximately half the upper limit of normal. These changes in executive function are of particular interest, as problems with behavioral regulation, planning, monitoring progress, purposeful problem solving, etc. are known to compromise the day-to-day function of UCD patients, even those with normal IQ[3,4]. While necessarily uncontrolled, the absence of change in other neuropsychological test scores during the 12 months of treatment, particularly the CBCL which is a parent report measure of the child's functioning in their day-today environment, suggests that these improvements in executive function do not represent a placebo response. Moreover, the improvement in executive function while taking GPB suggests that UCD patients exhibit neuropsychological abnormalities that may be reversible with effective treatment.

Finally, as a result of the significant barriers to conducting randomized, placebo controlled trials in rare disorders, the treatment of inborn errors of metabolism is often based on experience and expert opinion[15,16]. The present findings demonstrate that with effective public-private cooperation, rigorously controlled clinical trials are possible even in ultra-rare genetic diseases.

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List of abbreviations in order of appearance

UCDs	urea cycle disorders
NH_3-$AUC_{0\text{-}24hr}$	24-hour area under the curve for blood ammonia
NaPBA	sodium phenylbutyrate
CI	confidence interval
PBA	phenylbutyric acid
PAA	phenylacetic acid
PAGN	phenylacetylglutamine
WASI	Wechsler Abbreviated Scale of Intelligence
CBCL	Child Behavior Checklist
BRIEF	Behavior Rating Inventory of Executive Function
ITT	intention to treat

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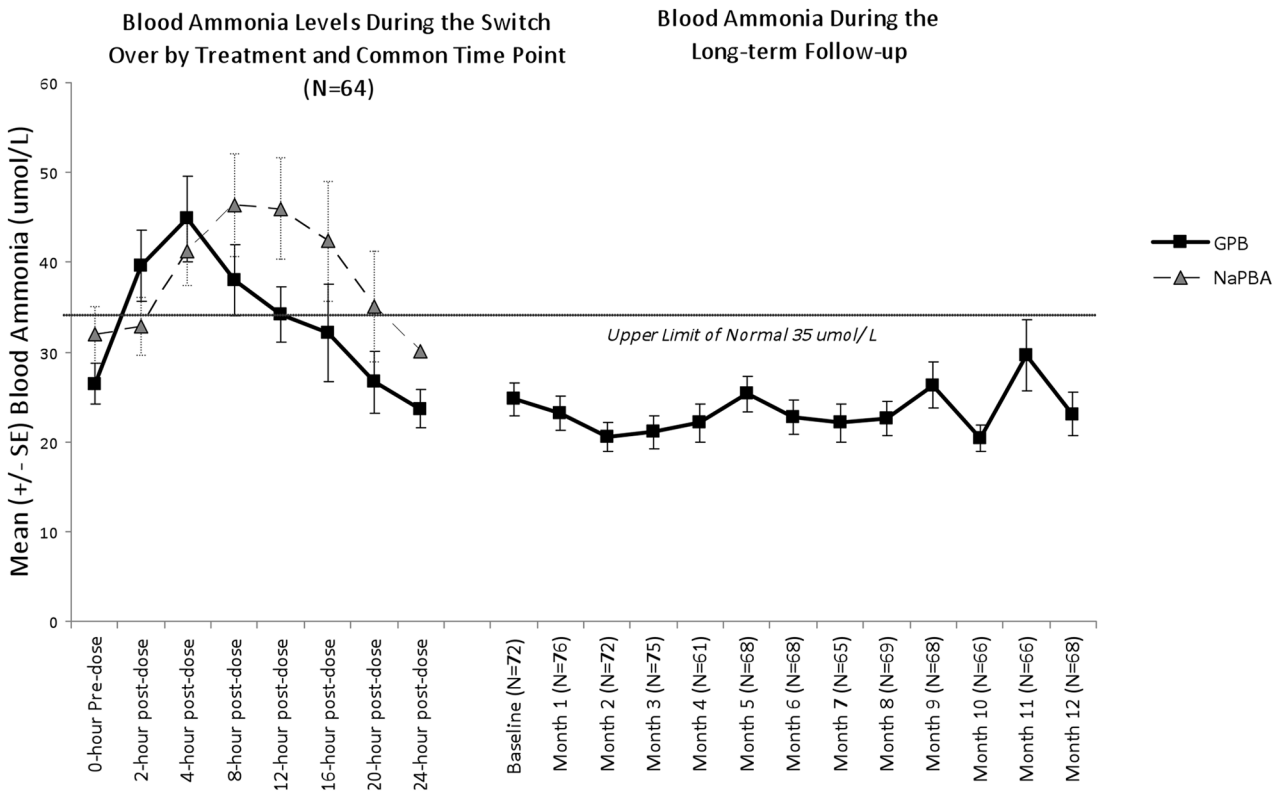

Figure 1.

Short- and Long-Term Blood Ammonia Levels in UCD Patients. This figure depicts the pooled results of ammonia control during short term (2 to 4 week) treatment with sodium phenylbutyrate (NaPBA) or glycerol phenylbutyrate (GPB) (left panel) as well as of long term (up to 1 year) treatment with glycerol phenylbutyrate (right panel). The vertical bars represent standard error (SE). All ammonia values were normalized to a standard range of 9–35 umol/L, and the numbers at the bottom of the right panel indicate the number of patients for whom data were available at each timepoint.

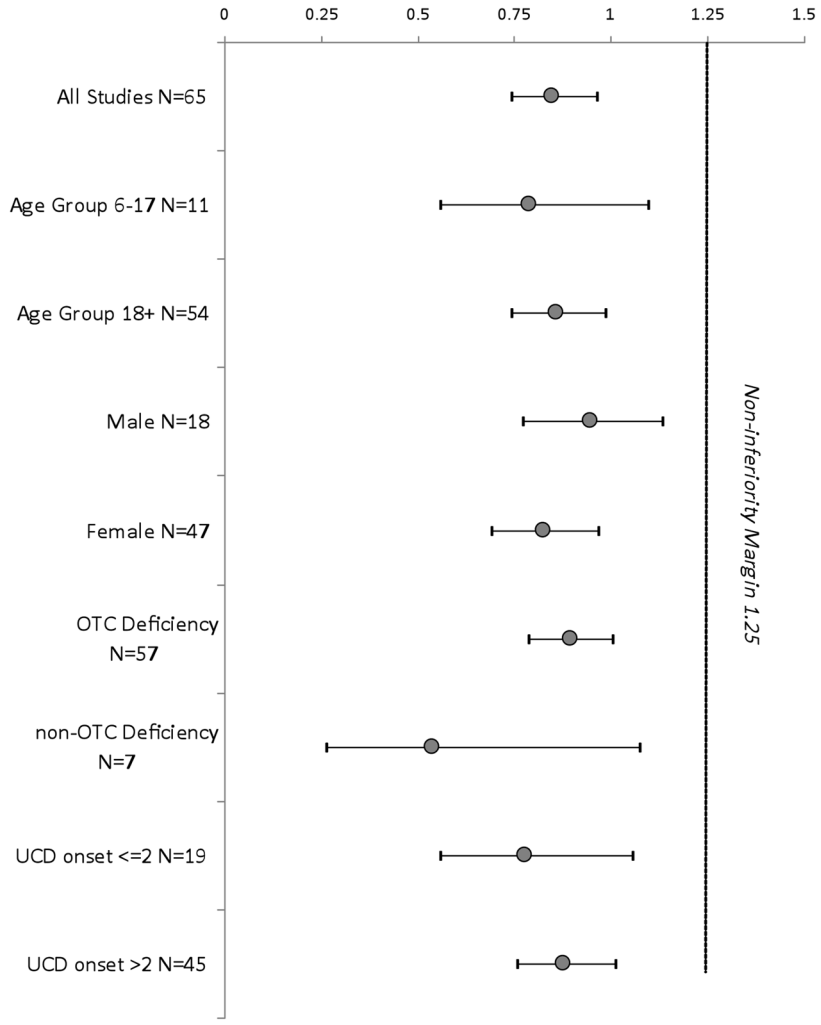

Figure 2.

Pooled Analysis of Blood Ammonia Across Subpopulations. The ratio of geometric means for blood ammonia, assessed as 24 hour area under the curve, during treatment with glycerol phenylbutyrate relative to treatment with NaPBA is depicted along with respective upper and lower 95% confidence intervals. An upper 95% CI of less than 1.25 was pre-specified as demonstrating non-inferiority. An upper 95% CI of less than 1.0 was pre-specified as indicating superiority.

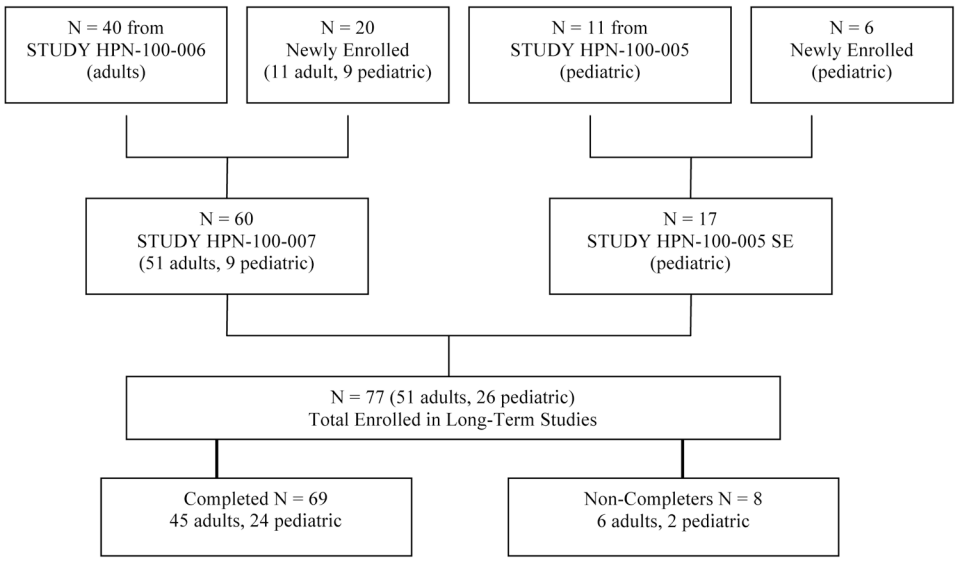

Figure 3.

UCD Patient Disposition. Forty of 44 patients completing Protocol HPN-100-006 enrolled into the 12-month safety protocol, HPN-100-007, in addition to 11 adult and 9 pediatric patients, for a total of 60. All patients completing the switchover part of Protocol HPN-100-005 entered the safety extension of this protocol, HPN-100-005SE, along with 9 additional pediatric patients who enrolled directly into HPN-100-005SE. Of the 77 patients total who enrolled in either HPN-100-007 or HPN-100-005SE, 69 completed, including 45 adult and 24 pediatric patients.

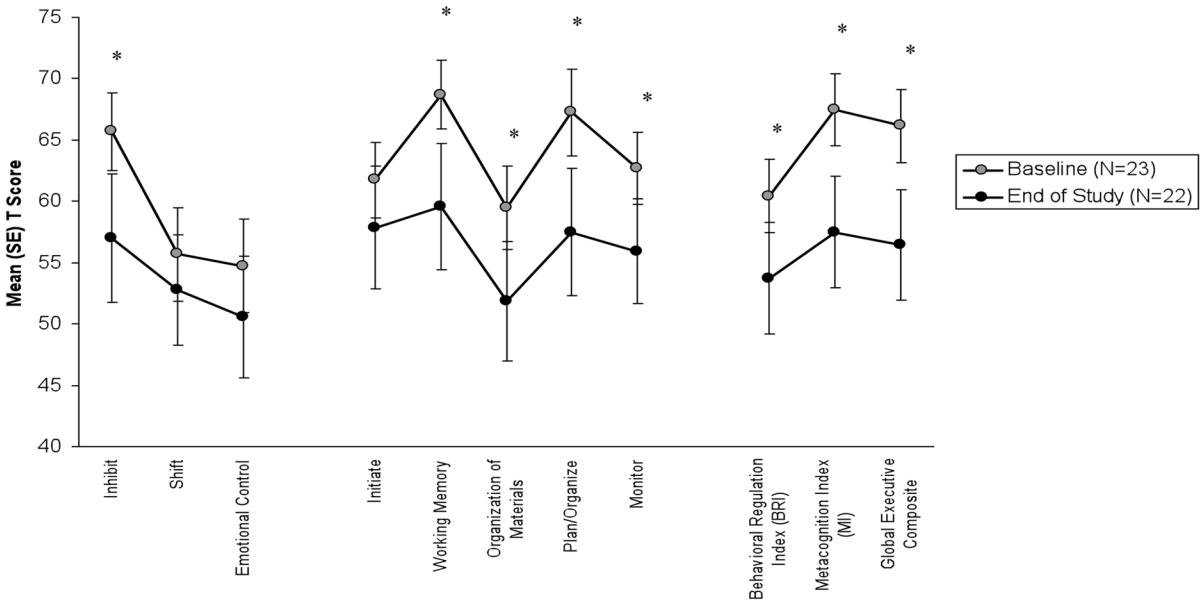

Figure 4.

BRIEF Domain T scores in Pediatric Patients (6–17 yr) Treated with Glycerol Phenylbutyrate for 12 Months Scores are shown at baseline (grey symbols) and at the end of 12 months of glycerol phenylbutyrate treatment (black symbols) for pediatric patients ages 6–17. The T scores of 50 with a standard deviation (SD) of 10 are considered normative means for all BRIEF clinical scales, and a T score of 65 is generally considered clinically significant executive dysfunction (Krivitzky 2009). An asterisk indicates statistically significant improvement (*$p<0.05$). BRIEF stands for Behavior Rating Inventory of Executive Function HEP-12-1233

Table 1

Patient Demographics and Disposition

Protocol Number (Safety Population)		**UP 1204-003 (N = 14)**	**HPN-100-005 (N = 11)**	**HPN-100-006 (N = 45)**	**HPN-100-005 SE HPN-100-007 (N = 77)**
Design		**Phase 2, open-label, fixed-sequence, switch-over**	**Phase 2, open-label, fixed-sequence, switchover**	**Phase 3, randomized, double-blind, crossover, active-controlled**	**12-month open label safety studies**
Sex, n (%)	Male	5 (35.7)	1 (9.1)	14 (31.1)	22 (28.6)
	Female	9 (64.3)	10 (90.9)	31 (68.9)	55 (71.4)
Age (years) at screening visit	Mean (SD)	35.71 (16.3)	10.18 (3.9)	32.73 (13.5)	24.68 (14.7)
	Median	30.00	10.00	28.00	22.00
UCD Subtype n (%)	OTC	12 (85.7)	9 (81.8)	40 (88.9)	63 (81.8)
	CPS 1	0	0	2 (4.4)	1 (1.3)
	ARG	0	0	–	1 (1.3)
	ASS	1 (7.1)	1 (9.1)	3 (6.7)	6 (7.8)
	ASL	0	1 (9.1)	–	3 (3.9)
	HHH	1 (7.1)	0	–	3 (3.9)
Age at Diagnosis n (%)	≤2 yrs old	4 (28.6)	6 (54.5)	10 (22.2)	26 (33.8)
	>2 yrs old	10 (71.4)	5 (45.5)	35 (77.7)	51 (66.2)
Daily dose of NaPBA prior to study (g)	Mean (SD)	13.49 (6.075)	12.41 (4.392)	14.54 (6.808)	NA
	Median	12.78	10.50	15.00	NA
Duration of NaPBA Treatment (mo)	Mean (SD)	97.89 (88.4)	74.68 (48.2)	128.57 (97.4)	NA
	Median	84.00	76.0	120.00	NA
HA crises within 12 months before enrollment, n (%)	Crises	8	7	18	24
	Patients With ≥ 1 crisis	6 (42.9%)	4 (36.4)	9 (20.0)	15 (19.5)
Dose during study (grams of PBA/day)	NaPBA	12.22 (4.048)	10.90 (3.858)	12.33 (5.582)	NA
	GPB	12.36 (3.917)	11.10 (3.805)	12.50 (5.529)	11.84 (5.179)
Completed the protocol	NA	10	11	44	69

Protocol Number (Safety Population)		UP 1204-003 (N = 14)	HPN-100-005 (N = 11)	HPN-100-006 (N = 45)	HPN-100-005 SE HPN-100-007 (N = 77)
Design		**Phase 2, open-label, fixed-sequence, switch-over**	**Phase 2, open-label, fixed-sequence, switchover**	**Phase 3, randomized, double-blind, crossover, active-controlled**	**12-month open label safety studies**
Continued in Safety Extension Studies	NA	NA	11	40	NA

ARG = arginase deficiency; ASS = argininosuccinate synthetase deficiency; ASL = argininosuccinate lyase deficiency; CPS = carbamoyl phosphate synthetase deficiency; HHH = ornithine translocase deficiency; OTC = ornithine transcarbamylase deficiency; SD = standard deviation; UCD = urea cycle disorder; NaPBA = sodium phenylbutyrate (BUPHENYL®); HA = Hyperammonemic Crisis; NA = not applicable HEP-12-1233

Table 2

Blood Ammonia, Plasma Glutamine and Urinary Excretion of Phenylacetylglutamine (PAGN)

		Across Studies			Pooled Primary Efficacy Analysis
		UP 1204-003	**HPN-100-005**	**HPN-100-006**	
N		10	11	44	65
Blood Ammonia $AUC_{0\text{-}24}$ (μmol·h/L)					
Mean (SD)	NaPBA	1303.5 (1082.25)	813.5 (322.11)	976.6 (865.35)	1008.4 (849.50)
	GPB	724.0 (314.95)	602.2 (188.09)	865.9 (660.53)	799.4 (568.53)
Ratio of geometric means [a]		0.63	0.78	0.91	0.84
95% CI[a]		(0.361, 1.116)	(0.556, 1.095)	(0.799, 1.034)	(0.739, 0.962)
p-value[b]		0.075	0.047	0.211	0.016
p-value[c]		0.084	0.054	0.315	0.013
Plasma Glutamine (μmol/L)					
Mean (SD)	NaPBA	815.2 (315.64)	725.1 (204.17)	805.5 (246.60)	792.7 (247.26)
	GPB	751.0 (410.52)	650.3 (187.33)	761.2 (243.20)	740.7 (262.82)
p-value[b]		0.219	0.096	0.064	0.006
p-value[c]		0.156	0.083	0.048	0.004
Urinary PAGN Excretion					
Mean (CV%) (g) 0–24 hr	NaPBA	12.2 (48.2)	12.5 (51.3)	13.6 (52.0)	NA
	GPB	10.8 (25.9)	12.5 (56.9)	13.5 (52.5)	NA
Mean recovery of PBA as PAGN[d]	NaPBA	54%	69 %	71%	71%
	GBP	54%	66 %	69%	68%
% excreted from 0–12 hr[e]	NaPBA	61%	57%	60%	NA
	GPB	50%	45%	52%	NA
% excreted from 12–24 hr[e]	NaPBA	39%	43%	40%	NA
	GBP	50%	55%	48%	NA

AUC = area under the curve; CI = confidence interval; GPB = glycerol phenylbutyrate; ITT = intent-to-treat; max = maximum; min = minimum; NaPBA = sodium phenylbutyrate; SD= standard deviation; CV% = coefficient of variation; PBA = phenylbutyric acid; PAGN = phenylacetylglutamine.

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

[b] p-value obtained from a paired *t*-test

[c] p-value obtained from a Wilcoxon signed-rank test

[d] % of PBA recovered in urine as PAGN

[e] % of total urinary PAGN excretion occurring from 0–12 or 12–24 hours

NA: Not available