

## Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: Safety, pharmacokinetics and ammonia control

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### 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-h 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 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; 2 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  $\mu\text{mol/L}$ ; C<sub>max</sub> = 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 (AUC<sub>0–24</sub>) to PBA on GPB was 27% lower than on NaPBA (540 vs. 739  $\mu\text{g h/mL}$ ), whereas exposure to phenylacetic acid (PAA) (575 vs. 596  $\mu\text{g h/mL}$ ) and phenylacetylglutamine (PAGN) (1098 vs. 1133  $\mu\text{g h/mL}$ ) 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.

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**Abbreviations:** ASS, arginosuccinate synthetase deficiency; AUC<sub>0–24</sub>, 24-h area under the curve; GPB, glycerol phenylbutyrate, generic name for glyceryl tri (4-phenylbutyrate); 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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### 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 two 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 three 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 g 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/m<sup>2</sup> 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-h 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 h 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-h 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 min and 1, 2, 4, 5, 6, 8, 10, 12, and 24 h post-first dose. Urine was collected and analyzed for these same drug metabolites and collected in aliquots of 0–6 h (beginning with the time of the first dose of the day), 6–12 h and 12–24 h.

### 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 h, calculated using the linear trapezoid rule (AUC<sub>0–24</sub>), maximum plasma concentration at steady state (C<sub>max,ss</sub>), minimum plasma concentration at steady state (C<sub>min,ss</sub>), time maximum plasma concentration at steady state (T<sub>max,ss</sub>), and apparent clearance at steady state (CL<sub>ss</sub>/F) (calculated as Dose/AUC<sub>0–24</sub>). 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<sub>max,ss</sub> 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-h 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 two 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/m<sup>2</sup> (1.65) (range = 4.47–9.10 g/m<sup>2</sup>, 2 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/m<sup>2</sup> (BUPHENYL PI). All but 1 subject switched from 100% NaPBA to

100% GPB in a single step, and 1 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

**Table 1**  
Patients demographics.

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

<sup>a</sup> Ornithine transcarbamylase deficiency.

<sup>b</sup> Argininosuccinate synthetase deficiency.

<sup>c</sup> Ornithine translocase deficiency.

**Table 2**  
Summary of treatment-emergent adverse events<sup>a</sup>.

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)
<i>Gastrointestinal disorders</i>	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
<i>Metabolism and nutrition disorders</i>	3 (2)	1 (1)	3 (3)	3 (3)
Increased appetite	1	1	3	3
Hyperammonaemia	1	0	0	0
Dehydration	1	0	0	0
<i>Nervous system disorders</i>	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
<i>General disorders and administration site conditions</i>	1 (1)	1 (1)	1 (1)	1 (1)
Chills	1	1	0	0
Hunger	0	0	1	1
<i>Infections and infestations</i>	0	0	1 (1)	0
Herpes simplex	0	0	1	0
<i>Psychiatric disorders</i>	2 (2)	0	0	0
Food aversion	1	0	0	0
Mental status change	1	0	0	0
<i>Respiratory, thoracic and mediastinal disorders</i>	0	0	4 (2)	1 (1)
Pharyngolaryngeal pain	0	0	2	1
Cough	0	0	1	0
Rhinorrhoeas	0	0	1	0
<i>Skin and subcutaneous tissue disorders</i>	1 (1)	0	0	0
Skin odour abnormal	1	0	0	0
<i>Investigations</i>	0	0	1 (1)	1 (1)
Weight increased	0	0	1	1
<i>Musculoskeletal and connective tissue disorders</i>	1 (1)	0	0	0
Back pain	1	0	0	0

Source: UP 1204–003 Summary Tables 14.3.1 and 14.3.3.

<sup>a</sup> 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.

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-h concentration profiles are depicted in Fig. 1. Systemic exposure ( $AUC_{0-24}$ ) to PBA following GPB administration was 27% lower than that observed with NaPBA (540 vs. 739  $\mu\text{g h/mL}$ , respectively), whereas exposure levels of PAA (575 vs. 596  $\mu\text{g h/mL}$ , respectively) and PAGN (1098 vs. 1133  $\mu\text{g h/mL}$ , 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 (Ta-

**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)
<i>PBA in plasma</i>		
$AUC_{0-24}$ ( $\mu\text{g h/mL}$ )	540 (60.2)*	740 (49.1)*
$C_{\text{max,ss}}$ ( $\mu\text{g/mL}$ )	70.1 (64.7)	141 (44.3)
$C_{\text{min,ss}}$ ( $\mu\text{g/mL}$ )	2.87 (265)	0.588 (255)
<i>PAA in plasma</i>		
$AUC_{0-24}$ ( $\mu\text{g h/mL}$ )	575 (169)*	596 (124)*
$C_{\text{max,ss}}$ ( $\mu\text{g/mL}$ )	40.5 (147)	53.0 (94.7)
$C_{\text{min,ss}}$ ( $\mu\text{g/mL}$ )	7.06 (310)	3.56 (194)
<i>PAGN in plasma</i>		
$AUC_{0-24}$ ( $\mu\text{g h/mL}$ )	1098 (44.2)*	1133 (31.0)***
$C_{\text{max,ss}}$ ( $\mu\text{g/mL}$ )	71.9 (55.9)	83.3 (25.8)
$C_{\text{min,ss}}$ ( $\mu\text{g/mL}$ )	12.1 (134)	16.8 (86.3)
<i>PAGN in urine</i>		
Total excreted 0–24 h ( $\mu\text{g}$ )***	10 784 747 (25.9)	12 153 473 (48.2)
0–6 h ( $\mu\text{g}$ )	2381371 (61.3)	2452838 (41.6)
6–12 h ( $\mu\text{g}$ )	3027310 (44.9)	4859121 (54.7)
12–24 h ( $\mu\text{g}$ )***	5433033 (50.4)	4645447 (59.8)
Recovery of PBA as PAGN (%)	54 (15)	54 (16)
<i>Total urinary nitrogen in 24 h</i>		
Mean (SD) g	9.0 (3.0)**	9.6 (3.9)**
<i>Ammonia</i>		
TNAUC ( $\mu\text{mol/L}$ )	26.2 (38.9)	38.4 (51.0)
$C_{\text{max,ss}}$ ( $\mu\text{mol/L}$ )	56.3 (49.5)	79.1 (50.6)
% normal ammonia values†	59.5 (34.04)	73.1 (27.04)
<i>Mean ammonia ratio</i>		
Glycerol phenylbutyrate /NaPBA	0.71	
95% CI of ratio	0.44–1.14	

$AUC_{0-24}$ , area under the concentration from time 0 (pre-dose) to 24 h;  $C_{\text{max,ss}}$ , maximum plasma concentration at steady state;  $C_{\text{min,ss}}$ , minimum plasma concentration at steady state; TNAUC, time-normalized area under the curve.

† % Normal ammonia values are presented as mean (SD).

\* n = 8.

\*\* n = 7.

\*\*\* n = 9.

ble 3). Peak urinary PAGN excretion for NaPBA occurred from 6–12 h after the first dose of the day as compared with 12–24 h for glycerol phenylbutyrate. Urinary PBA, PAA, PAG, PBG and PBGN each accounted for less than 1% of PBA administered. Total 24-h 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 ( $\mu\text{mol/dL}$ ) 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  $\mu\text{mol/L}$ ; n = 101 values total) and on GPB (range 2–106  $\mu\text{mol/L}$ , 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  $\mu\text{mol/L}$ , respectively) and  $C_{\text{max,ss}}$  (29% lower: 56.3 vs. 79.1  $\mu\text{mol/L}$ , respectively) (Table 3). Mean ammonia TNAUC values for individual subjects are depicted in Fig. 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  $\mu\text{mol/L}$  at the four sites), as compared with 39.6% while on NaPBA (Fig. 3). These differences were attributable to lower 'overnight' ammonia levels (12–24 h) and did not reach statistical significance (Fig. 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 0.44–1.14.

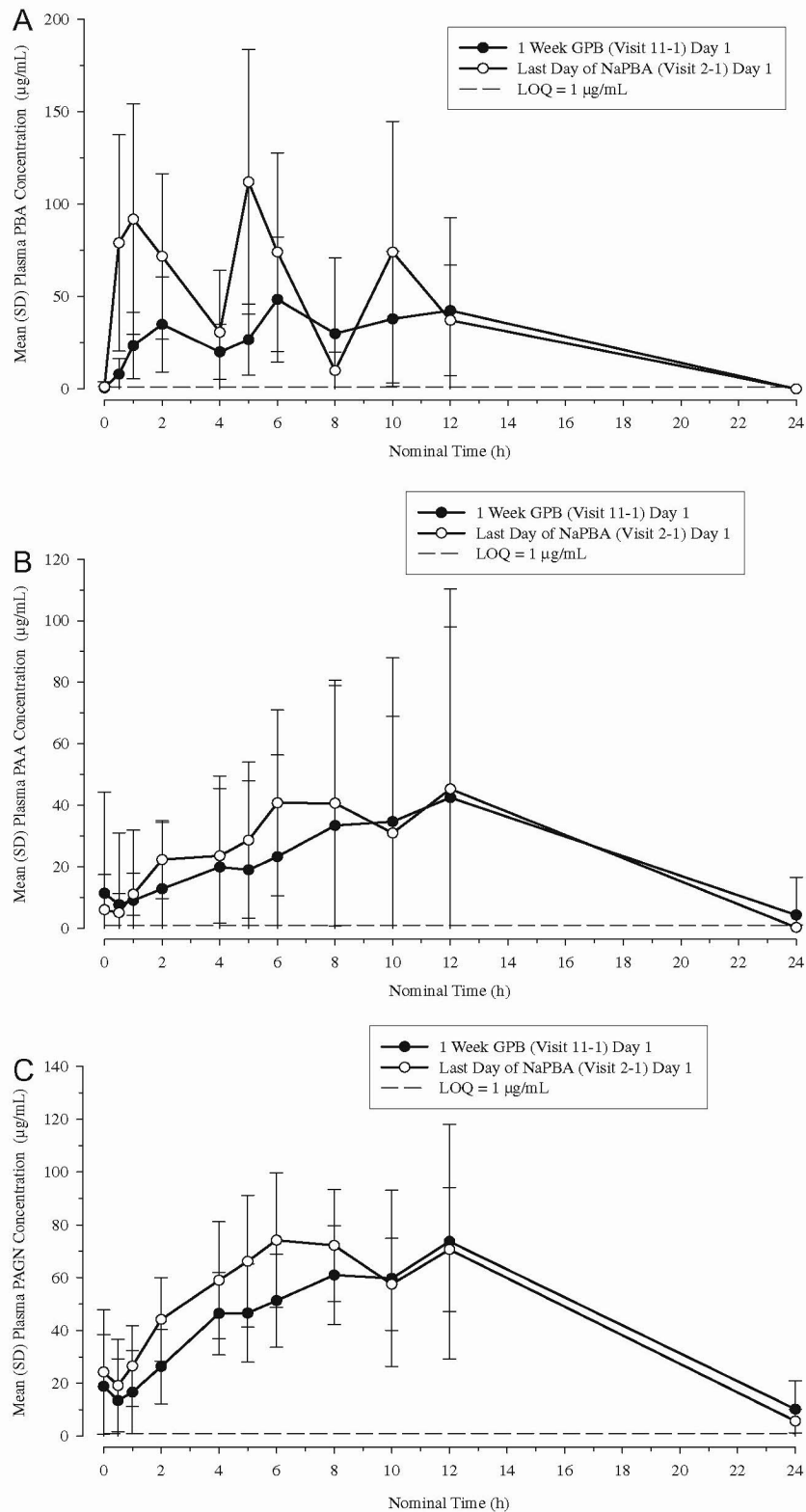
#### Correlates of blood ammonia

Blood ammonia assessed as TNAUC correlated strongly and inversely with 24-h urinary PAGN ( $r = -0.80$ ;  $p < 0.0001$ ) following administration of both NaPBA and GPB (Table 4 and Fig. 4); correlation with urinary PAGN output from 12–24 h 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 intra-



**Fig. 1.** (A) Plasma phenylbutyric acid (PBA), (B) phenylacetic acid (PAA) and (C) phenylacetylglutamine (PAGN) were measured for 24 h following one week of dosing with either sodium phenylbutyrate (NaPBA) or glycerol phenylbutyrate (GPB) and are displayed as means ± SD. Times 0 and 24 h correspond to just prior to dosing and breakfast.

hepatic / 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

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