Glycerol phenylbutyrate (GPB) [or glyceryl tri-(4-phenylbutyrate), also referred to as HPN-100] is an oral investigational agent under development for hepatic encephalopathy (HE) and urea cycle disorders (UCDs). It is a pro-drug of phenylbutyric acid (PBA), currently marketed as sodium phenylbutyrate (NaPBA), for the treatment of UCDs. It consists of glycerol with three molecules of PBA linked as esters. GPB is a pale yellow, nearly odorless and tasteless oil, whereas NaPBA has palatability issues, high sodium content, and high pill burden. The maximum approved daily dose of NaPBA (20 g) corresponds to 40 tablets containing ≈2,400 mg of sodium, which exceeds the daily allowance of 2,300 mg/day recommended in the US Department of Health and Human Services *Dietary Guidelines for Americans, 2005* for the general population and 1,500 mg/day for individuals with hypertension or sodium retaining states.[1] The corresponding dose of GPB is 17.4 mL, which contains no sodium.

NaPBA mediates excretion of waste nitrogen as shown in Fig. 1. PBA is absorbed from the intestine and converted by way of β-oxidation to the active moiety, phenylacetic acid (PAA). PAA is conjugated with glutamine in the liver and kidney by way of *N*-acyl coenzyme A-L-glutamine *N*-acyltransferase to form phenylacetylglutamine (PAGN).[2] Like urea, PAGN incorporates two waste nitrogens and is excreted in the urine.[3]

Because GPB contains no sodium and may be better tolerated than NaPBA, its safety and pharmacology were studied in healthy adults and adults with cirrhosis, as was the handling of GPB by human pancreatic lipases. Monte Carlo simulations were performed to assess metabolites blood levels and therefore clinical safety at doses approximating the highest approved dose of NaPBA for treatment of UCDs.

Materials and Methods

In Vitro *Hydrolysis of GPB by Pancreatic Enzymes*

Recombinant human pancreatic triglyceride lipase (PTL), pancreatic lipase-related protein 2 (PLRP2), colipase, and carboxyl ester lipase (CEL) were expressed in yeast and purified as described.[4-7] Lipase activity against GPB was measured by titration of the released fatty acid (PBA) at 23°C using a Radiometer TIM 854 pH-stat.[8] The assay buffer contained 0.5 mL (550 mg) of emulsified GPB and 1 mM Tris-HCl (pH 8.0), 2 mM $CaCl_2$, 150 mM NaCl, and 0.5 or 4 mM sodium taurodeoxycholate for PTL and PLRP2 or 10 mM sodium cholate for CEL assays. PTL activity was determined with 3 μg of PTL ± 3 μg of colipase

Fig. 1. Urea cycle and removal of waste nitrogen as hippuric acid following administration of sodium benzoate and as phenylacetylglutamine following administration of sodium phenylbutyrate. [Adapted from Summar and Tuchman, J Pediatr 2001;138(Suppl.):S6-S10.]

added at time zero. PLRP2 activity was determined with 10 μg of PLRP2 ± 10 μg of colipase added at time zero. CEL activity was determined with 10 μg of CEL in the absence of colipase. Each reaction was monitored for 5 minutes. The reaction rate was determined from the slope of the linear curve. The rate of 100 mM NaOH titration during the assay was set to maintain a constant pH of 8.0 for PTL and PLRP2 and 50 mM NaOH for CEL. The activity of PTL and PLRP2 against tributyrin and triolein in 1 mM Tris-HCl (pH 8.0), 2 mM $CaCl_2$, 150 mM NaCl, and 4 mM sodium taurodeoxycholate and of CEL against tributyrin and triolein in the same buffer with 10 mM sodium cholate and no taurodeoxycholate was determined using the same methodology.

Study Design and Treatments

UP 1204-001. This was a phase 1, randomized, crossover, open-label study designed to assess safety, tolerability, pharmacokinetic (PK) equivalence, and bioequivalence in healthy adult subjects. Intravenous AMMONUL (a 10%/10% solution of sodium phenylacetate and sodium benzoate) and a formulated oral preparation of GPB were administered in addition to GPB (unformulated) and NaPBA, but only the results for NaPBA and unformulated GPB are reported in this study. Subjects received a single dose of either NaPBA or GPB on separate dosing days, at least 7 days apart. NaPBA and GPB were administered at a dose equivalent to 3 g/m^2 of PBA. PK samples were taken predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose. Urine was collected from 0-4, 4-8, 8-12, and 12-24 hours postdose. PK variables were calculated for PBA, PAA, phenylacetylglycine (PAG), PAGN, phenylbutyrylglycine (PBG), and phenylbutyrylglutamine (PBGN). A test for intact GPB was also conducted in subjects receiving GPB.

Bioequivalence was assessed by calculating 90% confidence intervals for the ratio of geometric means between test and reference treatments. The ratios and confidence intervals were calculated in an analysis of variance model for log-transformed pharmacokinetic variables including treatment, period, and the treatment by period interaction as fixed effects and subject as a random effect.

UP 1204-002. This was an open-label study of the safety and PK equivalence of GPB in subjects with cirrhosis (Child-Pugh score A, B, or C [n = 8 in each group]) compared with age- and sex-matched healthy subjects with normal hepatic function (n = 8). Subjects received a single oral GPB dose (100 mg/kg/day) on day 1, two doses per day (12 hours apart) on days 8-14 (200 mg/kg/d), and a single dose on day 15 (100 mg/kg/d). The single oral dose on day 1 was a fasting dose, whereas the first dose on day 8 was given with a meal. The last GPB dose was administered on the morning of day 15 and was followed by 48 hours of plasma PK sampling and urine collection. PK blood samples were drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose on days 1, 8, and 15, and at 48 hours after dosing on days 1 and 15. Urine was collected from 0-4, 4-8, 8-12, and 12-24 hours postdose on days 1, 8, and 15 and at 24-48 hours postdose on days 1 and 15. PK samples were drawn fasting prior to the morning dose (trough) and 2 hours postdose on days 9-14. A 12-lead electrocardiogram was performed at screening on days 0 and 7, 2 hours postdose on days 1 and 15 (between 9:00 AM and 10:00 AM), and at follow-up (7 days after day 15).

Pharmacokinetic Analyses

Plasma and urine PK parameters were calculated for all subjects and summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum). PK parameters were calculated using time concentration profiles for each subject, including area under the concentration versus time curve from time 0 (predose) to 24 hours (AUC_{0-24}), calculated using the linear trapezoidal rule; maximum plasma concentration at steady state (C_{max}); and the time of maximum plasma concentration at steady state. The amount of PAGN excreted in urine over 24 hours was calculated from urinary concentration (by multiplying the urinary volume with urinary concentrations).

Pharmacokinetic Modeling/Dosing Simulations

Monte Carlo simulations were performed to predict the average and uncertainty (5% and 95% prediction intervals) for simulated plasma PBA, PAA, and PAGN concentrations in a hypothetical clinical trial with 5,000 cirrhotic subjects dosed with GPB at 9 mL (≈9.9 g) twice daily. A concentration time profile was developed for each analyte corresponding to the mean as well as the 5% of patients with the highest and lowest levels.

The population PK model and corresponding PK parameter estimates used for the Monte Carlo simulations were developed using Nonmem VI (NONMEM; ICON Development Solutions, Ellicott City, MD) and PK data from protocols UP 1204-001 and UP 1204-002 and a phase 2 study in UCD patients (protocol UP 1204-003).[9] Simulations were preformed

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