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Glycerol phenylbutyrate treatment in children with urea cycle disorders: Pooled analysis of short and long-term ammonia control and outcomes☆,☆☆

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ABSTRACT

Objective: To evaluate glycerol phenylbutyrate (GPB) in the treatment of pediatric patients with urea cycle disorders (UCDs).

Study design: UCD patients (n = 26) ages 2 months through 17 years were treated with GPB and sodium phenylbutyrate (NaPBA) in two short-term, open-label crossover studies, which compared 24-hour ammonia exposure (AUC_{0-24}) and glutamine levels during equivalent steady-state dosing of GPB and sodium phenylbutyrate (NaPBA). These 26 patients plus an additional 23 patients also received GPB in one of three 12-month, open label extension studies, which assessed long-term ammonia control, hyperammonemic (HA) crises, amino acid levels, and patient growth.

Results: Mean ammonia exposure on GPB was non-inferior to NaPBA in each of the individual crossover studies. In the pooled analyses, it was significantly lower on GPB vs. NaPBA (mean [SD] AUC_{0-24}: 627 [302] vs. 872 [516] μmol/L; p = 0.008) with significantly fewer abnormal values (15% on GPB vs. 35% on NaPBA; p = 0.02). Mean ammonia levels remained within the normal range during 12 months of GPB dosing and, when compared with the 12 months preceding enrollment, a smaller percentage of patients (24.5% vs. 42.9%) experienced fewer (17 vs. 38) HA crises. Glutamine levels tended to be lower with GPB than with NaPBA during short-term dosing (mean [SD]: 660.8 [164.4] vs. 710.0 [158.7] μmol/L; p = 0.114) and mean glutamine and branched chain amino acid levels, as well as other essential amino acids, remained within the normal range during 12 months of GPB dosing. Mean height and weight Z-scores were within normal range at baseline and did not change significantly during 12 months of GPB treatment.

Conclusions: Dosing with GPB was associated with 24-hour ammonia exposure that was non-inferior to that during dosing with NaPBA in individual studies and significantly lower in the pooled analysis. Long-term GPB dosing was associated with normal levels of glutamine and essential amino acids, including branched chain amino acids, age-appropriate growth and fewer HA crises as compared with the 12 month period preceding enrollment.

Abbreviations: ASL, argininosuccinate lyase; ASS, argininosuccinate synthase; AUC_{0-24}, 24 hour area under the curve; GPB, glycerol phenylbutyrate (generic name for glyceryl tri (4-phenylbutyrate), also referred to as HPN-100 or RAVICTI®); NaPBA, sodium phenylbutyrate; OTC, ornithine transcarbamylase; PAA, phenylacetic acid; PAGN, phenylacetylglutamine; PBA, phenylbutyric acid; PK, pharmacokinetic; UCD, urea cycle disorder.

☆ ClinicalTrials.gov identifiers: NCT00947544, NCT01347073, and NCT00947297.

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1. Introduction

Urea cycle disorders (UCDs) are inherited deficiencies of one of the enzymes or transporters involved in the urea cycle that convert ammonia to urea. Deficiency of any of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients [1]. UCDs can present in the neonatal period or later in life depending on the severity and type of defect [1–3]. Medical management of UCDs is aimed at reducing waste nitrogen by restricting protein intake, the use of amino acid supplements and, when necessary, the use of alternative pathway drugs such as sodium phenylbutyrate (NaPBA). NaPBA lowers ammonia by enhancing excretion of waste nitrogen in the form of phenylacetylglutamine (PAGN), a urea surrogate that provides an alternative pathway for waste nitrogen excretion [4–6].

Glycerol phenylbutyrate (GPB; also known as HPN-100 or RAVICTI®) was approved in the US in 2013 for the treatment of UCD patients ages 2 years and above whose ammonia levels cannot be managed through dietary restriction of protein alone. GPB has the same mechanism of action as NaPBA, but is a sodium- and sugar-free pre-pro-drug of phenylacetic acid (PAA) that has little odor or taste. It consists of three molecules of phenylbutyrate (PBA) joined to glycerol in an ester linkage and is hydrolyzed in the small intestine to release the pro-drug PBA and glycerol. PBA is then converted to the active moiety, PAA. Because GPB requires digestion by pancreatic lipases, PBA delivered orally as GPB is absorbed about 75% more slowly as compared with NaPBA [6–8].

Short-term studies in pediatric UCD patients indicated that GPB provides at least equivalent ammonia control compared to NaPBA [9,10] and a long-term study among pediatric patients ages 6 through 17 showed that average ammonia levels remained within the normal range during 12 months of GPB treatment [11]. However, limited data are available for young pediatric patients who, by virtue of their earlier age of diagnosis, would be expected to have more severe urea synthetic deficits than adults. Prior reports have described the results of short-term dosing of pediatric patients ages 2 months through 5 years and 6 through 17 years with GPB vs. NaPBA [9–11]. The present report includes a comparative pooled analysis of ammonia control among all pediatric patients during short-term dosing with NaPBA vs. GPB as well as new data on long-term GPB dosing in pediatric patients pertaining to ammonia, amino acid levels, dietary intake, growth and the incidence of hyperammonemic (HA) crises.

2. Materials and methods

2.1. Study design and treatments

Protocol HPN-100-012 enrolled patients aged 29 days to <6 years and protocols HPN-100-005 and HPN-100-007 enrolled patients aged 6 to 17 years. Protocols HPN-100-005 and HPN-100-012 (both open-label, Phase 2 studies) were comprised of two periods: i) a 7- or 10-day crossover period to compare equivalent doses of GPB and NaPBA and ii) a long-term treatment period with GPB for up to 12 months [9,10]. Protocol HPN-007 was an open-label, Phase 3 study comprising up to 12 months of GPB treatment that included pediatric patients who had not participated in a crossover study [11]. All protocols were registered with ClinicalTrials.gov (NCT00947544, NCT01347073, and NCT00947297) and have been described in detail elsewhere [9–11]. The protocol and informed consent for each study were reviewed and approved by the Investigational Review Boards of each participating institution prior to the initiation of any study procedures.

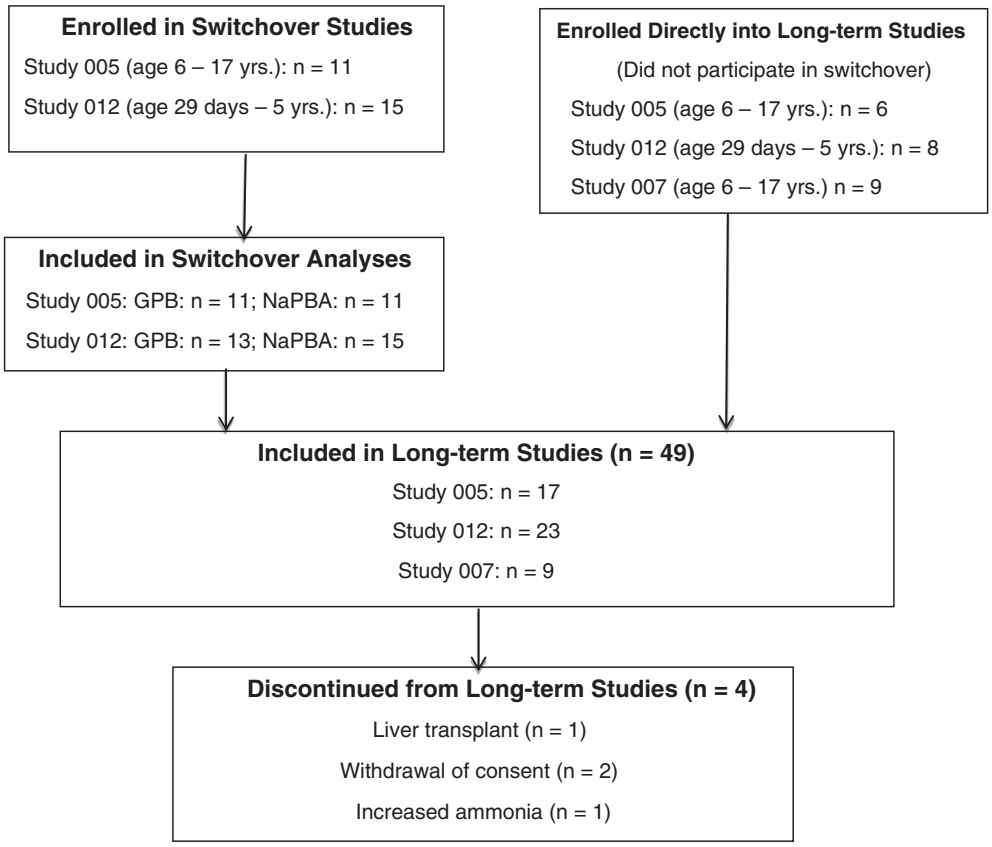

Fig. 1. Patient disposition in relation to protocols HPN-100-005 (Study 005), HPN-100-012 (Study 012) and HPN-100-007 (Study 007).