## Title

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# Self-Reported Treatment-Associated Symptoms among Patients with Urea Cycle Disorders Participating in Glycerol Phenylbutyrate Clinical Trials

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## Abstract

**Background—**Health care outcomes have been increasingly assessed through health-related quality of life (HRQoL) measures. While the introduction of nitrogen-scavenging medications has improved survival in patients with urea cycle disorders (UCDs), they are often associated with side effects that may affect patient compliance and outcomes.

**Methods—**Symptoms commonly associated with nitrogen-scavenging medications were evaluated in 100 adult and pediatric participants using a non-validated UCD-specific questionnaire. Patients or their caregivers responded to a pre-defined list of symptoms known to be associated with the use of these medications. Responses were collected at baseline (while patients were receiving sodium phenylbutyrate [NaPBA]) and during treatment with glycerol phenylbutyrate (GPB).

**Results—**After 3 months of GPB dosing, there were significant reductions in the proportion of patients with treatment-associated symptoms (69% vs. 46%; $p<0.0001$), the number of symptoms per patient (2.5 vs. 1.1; $p<0.0001$), and the frequency of the more commonly reported individual symptoms such as body odor, abdominal pain, nausea, burning sensation in mouth, vomiting, and heartburn ($p<0.05$). The reduction in symptoms was observed in both pediatric and adult patients. The presence or absence of symptoms or change in severity did not correlate with plasma ammonia levels or NaPBA dose.

**Conclusions—**The reduction in symptoms following 3 months of open-label GPB dosing was similar in pediatric and adult patients and may be related to chemical structure and intrinsic characteristics of the product rather than its effect on ammonia control.

### Keywords

treatment-related symptoms; glycerol phenylbutyrate; sodium phenylbutyrate; ammonia; patient-reported outcomes; health-related quality of life

## 1 Introduction

Urea cycle disorders (UCDs) are rare inborn errors of metabolism involving deficiencies of enzymes or transport proteins required for ureagenesis. UCDs are characterized by acute and chronic hyperammonemia, and hence, medical management is aimed at reducing waste nitrogen through the restriction of protein intake and the use of nitrogen-scavengers such as sodium phenylbutyrate (NaPBA) and sodium benzoate [1]. While these treatments have improved the lifespan of patients with UCDs, their associated treatment burden, palatability issues, and side effects, especially with NaPBA, may affect patient compliance. With the availability of such life-saving therapies for rare diseases, health outcomes have increasingly been examined not only through morbidity and mortality, but also health-related quality of life (HRQoL) [2].

As part of development of glycerol phenylbutyrate (GPB; RAVICTI®, Horizon Therapeutics, Inc., formerly known as Hyperion Therapeutics, Inc.) for UCDs, a survey involving patients with UCDs, their caregivers, and physicians was conducted to better understand the burden of disease, symptoms associated with UCD medications, compliance with prescribed medications, and barriers to compliance. The survey revealed that compliance with dietary supplements and drugs was challenging and identified a number of commonly reported symptoms associated with their use. Caregivers and/or patients identified the following symptoms as commonly experienced with NaPBA: body odor, nausea or vomiting, decreased appetite, stomachache/gastric distress, burning sensation in mouth or throat, fatigue, heartburn, headaches, light headedness, irregular menstrual cycle, and rash.

These findings were used as the basis for prospective data collection among patients with UCDs on chronic NaPBA treatment who participated in clinical trials of GPB, an ammonia-lowering agent approved in the US for treatment of patients ≥ 2 years of age with UCDs that cannot be managed by dietary measures alone. Information on the presence or absence of the most common symptoms identified through the survey was collected retrospectively at the time of enrollment (i.e., while patients were receiving NaPBA) and prospectively during long-term GPB studies. Because previous analyses have indicated that ammonia levels tend to be lower during dosing of GPB as compared to NaPBA, symptoms were analyzed in relation to ammonia levels, as well as in relation to other baseline characteristics such as age, gender, race, and drug dose [3, 4].

## 2 Materials and Methods

### 2.1 Clinical Studies

Adult and pediatric patients with UCDs who had been chronically treated with NaBPA were enrolled in one of three 12-month safety studies of GPB as previously described [4–7]. These studies collectively enrolled 100 patients between 2 months and 76 years of age (49 pediatric and 51 adult) [4, 8]. All protocols were registered with ClinicalTrials.gov (NCT00551200, NCT00947544, NCT00947297, NCT00992459, NCT01347073). The protocol and informed consent for each study were reviewed and approved by the Investigational Review Board of each participating Institution prior to the initiation of any study procedures. Informed consent was obtained from all patients prior to being included in the study.

Eligible patients had a confirmed or clinically suspected diagnosis of UCD and had been receiving a stable dose of NaPBA for management of their UCD. Major exclusion criteria included liver transplant, hypersensitivity to PBA, and laboratory abnormalities or ECG findings viewed as clinically significant by the Investigator. In all studies, patients started receiving GPB at a daily dose and regimen equivalent to their previously prescribed NaPBA dose. However, investigators were permitted to adjust the dose if clinically indicated.

Venous blood samples for ammonia analyses were collected monthly. An accredited hospital laboratory at each study site measured ammonia concentrations and values were normalized to a standard range of 9 to 35 μmol/L.

### 2.2 Treatment-associated Signs and Symptoms

A survey previously conducted to understand barriers to drug adherence in the treatment of UCDs identified symptoms commonly associated with the use of NaPBA (Supplementary Table 1). Based on this survey, a questionnaire was developed to evaluate the occurrence of these symptoms during the clinical studies of GPB (see Supplementary data). Patients or caregivers (if patients could not reliably respond) were provided with a paper questionnaire, and asked to read and respond to questions during study visits. Every patient or the caregiver was provided the same questionnaire, which they completed during the study visits in a non-directive manner without the involvement of the physician or study coordinator. The questionnaire was completed by all subjects at baseline and after 3 months of GPB therapy. Additionally, UCD questionnaires were completed at months 6, 9, and 12 for 23 pediatric patients < 6 years of age (Supplementary Figure 1). At baseline, patients or caregivers were asked “since the patient started receiving NaPBA for his/her UCD, has the patient experienced any of the following symptoms believed to be caused by NaPBA?” At follow-up visits, patients (or caregivers) were asked exactly the same questions pertaining to their GPB treatment, specifically regarding the presence or absence of symptoms and their severity as compared to baseline. For children < 6 years of age, the caregivers were asked to answer the questions and, if a symptom could not be assessed reliably (such as heartburn), a “not assessed (NA)” option was to be checked. The specific symptoms included in the each of the questionnaires are summarized in Supplementary Tables 2 to 4. The following

symptoms were evaluated in all studies: abdominal pain/distress, nausea, burning symptoms in the mouth/throat, body odor, vomiting, heartburn, and headache.

In addition to these self-reported treatment associated symptoms, adverse events during GPB treatment were collected independently for up to 12 months during GPB treatment, in accordance with good clinical practice principles, regardless of relationship to treatment, causality, or perception of the patients or caregivers as to whether they were caused by GPB, and have been previously reported [3, 4].

### 2.3 Statistical Analyses

Baseline data was defined as the screening or month 0 data collected while the patient was on NaPBA prior to receiving GPB. Patient characteristics (age, gender, race, and UCD subtype) and data regarding the common treatment-associated symptoms were summarized across all studies using descriptive statistics (Supplementary Tables 2 to 4). Comparisons between baseline and follow-up visits for the proportion of patients with no symptoms or at least 1, 2, or 3 symptoms, the proportion of patients with individual symptoms, and the mean number of symptoms per patient were performed using the Bhapkar test of homogeneity, the McNemar test, and the Wilcoxon signed rank test, respectively [9–11]. Comparisons were performed for all patients and also by patient age groups.

Blood ammonia levels for patients with no symptoms at baseline or at least one symptom at baseline were compared using the two-sample t-test. A Spearman correlation between the change in the number of symptoms and the change in ammonia concentrations from baseline to month 3 was performed for all patients.

Adverse events collected independently of the symptom questionnaires were also summarized during GPB treatment over 3-month intervals.

## 3 RESULTS

A total of 100 patients (77 ages ≥ 6 years; 23 ages < 6 years) were enrolled in the studies and administered the questionnaires at baseline. All patients were switched from NaPBA to GPB treatment in a single step without clinically significant adverse events. A total of 74 of the 77 patients (or their caregivers) ≥ 6 years of age completed the questionnaire after 3 months of GPB treatment. All caregivers for patients < 6 years of age responded to the questions about vomiting, body odor, episodic lethargy, and irritability at both the baseline and 3 month visits, but some caregivers did not assess the following symptoms (number of caregivers recording NA): abdominal pain (6), nausea (10), heartburn (12), headache (13), burning sensation (9), and protein intolerance (6).

A majority of patients (67%) were female, 51% were adults, and 81% were white. The median (range) duration of prior NaPBA treatment was 35 (0.2 to 183) months for pediatric patients and 120 (0.5 to 300) months for adult patients. Overall, 46% received the powder form of NaPBA and 14% received NaPBA through a gastrointestinal tube. The distribution of UCD subtypes was representative of the at-large population of patients with UCDs (Table

1). Overall, 92% of pediatric patients and 82% of adult patients completed the 12 months of treatment with GPB.

At baseline, while patients were taking NaPBA, 69% reported experiencing at least one of the treatment-associated symptoms as compared with 46% of patients after 3 months of GPB dosing (McNemar $\chi^2$=13.4, p<0.001). The proportions of patients with at least two and three symptoms also significantly decreased after 3 months of GPB dosing (Figure 1A). The mean (SD) number of symptoms per patient was 2.5 (3.0) at baseline and 1.1 (1.5) at month 3 ($p < 0.0001$; Wilcoxon signed rank sum test) and the reduction in the number of symptoms was observed across all age groups of patients (Figure 1B). Overall, approximately 55% of patients had a decrease in the reported number of treatment-associated symptoms, 35% had no change, and 10% had an increase in the number of symptoms after treatment with GPB.

In reply to: the subset of pediatric patients < 6 years of age, parents or caregivers responded to the questionnaire quarterly for 12 months. In this subgroup, the proportion of patients with no treatment-associated symptoms increased from 21.7% at baseline to 43.5%, 40.9%, 52.4%, and 61.9% at months 3, 6, 9, and 12, respectively, with a corresponding decrease in the mean number of symptoms per patient from 2.6 at baseline to 1.6, 1.1, 1.1, and 1.1, respectively (Figure 1C).

The most frequently reported symptoms at baseline for all patients were body odor (32%), abdominal pain (31%), nausea (26%), burning sensation in mouth (24%), vomiting (24%), heartburn (21%), and headache (14%). After 3 months of GPB treatment, there were decreases in the proportions of patients with each of these symptoms and these decreases were statistically significant for all symptoms except headache in the pooled analysis of all patients (Figure 2A). Decreases in treatment-associated symptoms after 3 months of GPB treatment were also observed in pediatric patients (Figure 2B).

For all treatment-associated symptoms reported at baseline, more patients who reported at least one symptom at baseline showed an improvement in the symptom (i.e., a reduction in frequency or absence of a baseline symptom) than a worsening (i.e., an increase in frequency or occurrence of new symptom not present at baseline) (Figure 3).

Simple correlation analyses were conducted to assess whether the decrease in symptoms could be correlated with dose of medication or differences in ammonia control. We found no correlation (r=0.068; p=0.52) between the change in the total number of symptoms and the change in ammonia levels from baseline to month 3. Similarly there was no correlation between baseline number of symptoms and NaPBA dose (r=0.11; p=0.289).

During long-term GPB treatment, the proportion of patients reporting new onset adverse events regardless of relationship to GPB or their perception of causality to GPB generally decreased over time (Table 2).

## 4 DISCUSSION

This study prospectively evaluated the occurrence of treatment-associated symptoms in patients with UCDs who were enrolled in 12-month GPB dosing studies. The study

population included 100 patients (51 adult, 49 pediatric) who had been treated with NaPBA for a median duration of 56 months prior to enrolling in long-term GPB studies. The questionnaire was designed to complement conventional safety reporting that does not capture baseline symptoms as adverse events and was based on the findings of a prior survey of UCD patients, caregivers, and physicians, which indicated that many patients with UCDs have difficulty tolerating NaPBA and that physicians often prescribe a lower than ideal dose of NaPBA due to tolerability issues [12].

The study had several important limitations. First, the clinical studies were open-label and patients and caregivers who completed the questionnaires were not blinded to treatment. Second, the questionnaires were not validated but they were rather designed to capture common treatment-associated symptoms. Third, the questionnaires reflect the patient's perspective of their symptoms and in the case of young children, represent the caregivers' assessment.

All patients switched from NaPBA to GPB in a single step without difficulty. After 3 months of GPB dosing there were statistically significant reductions in the proportion of patients reporting any symptoms as well as in the number of symptoms per patient. These findings were observed among adult as well as pediatric patients. The improvement in these symptoms appeared to be durable over 12 months in the youngest pediatric patients (< 6 years), the only group for which extended data were collected. Additionally, there were significant reductions in the proportion of patients with each of the most frequently reported treatment-associated symptoms (body odor, abdominal pain, nausea, burning sensation in mouth, vomiting, and heartburn). Among the youngest patients (< 6 years) for whom data were gathered every 3 months, the incidence of these symptoms tended to decrease over time.

These changes in symptoms could potentially be related to chemical structure of GPB and improved tolerability of GPB compared with NaPBA. The lack of correlation between NaPBA dose or changes in ammonia and reduction in symptoms suggests that the intrinsic tolerability characteristics of GPB (e.g., little odor or taste, absence of sodium, and minimal odor and taste, relative to NaPBA) may be the important factor. This interpretation would also be consistent with the finding that the reduction in symptoms was greatest in gastrointestinal related symptoms and among the youngest patients, who also tend to require higher drug doses for body weight.

Finally, with advent of life saving drugs for rare diseases resulting in normal or near normal life span, HRQoL measures and patient-reported outcomes are viewed as increasingly important clinical outcomes that often focus not only on disease characteristics, but also side effects of treatment [13]. In that regard, this work may serve as the first step towards development of a patient-reported outcome tool specific to UCDs measuring HRQoL.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## List of Abbreviations

| | |
|---|---|
| **GPB** | glycerol phenylbutyrate |
| **NaPBA** | sodium phenylbutyrate |
| **HRQoL** | health-related quality of life |
| **UCD** | urea cycle disorder |

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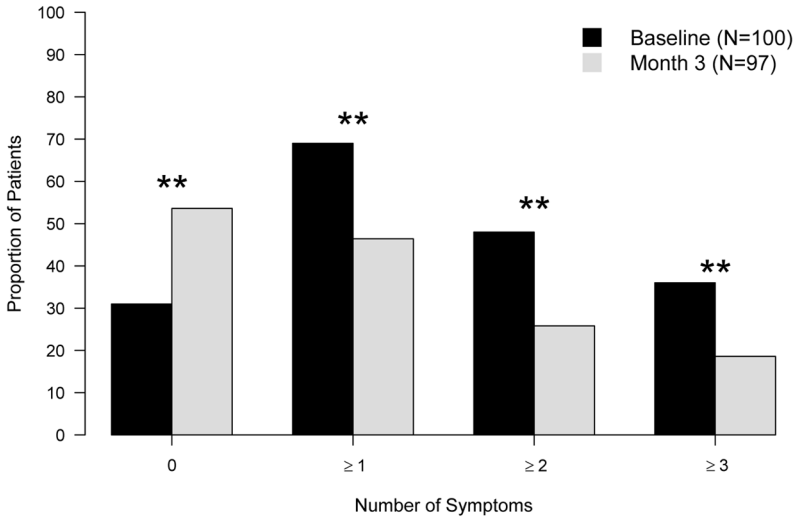
**A**

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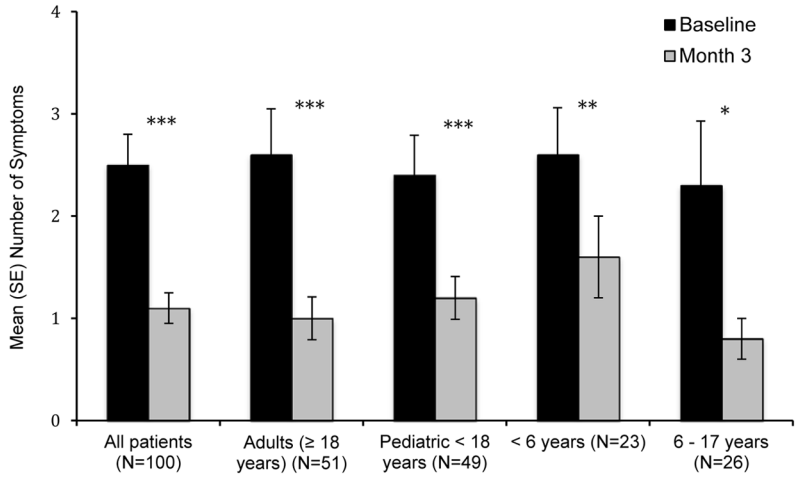

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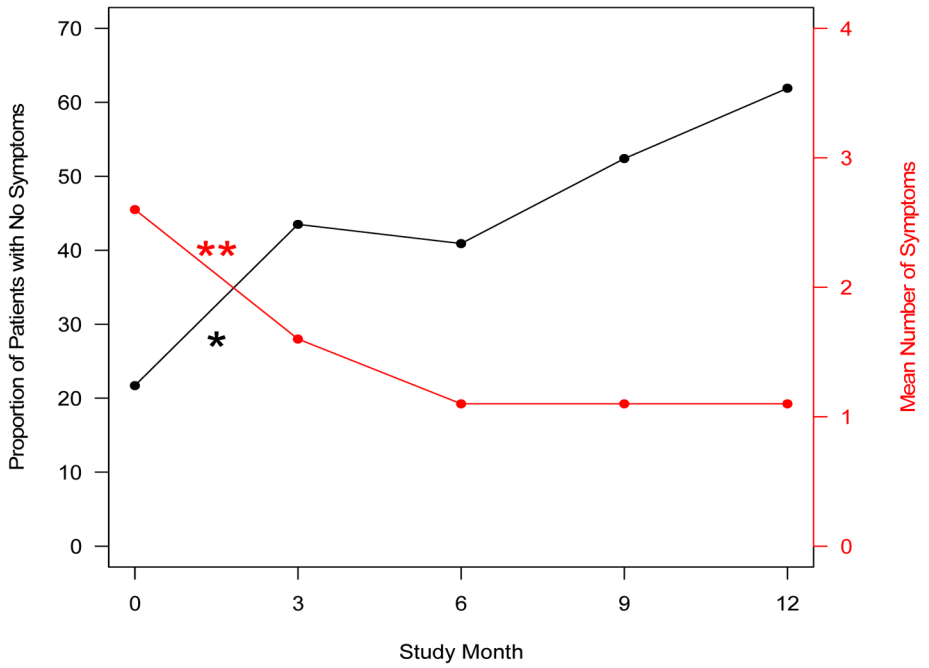


**Figure 1.**

**A:** Proportion of patients with common treatment-associated symptoms while on NaPBA therapy (baseline) compared with after 3 months of GPB therapy (pooled data from all patients; Bhapkar test of homogeneity $p<0.0001$; individual McNemar test p-values shown: *$p<0.05$; **$p<0.001$).

**B:** Mean number of symptoms per patient while on NaPBA therapy (baseline) compared with after 3 months of GPB therapy (*$p<0.05$; **$p<0.001$; ***$p<0.0001$).

**C:** Changes in symptoms from baseline to quarterly visits in study HPN-100-012 in pediatric patients under 6 years of age (N=23). Left axis (black line) percentage of patients who reported symptoms at each visit; right axis (red line) corresponding mean number of symptom reported. (*$p<0.05$; **$p<0.01$ comparing month 3 and baseline).

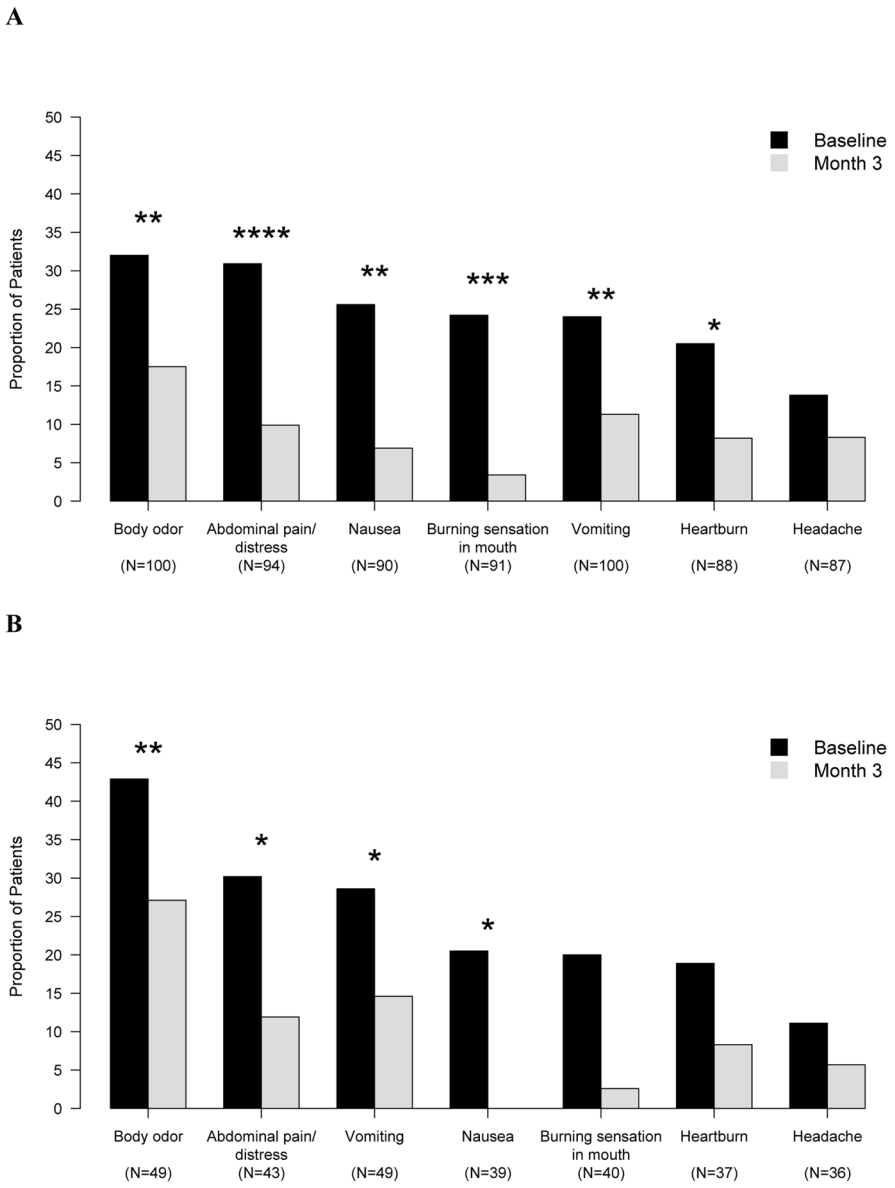


**Figure 2.**

Comparison of the most frequently reported symptoms patients while on NaPBA therapy (baseline) compared with after 3 months of GPB therapy. A: all patients; B: pediatric patients (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

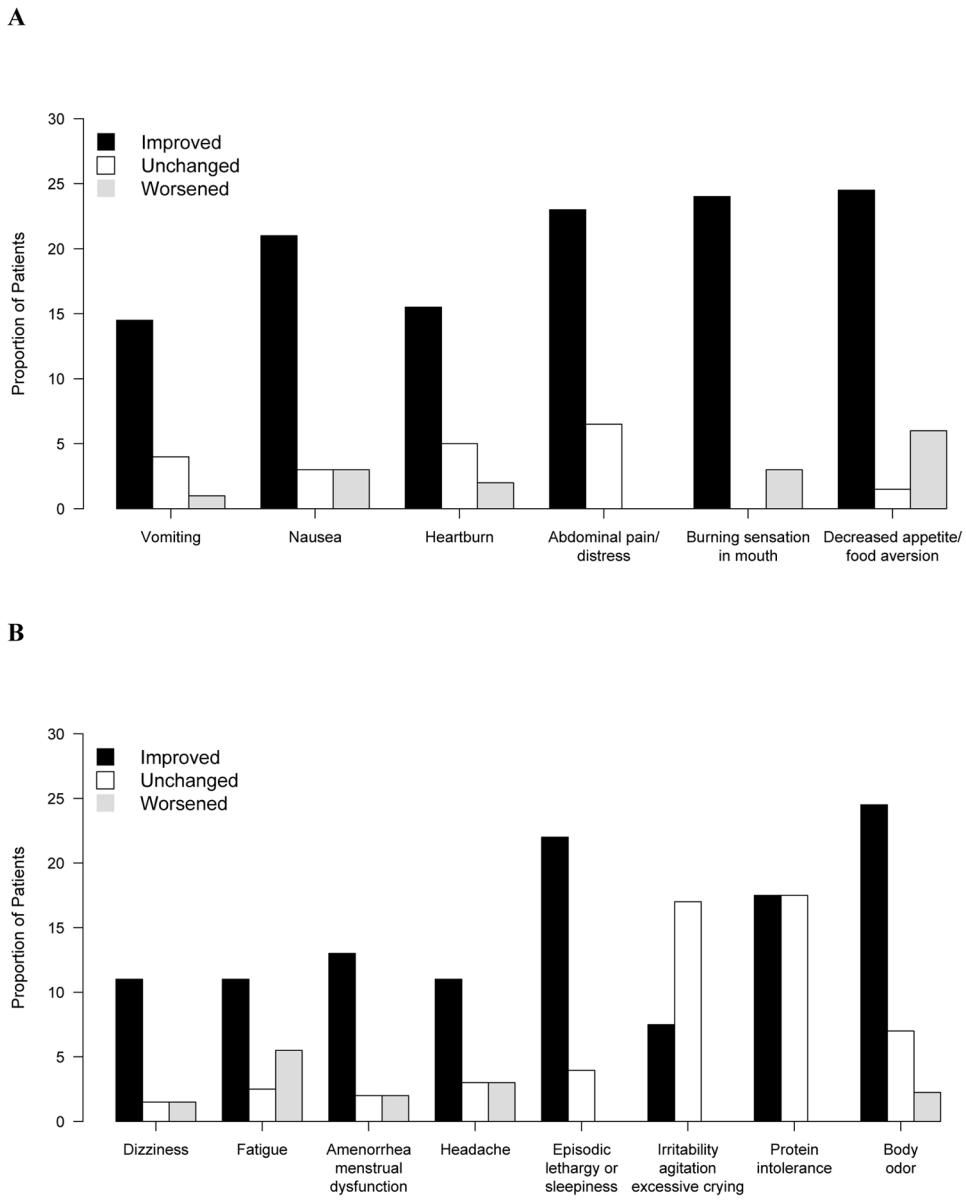


**Figure 3.**

**A** and **B**: Changes in symptoms from baseline to month 3 in all patients (N=100). Improved: reduction in frequency or absence of a baseline symptom; worsened: increase in frequency or occurrence of new symptom not present at baseline. Unchanged indicates patients who had a symptom at baseline and reported no change at follow up. Patients not reporting any symptom at baseline or month 3 are not presented. A: Gastrointestinal symptoms; B: all other symptoms

## Table 1

Baseline Characteristics of Patients

| | N=100 |
|---|---|
| **Age at Baseline:** median (range) | 18 yrs (2 mo–60yr) |
| Age group (years): n (%): | |
| < 2 | 7 (7.0) |
| 3 – 5 | 16 (16.0) |
| 6 – 7 | 10 (10.0) |
| 8 – 11 | 7 (7.0) |
| 12 – 18 | 9 (9.0) |
| 18+ | 51 (51.0) |
| **Gender:** n (%) | |
| Male | 33 (33.0) |
| Female | 67 (67.0) |
| **Race:** n (%) | |
| White | 81 (81.0) |
| Non-white | 19 (19.0) |
| **Duration of Prior NaPBA Treatment:** median (range) months | 56 (0.2 – 300) |
| **UCD Subtype:** n (%) | |
| OTC | 69 (69.0) |
| ASL | 13 (13.0) |
| ASS1 | 12 (12.0) |
| HHH | 3 (3.0) |
| ARG1 | 2 (2.0) |
| CPS1 | 1 (1.0) |
| **With Symptoms:** % | |
| No symptoms | 31.0 |
| At least 1 symptom | 69.0 |
| At least 2 symptoms | 48.0 |
| 3 or more symptoms | 36.0 |

ARG1: arginase 1; ASL argininosuccinate lyase; ASS1: argininosuccinate synthase 1; BUN: blood urea nitrogen; CPS: carbamoyl-phosphate synthase; HHH: hyperornithinemia–hyperammonemia–homocitrullinuria; OTC: ornithine transcarbamylase; UCD: urea cycle disorder.

## Table 2

Adverse Events Reported by ≥2 Patients During 12 Months of GPB Treatment

| Symptom | 0 to < 3 Months (N=100) | 3 to < 6 Months (N=98) | 6 to < 9 Months (N=93) | 9 to < 12 Months (N=91) |
|---|---|---|---|---|
| | Number (%) Patients | | | |
| Vomiting | 18 (18.0) | 7 (7.1) | 11 (11.8) | 10 (11.0) |
| URI | 15 (15.0) | 13 (13.3) | 13 (14.0) | 14 (15.4) |
| Nausea | 12 (12.0) | 2 (2.0) | 3 (3.2) | 2 (2.2) |
| Decreased appetite | 10 (10.0) | 2 (2.0) | 2 (2.2) | 1 (1.1) |
| Cough | 10 (10.0) | 4 (4.1) | 3 (3.2) | 3 (3.3) |
| Pyrexia | 7 (7.0) | 4 (4.1) | 4 (4.3) | 3 (3.3) |
| Diarrhea | 6 (6.0) | 4 (4.1) | 6 (6.5) | 6 (6.6) |
| Hyperammonemia | 4 (4.0) | 8 (8.2) | 6 (6.5) | 7 (7.7) |
| Headache | 4 (4.0) | 4 (4.1) | 2 (2.2) | 3 (3.3) |
| Nasopharyngitis | 2 (2.0) | 6 (6.1) | 3 (3.2) | 2 (2.2) |
| Gastroenteritis | 2 (2.0) | 4 (4.1) | 1 (1.1) | 3 (3.3) |
| Flatulence | 2 (2.0%) | 0 | 0 | 1 (1.1%) |

Includes events reported by ≥2 patients regardless of relationship to treatment.

Baseline symptoms while on NaPBA were not reported as AEs.

URI=upper respiratory infection.