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# The Pharmacokinetics of Taste-Masked Sodium Phenylbutyrate (ACER-001) for the Treatment of Urea Cycle Disorders Under Fasting and Fed Conditions in Healthy Volunteers

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## BACKGROUND

- The primary urea cycle disorders (UCDs) result from an inherited defect in one of the 6 enzymes or 2 transporters of the urea cycle[1]
- A defect in any of the urea cycle enzymes leads to the accumulation of ammonia, resulting in deleterious effects on the central nervous system, including brain damage, coma, and death[2,3]
- Treatment of UCDs includes the use of nitrogen-scavenging agents, such as sodium phenylbutyrate (salt of 4-phenylbutyric acid; NaPBA) or glycerol phenylbutyrate, which provide an alternative pathway for nitrogen disposal through the urinary excretion of phenylacetylglutamine[3]
- While these treatments are effective, treatment with NaPBA may be limited in some patients by aversive odor, taste, and gastrointestinal symptoms, making compliance with chronic treatment problematic[4,5]
- ACER-001 is a novel formulation of NaPBA designed for tolerability and is currently being developed as a treatment option for patients with UCDs

## OBJECTIVES

- To determine the bioequivalence of ACER-001 administered as a suspension relative to NaPBA powder administered as a solution in healthy adult volunteers after a single dose under fasting and fed conditions
- To assess the effect of a high-fat meal on the pharmacokinetics of ACER-001

## METHODS

### Design

- Two Phase 1 studies utilizing single-dose (5-g active pharmaceutical ingredient [API] NaPBA), 3-period, 3-sequence crossover design in healthy adult volunteers
- Study drugs were administered on days 1-3
  - In Study 1, subjects received ACER-001 fasted, ACER-001 with a high-fat meal (fed), and NaPBA powder fasted. ACER-001 was prepared with Thick-It®, which is the intended commercial formulation
  - In Study 2, subjects received ACER-001 with Thick-It, ACER-001 without Thick-It, and NaPBA powder, all under fed conditions. Only results for ACER-001 with the intended commercial formulation Thick-It are reported (ACER-001 without Thick-It is an exploratory formulation)
- Subjects fasted for 10 hours overnight prior to receiving study drug
- During the fasted periods, subjects remained fasted for 4 hours after receiving study drug, whereas during the fed period (Study 1 only), subjects consumed a high-fat meal within 30 minutes of study drug administration

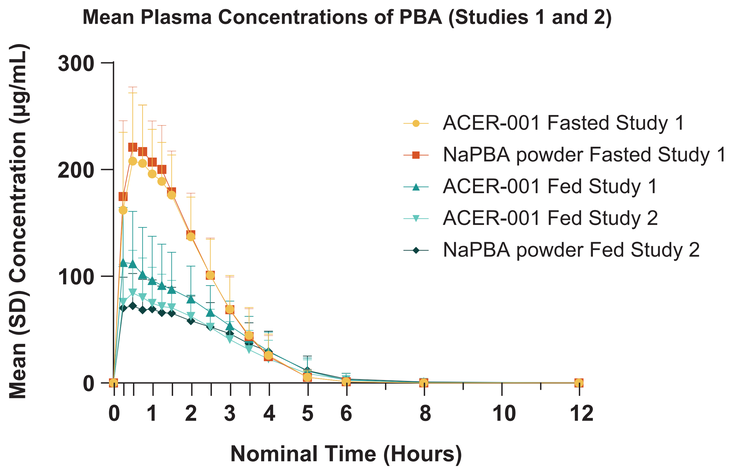
### Assessments

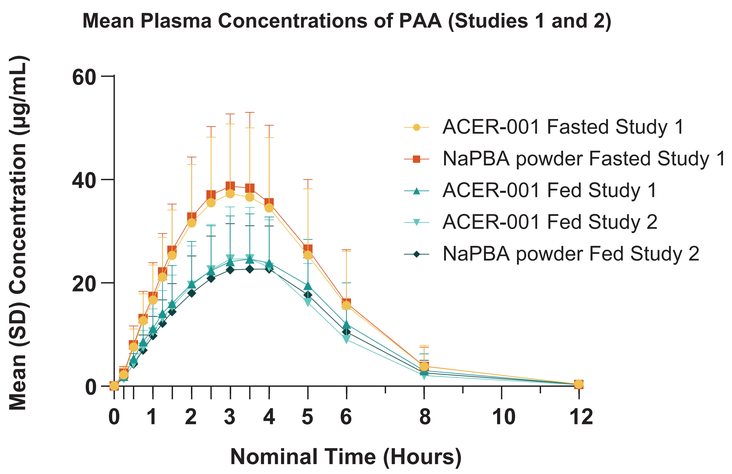
- Plasma pharmacokinetic (PK) samples were collected from all subjects prior to dosing and at multiple timepoints following study drug administration
- Plasma concentrations of phenylbutyrate (PBA) and the active metabolite phenylacetic acid (PAA) were determined using liquid chromatography-tandem mass spectrometry
- Maximum concentration ($C_{max}$), area under the concentration-time curve ($AUC_{last}$ and $AUC_{inf}$), and elimination half-life ($t_{1/2}$) for PBA and PAA were determined using non-compartmental PK analyses
- A linear mixed model was fitted to ln-transformed data with treatment, sequence, and period as fixed effects and subject within sequence as a random effect to calculate the ratio and the corresponding 90% confidence intervals (CIs) for the difference between treatments for PBA and PAA
- ACER-001 and NaPBA powder were considered bioequivalent if the 90% CIs for the LS mean ratios of PK parameters were between 80% and 125% for PBA and PAA

## RESULTS

- For PBA, absorption was rapid with time to $C_{max}$ occurring at 0.5-hours post-dose under the fasted and fed states for ACER-001 and NaPBA powder. $t_{1/2}$ was ~0.5 hours in the fasted state and slightly longer in the fed state (0.6–0.8 hours) for both ACER-001 and NaPBA powder **(Figure 1)**
- For PAA, time to $C_{max}$ occurred between 3.25- and 3.5-hours post-dose under the fasted and fed states for ACER-001 and NaPBA powder. $t_{1/2}$ was ~1.2 hours in the fasted and fed states for both ACER-001 and NaPBA powder **(Figure 1)**

**Figure 1. Plasma concentrations of PBA and PAA under fasted and fed conditions.**




- For both PBA and PAA, total systemic exposures ($AUC_t$, $AUC_{inf}$) and peak exposures ($C_{max}$) were bioequivalent for ACER-001 and NaPBA powder in the fasted and fed states with the 90% CIs of the geometric mean ratios fully contained within the interval (0.80, 1.25) **(Table 1)**

**Table 1. Statistical analysis of bioequivalence of PBA and PAA between ACER-001 and NaPBA powder under fasted and fed conditions**

| Parameter | | Geometric LS Mean ACER-001 N=36 | Geometric LS Mean NaPBA N=36 | Ratio of Geometric LS Mean Estimate (90% CI) |
|---|---|---|---|---|
| **Under fasted conditions (Study 1)** | | | | |
| PBA | $C_{max}$ (µg/mL) | 224 | 237 | 0.9487 (0.8691, 1.0357) |
| | $AUC_t$ (h•µg/mL) | 494 | 508 | 0.9708 (0.9165, 1.0284) |
| | $AUC_{inf}$ (h•µg/mL) | 494 | 509 | 0.9709 (0.9172, 1.0277) |
| PAA | $C_{max}$ (µg/mL) | 36.2 | 37.5 | 0.9677 (0.9205, 1.0173) |
| | $AUC_t$ (h•µg/mL) | 167 | 173 | 0.9673 (0.9216, 1.0153) |
| | $AUC_{inf}$ (h•µg/mL) | 168 | 173 | 0.9677 (0.9222, 1.0153) |
| **Under fed conditions (Study 2)** | | | | |
| PBA | $C_{max}$ (µg/mL) | 89.7 | 79.8 | 1.1234 (1.0364, 1.2177) |
| | $AUC_t$ (h•µg/mL) | 231 | 234 | 0.9849 (0.9359, 1.0365) |
| | $AUC_{inf}$ (h•µg/mL) | 234 | 242 | 0.9689 (0.9196, 1.0208) |
| PAA | $C_{max}$ (µg/mL) | 23.9 | 22.4 | 1.0655 (0.9849, 1.1527) |
| | $AUC_t$ (h•µg/mL) | 107 | 108 | 0.9949 (0.9430, 1.0496) |
| | $AUC_{inf}$ (h•µg/mL) | 108 | 108 | 0.9956 (0.9429, 1.0513) |

- For both PBA and PAA, total systemic exposures and peak exposures of ACER-001 in the fed state vs ACER-001 in the fasted state were significantly decreased with 90% CIs of the geometric mean ratios falling below the no effect interval (0.80) **(Table 2)**.

**Table 2. Statistical analysis of the effect of food on PBA and PAA with ACER-001 treatment (Study 1)**

| Parameter | | Geometric LS Mean ACER-001 Fed N=36 | Geometric LS Mean ACER-001 Fasted N=36 | Ratio of Geometric LS Mean Estimate (90% CI ) |
|---|---|---|---|---|
| PBA | $C_{max}$ (µg/mL) | 113 | 224 | 0.5046 (0.4622, 0.5509) |
| | $AUC_t$ (h•µg/mL) | 301 | 494 | 0.6088 (0.5748, 0.6449) |
| | $AUC_{inf}$ (h•µg/mL) | 304 | 494 | 0.6142 (0.5795, 0.6510) |
| PAA | $C_{max}$ (µg/mL) | 24.5 | 36.2 | 0.6751 (0.6422, 0.7097) |
| | $AUC_t$ (h•µg/mL) | 118 | 167 | 0.7043 (0.6710, 0.7392) |
| | $AUC_{inf}$ (h•µg/mL) | 118 | 168 | 0.7050 (0.6720, 0.7398) |

## SAFETY

- No safety signals were observed
- Table 3 reflects the incidence of adverse events for ACER-001 fasted, ACER-001 fed, and NaPBA fed

**Table 3. Treatment-emergent adverse events**

| | Study 1 | | | Study 2 | |
|---|---|---|---|---|---|
| | ACER-001 Fasted N=36 n, % | ACER-001 Fed N=36 n, % | NaPBA Fasted N=36 n,% | ACER-001 Fed N=37 n,% | NaPBA Fed N=36 n, % |
| All TEAEs[a] | 7 (19.4) | 5 (13.9) | 14 (38.9) | 6 (16.2) | 3 (8.3) |
| Nervous system disorders | 6 (16.7) | 2 (5.6) | 13 (36.1) | 5 (13.5) | 1 (2.8) |
| Dizziness | 4 (11.1) | 1 (2.8) | 9 (25.0) | 1 (2.7) | 0 |
| Headache | 3 (8.3) | 1 (2.8) | 8 (22.2) | 4 (10.8) | 1 (2.8) |
| Dysgeusia | 1 (2.8) | 0 | 1 (2.8) | 0 | 0 |
| Somnolence | 0 | 1 (2.8) | 0 | 0 | 0 |
| GI disorders | 2 (5.6) | 1 (2.8) | 5 (13.9) | 2 (5.4) | 1 (2.8) |
| Nausea | 2 (5.6) | 0 | 5 (13.9) | 0 | 1 (2.8) |
| Vomiting | 0 | 0 | 0 | 1 (2.7) | 1 (2.8) |
| Abdominal discomfort | 1 (2.8) | 0 | 0 | 1 (2.7) | 0 |
| Flatulence | 0 | 1 (2.8) | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 1 (2.7) | 0 |
| Oral hypoesthesia | 1 (2.8) | 0 | 0 | 0 | 0 |
| Dry lips | 0 | 0 | 1 (2.8) | 0 | 0 |
| General disorders[b] | 0 | 1 (2.8) | 1 (2.8) | 0 | 1 (2.8) |
| Feeling abnormal | 0 | 1 (2.8) | 0 | 0 | 0 |
| Feeling hot | 0 | 0 | 1 (2.8) | 0 | 0 |
| Vessel puncture site bruise | 0 | 0 | 0 | 0 | 1 (2.8) |
| Vascular disorders | 2 (5.6) | 0 | 0 | 0 | 0 |
| Flushing | 2 (5.6) | 0 | 0 | 0 | 0 |
| Reproductive system | 0 | 1 (2.8) | 0 | 0 | 0 |
| Irregular menses | 0 | 1 (2.8) | 0 | 0 | 0 |
| Respiratory, thoracic, mediastinal disorders | 0 | 0 | 1 (2.8) | 0 | 0 |
| Dry throat | 0 | 0 | 1 (2.8) | 0 | 0 |

GI, gastrointestinal; TEAE, treatment-emergent adverse event.
[a]Defined as any event not present before administration of study drug or any event that was already present but worsens in either intensity or frequency following exposure to study drug.
[b]Includes administration site conditions.

## CONCLUSIONS

- ACER-001 was bioequivalent to NaPBA powder under both fasting and fed conditions
- Higher levels of PBA and PAA were observed when ACER-001 was administered under fasting versus fed conditions
  - A similar reduction in the PK of NaPBA powder under fed conditions was observed between Study 1 and Study 2
- The adverse events in these studies showed no major safety signals and were similar to NaPBA
- These studies suggest investigating administration of nitrogen scavengers under fasting conditions is warranted, which may ultimately provide lower dose options and increased dosing flexibility

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