ACER-001: A Potential Alternative to Sodium and Glycerol Phenylbutyrate for Treatment of Urea Cycle Disorders

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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

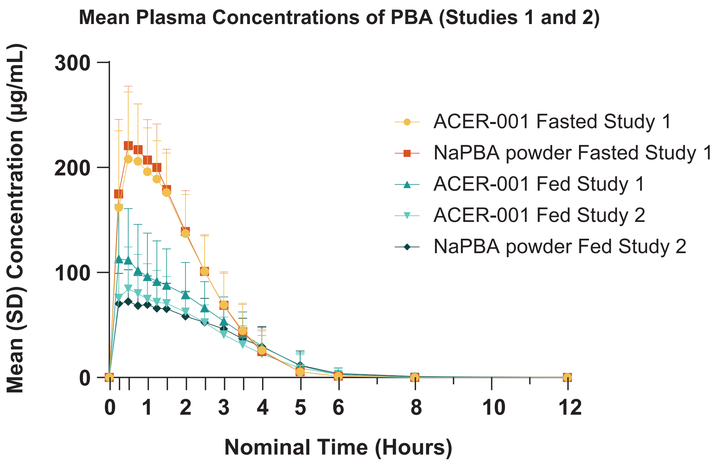
Assessments

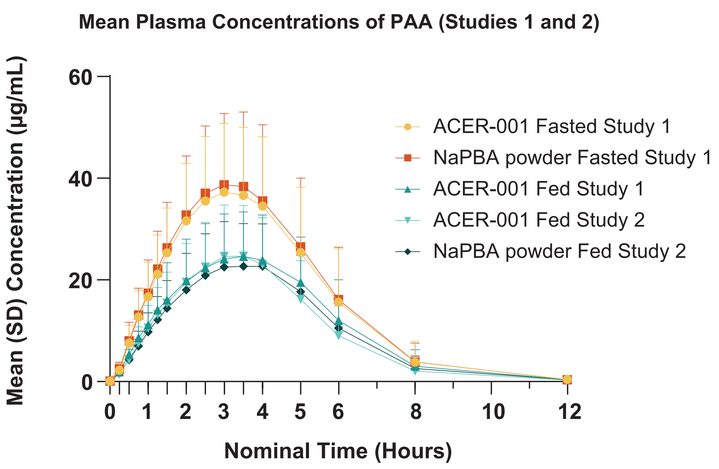
- Plasma pharmacokinetic (PK) samples were collected from all subjects prior to dosing and at multiple timepoints following study drug administration
- Plasma concentrations of phenylbutyrate (PBA) and the active metabolite phenylacetic acid (PAA) were determined using liquid chromatography-tandem mass spectrometry
- Maximum concentration (C_{max}), area under the concentration-time curve (AUC_t 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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