

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF OCR-002 (ORNITHINE PHENYLACETATE) IN PATIENTS WITH STABLE HEPATIC CIRRHOSIS



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Background

OCR-002 (ornithine phenylacetate) is a novel compound in development for the treatment of hyperammonemia and resultant hepatic encephalopathy in patients with acute liver failure and cirrhosis. This Phase 2a, randomized, double-blind, placebo-controlled ascending dose study was designed to evaluate the pharmacokinetics and safety of OCR-002 in a stable cirrhotic population.

OCR-002, an injectable systemic ammonia scavenger, directly reduces circulating ammonia levels by upregulating muscle glutamine synthetase and secreting glutamine as the conjugate phenylacetylglutamine (PAGN) in urine. Each mole of PAGN excreted results in two mole of nitrogen acting as a surrogate marker of ammonia excretion.

Preclinical data has demonstrated that OCR-002 reduces ammonia and intracranial pressure in ALF and can normalize ammonia and neurological function in HE^{1,2,3}. OCR-002 also reduces NFκB expression, restore eNOS activity and lowers portal pressure⁴.

OCR-002 is free of sodium content and can be administered in low fluid volumes.

Design

A double-blind, placebo-controlled study, in which cohorts of 6 stable Child's class A or B cirrhotics (n=43) were randomized to active or placebo (5:1) and received single ascending doses of study drug (1,3, 10, 20, 40g over 4h or 10, 20, 40g over 24h).

Inclusion criteria: Male or female, BMI 18-30 Kg/m², 18-55 yrs of age. MELD < 15, West Haven Score < 2 with no history of decompensation (GI bleed, OHE, refractory ascites)

Patient population: 62.8% male, 74.3% Child Pugh A, mean age 52.7y

Primary PK/PD analytes: phenylacetate (PAA), ornithine (ORN), phenylacetylglutamine (PAGN) in plasma and PAGN in urine.

Safety evaluations included AE reporting, vital signs, pulse rate, body temperature, ECG, and standard clinical lab.

All patients were monitored up to 48h post dose with a 1 week follow up visit

Safety and Tolerability

Table 1. Related Treatment Emergent AEs (>1 event reported)

	1g/4h n=5	3g/4h n=5	10g/4h n=5	20g/4h n=5	40g/4h n=2	10g/24h n=5	20g/24h n=3	40g/24h n=5	Placebo n=8
Chills	1		1	2	1				1
Thirst	3								
Headache	2			2	2	1		1	3
Dizziness			1	1	1	1			1
Somnolence				1	2			2	
N&V				1	2				1
Tachycardia					2				

- No SAEs or AEs leading to study discontinuation and no deaths reported
- No significant findings related to clinical labs or physical examinations
- All TEAEs were considered mild to moderate; 14 AEs considered moderate
- Dose limiting AEs include chills, nausea & vomiting, headache, dizziness & somnolence
- Moderate increases in heart rate were observed at the 5g/h and 10g/h infusion rates
- There was no effect of OCR-002 on cardiac repolarization as measured by QTcF
- The MTD reported was 20g/4h (5g/h) or 40g/24h (1.67g/h)

Pharmacokinetics / Pharmacodynamics

Figure 1. Mean exposure for PAA / ornithine

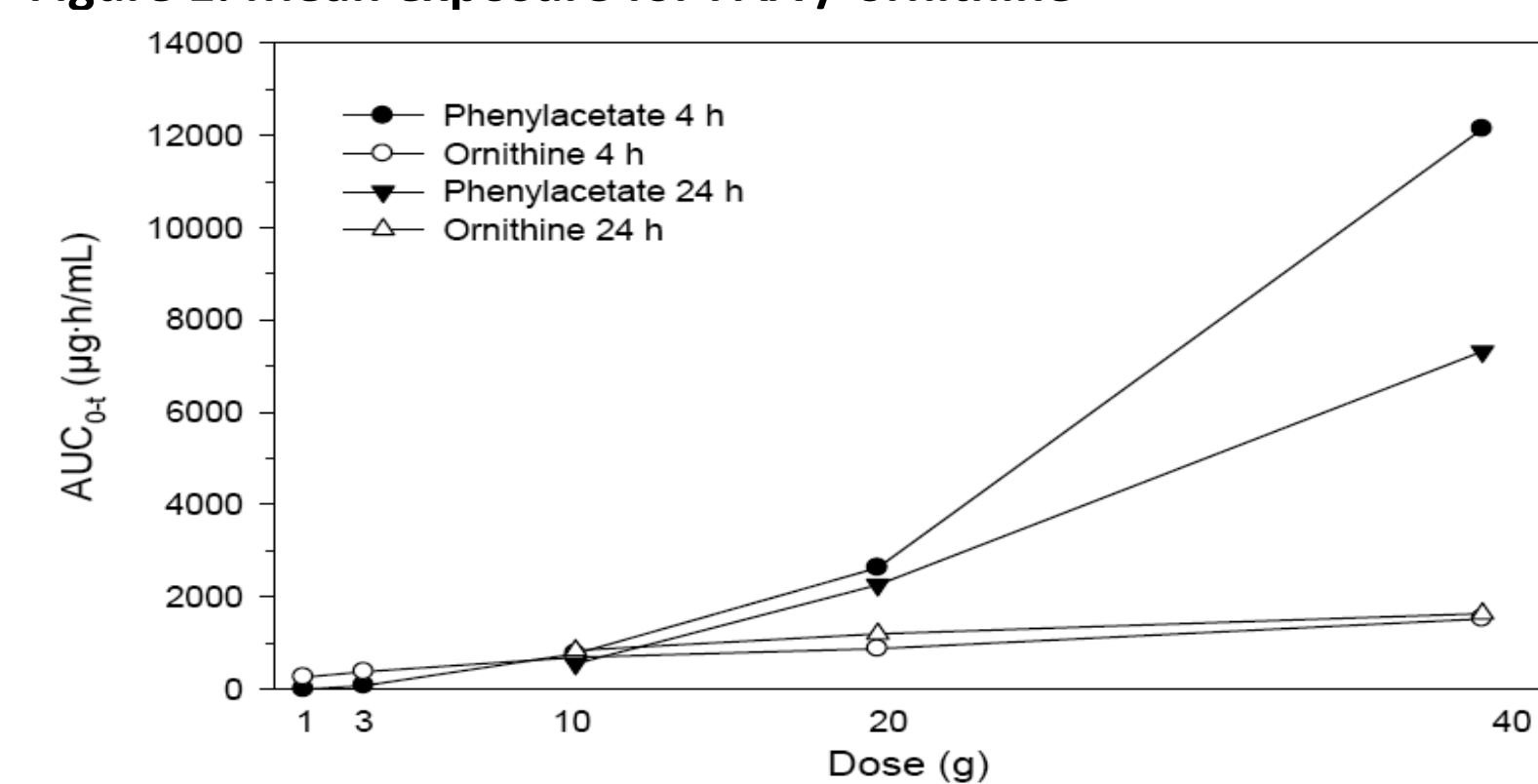


Figure 2. Mean C_{max} for PAA / ornithine

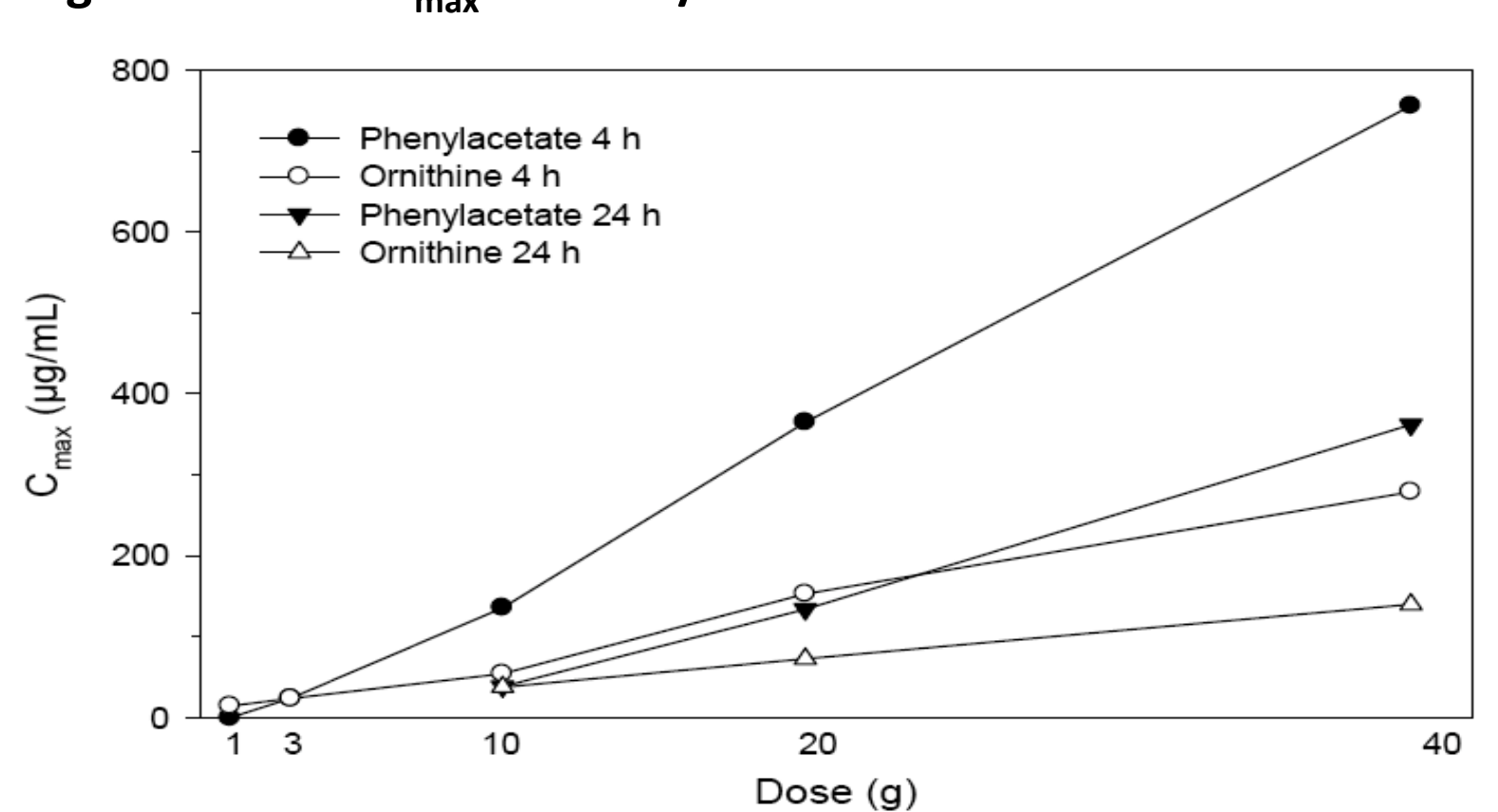


Figure 3. Cumulative PAGN urinary output

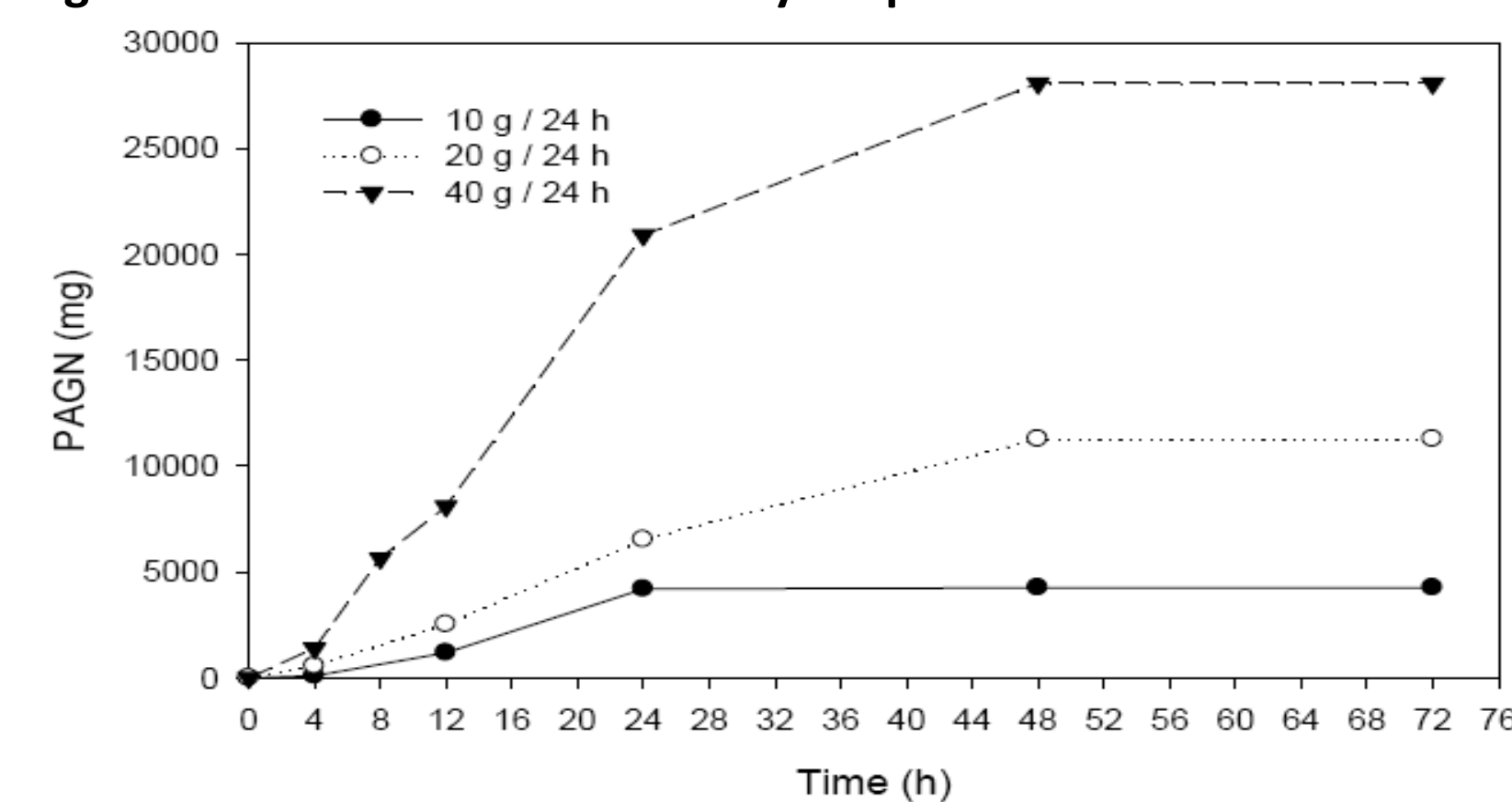


Table 2. Dose Normalized Plasma Pharmacokinetics (C_{max}, AUC_{0-t})

Dose (g/h)	ORN	PAA	PAGN
24h infusion			
10g (0.42g/h)	10.3 / 115.2	3.9 / 55.2	1.76 / 34.3
20g (0.83g/h)	3.6 / 60.0	6.7 / 113.1	3.14 / 70.5
40g (1.67g/h)	3.5 / 40.9	9.1 / 183.0	1.92 / 36.7
4h infusion			
10g (2.5g/h)	5.4 / 68.7	13.6 / 76.7	4.7 / 35.5
20g (5.0g/h)	7.7 / 43.7	18.3 / 131.5	4.0 / 41.9
40g (10.0g/h)	7.0 / 38.1	18.9 / 303.5	1.5 / 38.4

Units: C_{max}= μg/mL/g, AUC= μg.h/mL/g

Table 3. PAGN Urine output

Dose (g)	Mean (g)	Range (g)	s.d.
24h infusion			
10 (0.42g/h)	4.2	2.4 – 5.9	1.8
20 (0.83g/h)	11.3	6.0 – 16.5	7.4
40 (1.67g/h)	28.1	27.1 – 29.4	1.2
4h infusion			
10 (2.5g/h)	5.9	3.9 – 8.3	1.7
20 (5.0g/h)	12.4	9.8 – 14.7	2.4
40 (10.0g/h)	11.3	11.1 – 11.5	0.3

Conclusions

- OCR-002 is safe and well tolerated in a cirrhotic population at doses up to 10g/4h (2.5g/h) and 40g/24h (1.67g/h)
- Dose limiting AEs are likely related to phenyl acetate exposure and include nausea, vomiting, dizziness, somnolence and headache
- The MTD for OCR-002 is 20g/d for the 4h infusion and 40g/d for 24h infusion
- OCR-002 demonstrated dose linear kinetics at doses of ≤10g (PAA exhibits non-linear kinetics at doses ≥5g/h or >100μg/mL)
- OCR-002 dosing over 24h improves the tolerability (lowers PAA C_{max})
- Infusion rate had no significant impact on PAGN excretion, the biomarker of ammonia scavenging
- OCR-002 at 10g/24h (0.42 g/h) is safe and well tolerated, exhibits linear kinetics and produces significant urinary PAGN
- Efficacy and safety studies of OCR-002 for treatment of hyperammonemia in cirrhosis and Acute Liver Injury/Failure have been initiated



References

[1] Ytrebø L et al, Hepatology 2009, [2] Davies et al, Hepatology 2009, [3] Oria et al, J Hepatol 2010, [4] Balasubramanian et al, Am J Physiol Gastrointest Liver Physiol 2011