# An Open-Label Crossover Study of the Pharmacokinetics of Ornithine Phenylacetate (OCR-002) after IV and Oral Doses in Subjects with Cirrhosis

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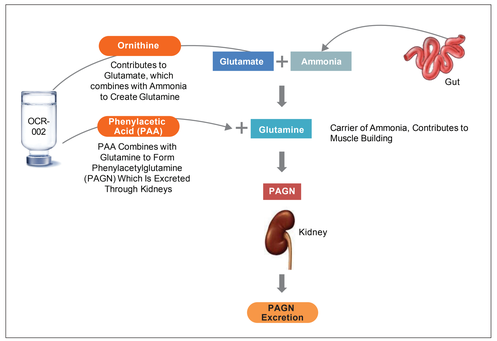
## Introduction

- OCR-002 is the ionically bound ornithine salt of phenylacetate (PAA) and serves as an ammonia scavenger by conjugating PAA with glutamine to facilitate the removal of ammonia in the form of phenylacetylglutamine (PAGN) via renal excretion (**Figure 1**). Intravenous (IV) OCR-002 is in clinical development to treat hepatic encephalopathy (HE) in patients with acute overt HE in patients with liver cirrhosis. An oral formulation of OCR-002, rather than an intravenous formulation, is more appropriate for longer term use in patients with decompensated cirrhosis at risk for developing HE.
- As part of oral formulation development, it is necessary to evaluate the oral bioavailability and pharmacokinetics of orally administered OCR-002. This information informs the selection of an appropriate dose and dosing regimen for further clinical studies. In order to understand whether the severity of the underlying cirrhosis can affect the pharmacokinetics (PK) of PAA, the active ammonia scavenging moiety of OCR-002, it is important to assess the PK characteristics of OCR-002 after oral administration across the targeted patient population. Part 1 of this study was conducted to evaluate the PK of PAA and its major metabolite, PAGN, following single dose administration of an oral solution of OCR-002 in comparison to a single dose of IV OCR-002 in patients with Child Pugh A and C stage cirrhosis. The influence of a fasting, a high fat meal, and lactulose on the PK of PAA and PAGN after oral OCR-002 was also examined.

*Figure 1. Effect of OCR-002 on Inter-Organ Ammonia Trafficking*



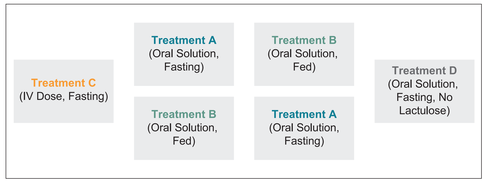

## Objective

- To evaluate the pharmacokinetics (PK) of PAA, the active moiety of OCR-002, and its major metabolite, PAGN, following single oral and IV doses of OCR-002 in subjects with cirrhosis.

## Methods

- This was an open-label, randomized crossover study evaluating 4 single-dose treatments with IV or oral OCR-002 in cirrhotic subjects with Child Pugh (CP) classification A or C, as outlined in **Figure 2**.

*Figure 2. Study Design*




### Subject Selection

- Adults ≥18 years of age and ≤70 years of age at the time of screening
- Evidence of cirrhosis
  - Child-Pugh Class A or C
- Diagnosis of liver cirrhosis was based on clinical, radiological or histological criteria
- Currently using lactulose for a minimum of 5 days prior to Day -1
- If using rifaximin at screening, it was discontinued at least 7 days before the first dose of study drug

### Study Treatments

- Subjects received the following 4 single-dose treatments in a randomized, crossover fashion over 4 dose periods, with a minimum 4-day washout interval between dose periods:
  - Treatment A: 5 g OCR-002 oral solution administered while fasting
  - Treatment B: 5 g OCR-002 oral solution administered with a high fat meal
  - Treatment C: 5 g OCR-002 infused intravenously over 60 minutes while fasting
  - Treatment D: 5 g OCR-002 oral solution administered while fasting and after discontinuing lactulose for at least 4 days

### Pharmacokinetic Evaluation

- Serial blood samples were obtained for up to 24 h post dose to measure plasma concentrations of PAA and PAGN using a validated LC/MS/MS method.
- Cumulative urine samples (0-4, 4-8, 8-12 and 12-24 h) were collected to measure urine concentrations of PAGN using a validated LC/MS/MS.
- The amount of PAGN excreted in urine over the collection interval was determined by multiplying PAGN concentration with the urine volume.

### Safety

- The most common adverse events reported were dysgeusia and somnolence.
- No serious adverse events were reported.
- No subjects were discontinued due to an adverse event.

## Results

- 12 subjects were enrolled in the study.
- 9 subjects (5 with Child-Pugh Class A and 4 with Child-Pugh Class C) contributed data for PK analyses.
- 3 subjects discontinued early due to problems with maintaining venous access adequate to draw blood samples.
- Baseline characteristics were comparable between groups (**Table 1**).

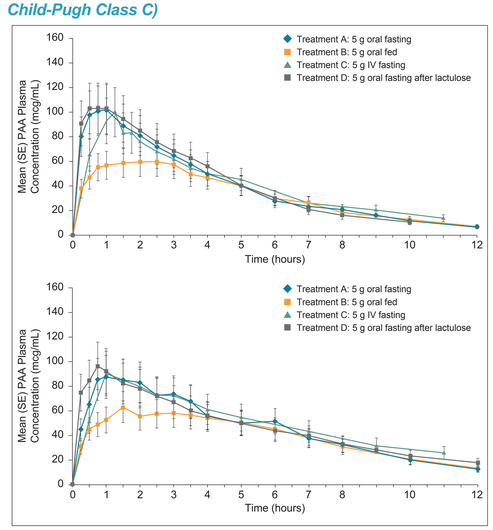
*Table 1. Baseline characteristics*

| Characteristic | Child-Pugh Class A (N=6) | Child-Pugh Class C (N=6) |
|---|---|---|
| Age range, y | 31 – 55 | 48 – 70 |
| Sex | 3 male, 3 female | 3 male, 3 female |
| Race | 6 white | 6 white |
| Hispanic or Latino | 5 | 5 |

### PAA Plasma Profiles

- Plasma PAA concentrations achieved high level after oral administration under fasting conditions, comparable to those after IV administration.
- Plasma PAA concentrations were reduced when oral OCR-002 was administered with a high-fat meal (**Figure 3**).

*Figure 3. Mean (SE) plasma PAA concentrations over time after 4 single IV or oral doses of OCR-002 (top Child-Pugh A; bottom Child-Pugh Class C)*




- PAA was rapidly absorbed and almost completely bioavailable (≥95%) from oral doses of OCR-002 with fasting in subjects with cirrhosis (**Table 2**).
- A high-fat meal delayed oral absorption of PAA and reduced mean PAA $C_{max}$ by 30%-40% and mean oral bioavailability of PAA by 15%-20%. (**Table 2**)
- In Child-Pugh C subjects, peak plasma concentration ($C_{max}$) of PAA was similar or slightly (<15%) lower and mean overall PAA plasma exposure ($AUC_{0\text{-}inf}$) was 35%-40% higher than that in Child-Pugh A subjects after a single oral OCR-002 dose.
- Plasma half-life of PAA is prolonged in subjects with cirrhosis, and increased to >2 fold longer in Child-Pugh C subjects (mean ~3.84 h) compared to that in Child-Pugh A subjects (mean ~1.64 h).
- In Child-Pugh Class A subjects, $C_{max}$ of PAA was ~20% lower and $AUC_{0\text{-}inf}$ of PAA was ~30% higher than those observed in healthy subjects from an earlier study.

*Table 2. Summary of Plasma PAA PK Parameters in Child-Pugh A and C Subjects*

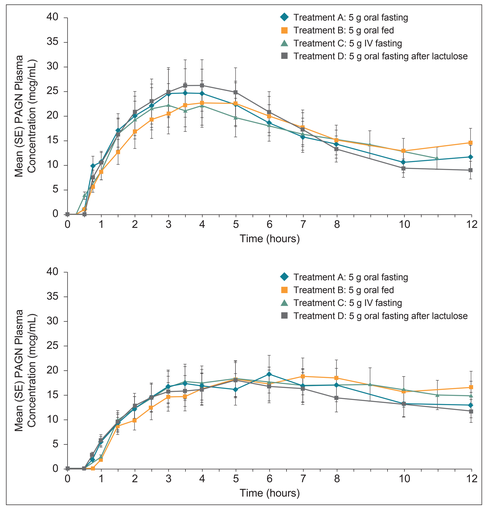
| | | Treatment | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A | | | B | | | C | | | D | | |
| **Child-Pugh A** | | N | Mean | CV% | N | Mean | CV% | N | Mean | CV% | N | Mean | CV% |
| $C_{max}$ | (ug/mL) | 5 | 105 | (27.6) | 5 | 66.7 | (21.0) | 5 | 103 | (35.5) | 5 | 113 | (23.4) |
| $t_{max}$ | (h) | 5 | 0.82 | (25.4) | 5 | 1.55 | (71.7) | 5 | 1.03 | (34.6) | 5 | 0.66 | (59.9) |
| $AUC_{last}$ | (h*ug/mL) | 5 | 440 | (47.6) | 5 | 360 | (43.4) | 5 | 397 | (62.2) | 5 | 458 | (35.7) |
| $AUC_{inf}$ | (h*ug/mL) | 5 | 453 | (46.6) | 5 | 374 | (42.0) | 5 | 433 | (61.0) | 5 | 486 | (36.7) |
| $t_{1/2}$ | (h) | 5 | 1.38 | (14.9) | 5 | 1.39 | (12.1) | 5 | 1.85 | (28.4) | 5 | 1.70 | (20.9) |
| Cl/F | (L/h) | 5 | 6.88 | (51.5) | 5 | 7.96 | (44.6) | 5 | 9.65 | (90.6) | 5 | 6.00 | (45.5) |
| $V_z/F$ | (L) | 5 | 13.2 | (44.3) | 5 | 15.7 | (42.9) | 5 | 21.5 | (62.6) | 5 | 13.7 | (23.7) |
| F | | 4 | 0.959 | (3.7) | 4 | 0.804 | (7.6) | | | | 4 | 1.037 | (14.2) |
| **Child-Pugh C** | | | | | | | | | | | | | |
| $C_{max}$ | (ug/mL) | 4 | 93.9 | (10.0) | 4 | 66.0 | (17.3) | 5 | 95.5 | (15.4) | 4 | 96.9 | (12.7) |
| $t_{max}$ | (h) | 4 | 0.94 | (45.5) | 4 | 2.13 | (100.5) | 5 | 1.10 | (20.3) | 4 | 0.88 | (49.5) |
| $AUC_{last}$ | (h*ug/mL) | 4 | 541 | (24.4) | 4 | 466 | (33.0) | 5 | 589 | (25.7) | 4 | 559 | (22.1) |
| $AUC_{inf}$ | (h*ug/mL) | 4 | 647 | (36.5) | 4 | 571 | (43.2) | 5 | 692 | (30.0) | 4 | 665 | (35.7) |
| $t_{1/2}$ | (h) | 4 | 3.54 | (85.9) | 4 | 3.68 | (55.6) | 5 | 3.78 | (33.2) | 4 | 3.71 | (56.4) |
| Cl/F | (L/h) | 4 | 4.40 | (41.0) | 4 | 5.13 | (43.4) | 5 | 4.03 | (38.9) | 4 | 4.20 | (35.3) |
| $V_z/F$ | (L) | 4 | 18.2 | (50.8) | 4 | 23.1 | (23.3) | 5 | 20.4 | (23.0) | 4 | 19.5 | (21.6) |
| F | | 4 | 0.947 | (5.7) | 4 | 0.827 | (12.9) | | | | 4 | 0.985 | (12.2) |

Treatment A: 5 g OCR-002 oral solution administered while fasting; Treatment B: 5 g OCR-002 oral solution administered with a high fat meal; Treatment C: 5 g OCR-002 infused intravenously over 30 minutes while fasting; Treatment D: 5 g OCR-002 oral solution administered while fasting and after discontinuing lactulose for at least 4 days.

### PAGN Plasma and Urine Profiles

- Plasma exposure and PK profiles of PAGN were comparable among all 4 treatments in subjects with Child-Pugh Class A and C cirrhosis (**Figure 4**).

*Figure 4. Mean (SE) plasma PAGN concentrations over time after 4 single IV or oral doses of OCR-002 (top Child-Pugh A; bottom Child-Pugh Class C)*




- Mean plasma half-life of PAGN was longer in cirrhotic subjects (2.8-3.3 h in Child-Pugh Class A and 3.5-5.1 h in Child-Pugh Class C) than in healthy subjects (1.4 h).
- These data indicate that PAGN disposition was formation-rate limited, and thus the plasma half-life of PAGN is affected by liver function (**Table 3**).
- Mean $AUC_{inf}$ of PAGN in Child-Pugh Class C subjects appeared about 48% higher than in Child-Pugh Class A subjects following IV dosing, most likely due to the prolonged plasma half-life.
- The mean PAGN to PAA molar AUC ratios were comparable across all four treatments with OCR-002, and were comparable between Child Pugh A and Child Pugh C subjects, averaging about 0.25.
- This finding suggests that the disposition of PAA follows linear kinetics at the 5 g OCR-002 dose level.

*Table 3. Summary of Plasma PAGN PK Parameters in Child-Pugh A and C Subjects*

| | | Treatment | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A | | | B | | | C | | | D | | |
| **Child-Pugh A** | | N | Mean | CV% | N | Mean | CV% | N | Mean | CV% | N | Mean | CV% |
| $C_{max}$ | (ug/mL) | 5 | 26.0 | (19.7) | 5 | 23.9 | (16.5) | 5 | 23.3 | (9.2) | 5 | 27.4 | (24.5) |
| $t_{max}$ | (h) | 5 | 4.02 | (25.2) | 5 | 4.42 | (19.1) | 5 | 3.43 | (31.9) | 5 | 3.93 | (19.0) |
| $AUC_{last}$ | (h*ug/mL) | 5 | 162 | (29.5) | 5 | 162 | (32.4) | 5 | 148 | (39.0) | 5 | 177 | (32.0) |
| $AUC_{inf}$ | (h*ug/mL) | 5 | 203 | (32.7) | 5 | 208 | (32.6) | 5 | 191 | (34.6) | 5 | 208 | (31.4) |
| $t_{1/2}$ | (h) | 5 | 3.03 | (43.3) | 5 | 3.09 | (28.5) | 5 | 3.31 | (30.4) | 5 | 2.81 | (28.9) |
| F | | 4 | 0.931 | (13.0) | 4 | 0.932 | (15.5) | | | | 4 | 0.916 | (13.4) |
| PAGN/PAA Conc. Ratio | | 5 | 0.260 | (37.9) | 5 | 0.310 | (35.9) | 5 | 0.295 | (51.0) | 5 | 0.238 | (36.8) |
| PAGN Cum. Urine (g) | | 5 | 3.31* | (22.3) | 5 | 3.45* | (19.0) | 5 | 3.51 | (30.8) | 5 | 4.17 | (14.9) |
| PAA Equi. Cum. (g) | | 5 | 1.71* | (22.3) | 5 | 1.78* | (19.0) | 5 | 1.81 | (30.8) | 5 | 2.15 | (14.9) |
| CLr (L/hr) | | 5 | 19.9* | (37.0) | 5 | 20.7* | (32.7) | 5 | 19.3 | (27.6) | 5 | 22.2 | (39.2) |
| % Dose Urine PAGN | | 5 | 67.2* | (22.3) | 5 | 70.1* | (19.0) | 5 | 71.4 | (30.8) | 5 | 84.7 | (14.9) |
| **Child-Pugh C** | | | | | | | | | | | | | |
| $C_{max}$ | (ug/mL) | 4 | 19.1 | (43.7) | 4 | 20.9 | (45.3) | 5 | 20.4 | (36.8) | 4 | 18.5 | (49.1) |
| $t_{max}$ | (h) | 4 | 5.25 | (36.1) | 4 | 6.50 | (26.6) | 5 | 6.80 | (60.8) | 4 | 5.88 | (48.3) |
| $AUC_{last}$ | (h*ug/mL) | 4 | 158 | (46.0) | 4 | 168 | (49.3) | 5 | 217 | (49.3) | 4 | 194 | (59.5) |
| $AUC_{inf}$ | (h*ug/mL) | 2 | 209 | (58.4) | 2 | 200 | (59.4) | 3 | 283 | (49.9) | 2 | 235 | (56.5) |
| $t_{1/2}$ | (h) | 2 | 3.51 | (16.3) | 2 | 3.78 | (22.8) | 3 | 5.06 | (26.9) | 2 | 4.45 | (5.8) |
| F | | 2 | 0.947 | (1.3) | 2 | 0.903 | (02.4) | | | | 2 | 1.073 | (1.0) |
| PAGN/PAA Conc. Ratio | | 2 | 0.220 | (31.4) | 2 | 0.253 | (35.3) | 3 | 0.223 | (18.9) | 2 | 0.233 | (34.8) |
| PAGN Cum. Urine (g) | | 4 | 2.18* | (34.9) | 5 | 2.54* | (37.9) | 6 | 3.47 | (27.3) | 4 | 3.26 | (27.8) |
| PAA Equi. Cum. (g) | | 4 | 1.12* | (34.8) | 5 | 1.31* | (37.9) | 6 | 1.79 | (27.2) | 4 | 1.68 | (27.7) |
| CLr (L/hr) | | 4 | 15.5* | (50.2) | 4 | 18.0* | (74.4) | 3 | 14.8 | (64.8) | 3 | 15.4 | (78.4) |
| % Dose Urine PAGN | | 4 | 44.3* | (34.9) | 5 | 51.6* | (37.9) | 6 | 70.6 | (27.4) | 4 | 66.3 | (27.8) |

Treatment A: 5 g OCR-002 oral solution administered while fasting; Treatment B: 5 g OCR-002 oral solution administered with a high fat meal; Treatment C: 5 g OCR-002 infused intravenously over 30 minutes while fasting; Treatment D: 5 g OCR-002 oral solution administered while fasting and after discontinuing lactulose for at least 4 days.

- Due to the relatively short urine collection period, 24 h, as compared to the relatively longer plasma half-life of PAGN in cirrhotic subjects, there was incomplete recovery of PAA dose as PAGN in urine in these subjects vs. healthy subjects (80%-85% of the PAA dose).
- Generally, the mean percent PAA dose recovered in urine as PAGN was lower in Child Pugh C subjects than in Child-Pugh A subjects, most likely due to the prolonged half-life of PAGN and incomplete urine collection in Child Pugh C subjects (**Table 3**).

## Conclusion

- **PAA was rapidly absorbed and almost completely bioavailable (≥95%) from oral doses of OCR-002 in subjects with cirrhosis.**
- **Single oral and IV doses of 5 g OCR-002 are well tolerated in cirrhotic subjects with Child Pugh A and C classification.**
- **Child-Pugh C subjects PK profile suggests a possible decreased PAA to PAGN transformation in this group compared to Child-Pugh A subjects.**
- **The prolonged plasma half-life of PAA in cirrhotic subjects may allow reduced dosing frequency of oral OCR-002.**
- **Dosing with food may be advantageous as is it reduces the potential for adverse events that are driven by $C_{max}$.**
- **Results of this study supported the rationale for the development of an oral formulation of OCR-002 for reducing ammonia levels in cirrhotic patients.**

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