STOP-HE: A Randomized, Double-blind, Placebo-controlled Study of OCR-002 in Patients With Hepatic Encephalopathy

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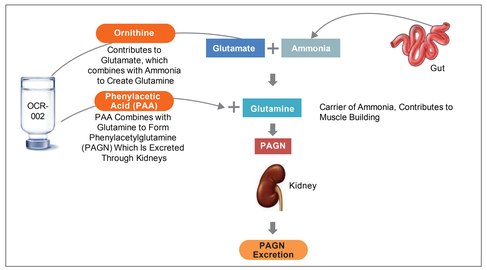
Introduction

- Hepatic encephalopathy (HE) is a major complication of cirrhosis that is associated with increased morbidity and mortality as well as increased use of health care resources.[1,2]
- 30% to 40% of cirrhotic patients will experience overt HE (OHE) at some time, and recurrent episodes of OHE are common within 6 months of the initial event.[2]
- OHE involves reestablishing hydration and electrolyte balance, treating the underlying triggering event, and trying to reduce ammonia produced from gut bacteria (commonly using lactulose and/or rifaximin, which target gut bacteria).[2-5]
- Rifaximin is indicated for prevention of recurrent episodes of OHE, but not for the acute care of hospitalized cirrhotic patients with HE, despite being commonly used.[6]
- Furthermore, lactulose and rifaximin are both orally-administered and as such less useful to administer to patients who have GI bleeding or have more severe encephalopathy.[7]
- OCR-002 (ornithine phenylacetate) provides a novel scavenger mechanism to lower ammonia levels independent of gut action (**Figure 1**).[8,9]
- Earlier studies in cirrhotic patients with gastrointestinal (GI) bleeding showed that OCR-002 lowered plasma ammonia levels, and the reduction was significant in patients with the Child-Pugh Class C.[10]

Figure 1. Effect of L-ornithine Phenylacetate (OCR-002) on Inter-Organ Ammonia Trafficking



Objective

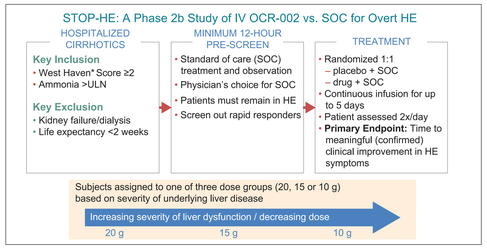
- To report efficacy, safety, and tolerability from a Phase 2b study of OCR-002 in patients with cirrhosis hospitalized with an acute episode of HE (Clinicaltrials.gov: NCT01966419).

Methods

Study Design

- Multicenter, randomized, double-blind, placebo-controlled study of intravenous (IV) OCR-002 (**Figure 2**)

Figure 2. Study Design



*Scored by a modified version of the West Haven Scale.

Patient Selection

- Hospitalized patients with cirrhosis and an acute episode of HE Stages 2-4, inclusive (Hepatic Encephalopathy Staging Tool [HEST])
- Venous ammonia level >ULN

Study Treatments

- Randomized 1:1 to IV OCR-002 or placebo for 5 days added to standard of care (SOC) determined by investigator judgment and institutional practice
- Randomization stratified by
  - MELD score ≤30 vs. >30
  - HEST Stage 2 vs. Stage 3/4
  - In North America, patients also were stratified by liver transplant centers ≥70 transplants/year vs. <70 transplants or centers not performing transplants
- The dose of OCR-002 was determined by the severity of hepatic failure to be 10, 15 or 20 g infused IV over 24 h

Study Outcomes

- Primary: Time to meaningful clinical improvement in HE symptoms (confirmed clinical response)
- Key Secondary:
  - Time to confirmed improvement to Stage 0/1
  - Cumulative proportion of patients fulfilling primary endpoint response criteria through 3 hours post end-of-infusion
  - Change from baseline in modified orientation log (MO-log)

Results

Baseline Characteristics

- Treatment groups were comparable for baseline characteristics (**Table 1**).

Table 1. Baseline Characteristics

Characteristic	OCR-002 (n=116)	Placebo (n=115)
Male	62%	68%
Mean age, y (range)	59 (26,79)	60 (27,79)
Child-Pugh A	2%	<1%
Child-Pugh B	33%	24%
Child-Pugh C	66%	75%
HEST Stage 2	59%	62%
HEST Stage 3	34%	26%
HEST Stage 4	5%	10%
Etiology of Inciting Factor (most common)		
Bacterial infection	15 (13%)	14 (12%)
Poor compliance (lactulose)	15 (13%)	13 (11%)
Dehydration	16 (14%)	9 (8%)
Transjugular intrahepatic portosystemic shunt	7 (6%)	9 (8%)
Constipation	8 (7%)	7 (6%)
Esophageal/gastric variceal bleeding	4 (3%)	7 (6%)

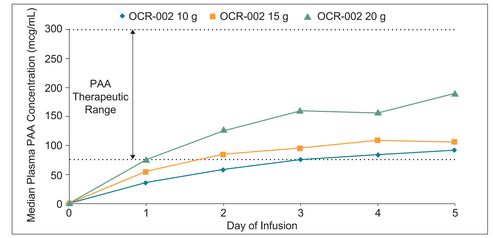
Table 2. Patient Disposition

	Number (%) of Patients			
		OCR-002		
	Placebo (N=115)	10 g/24 h (N=29)	15 g/24 h (N=60)	20 g/24 h (N=27)
Completed 5 days	59 (51)	14 (48)	32 (53)	16 (59)
Total Median OCR-002 infused (g/)	0	46	70	98
Reasons for discontinuation				
Early discharge from hospital	19 (17)	3 (10)	13 (22)	5 (19)
Investigator decision	13 (11)	2 (7)	7 (12)	5 (19)
Adverse event	8 (7)	3 (10)	4 (7)	0
Withdrawal by patient	3 (3)	1 (3)	2 (3)	0
Mechanical ventilation	2 (2)	0	0	0
Other	8 (7)	6 (21)	1 (2)	0

Pharmacokinetic Data

- PK data showed PAA steady state was reached in 3 days and a clear separation of the doses was noted (**Figure 3**).

Figure 3. Median Plasma PAA During IV Infusion



Efficacy (Primary and Secondary)

- Time to meaningful clinical improvement in HE symptoms was faster with OCR-002 vs. placebo (**Table 3**).

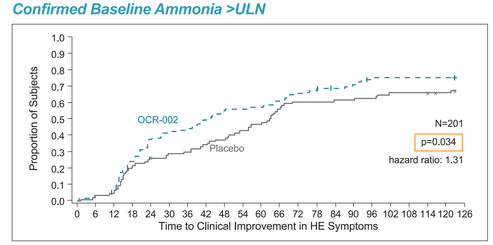
Table 3. Primary Endpoint – Time to Clinical Improvement

	Median Time to Clinical Improvement (hours)				
	OCR-002		Placebo		Statistical Comparison
Overall (ammonia levels determined locally)	N=116	47 h	N=115	64 h	p=0.129 HR: 1.25
With confirmed ammonia >ULN at baseline*	N=104	42 h	N=97	63 h	p=0.034 HR: 1.31

*Determined at a central laboratory.

- Among those with ammonia levels >ULN at baseline, time to meaningful clinical improvement was significantly p=0.034) shorter with OCR-002 (**Figure 4**).

Figure 4. Time to Clinical Improvement Among Patients With Confirmed Baseline Ammonia >ULN



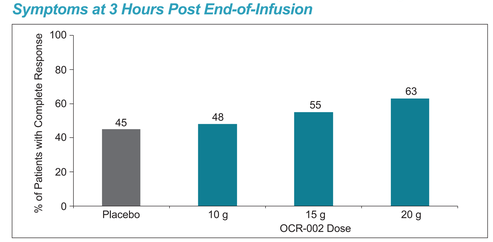
Key Secondary Endpoints

- Time to complete response to Stage 0/1 was faster with OCR-002 vs. placebo (**Table 4**) and the responder rate increased as the dose increased (**Figure 5**).

Table 4. Time to Complete Response – Confirmed Improvement to HEST Stage 0/1 (ITT)

	Median Time to Complete Response (hours)				
	OCR-002		Placebo		Statistical Comparison
Overall (ammonia levels determined locally)	N=116	87 h	N=115	102 h	p=0.361 HR: 1.16

Figure 5. Dose-Proportional Complete Response to Stage 0/1 in HE Symptoms at 3 Hours Post End-of-Infusion



- The cumulative proportion of responders for Clinical Improvement was higher than placebo, but the difference was not statistically significant (**Table 5**).

Table 5.Cumulative Proportion of Patients With Confirmed Primary Clinical Response 3 Hours Post End-of-Infusion or at Early Hospital Discharge/Early Termination (ITT Population)

	N (%) of Patients					
		OCR-002 Dose				
Planned Evaluation Time	Placebo	10 g/24 h	15 g/24 h	20 g/24 h	Total	p-value[a]
3 hours after the end of the infusion or at early hospital discharge/early termination	73/115 (63)	21/29 (72)	42/60 (70)	19/27 (70)	82/116 (71)	0.228

[a]2-sided p-values comparing OCR-002 and placebo for continuous results based on Wilcoxon Rank-Sum test; 2-sided p-values for categorical results based on the Chi-Square Test.

- Change from baseline in MO-log appears to have a dose-response trend, but does not demonstrate statistical significance (**Table 6**).

Table 6.Change From Baseline in MO-log 3 Hours Post End-of-Infusion or at Early Hospital Discharge/Early Termination

	N (%) of Patients				
		OCR-002 Dose			
	Placebo	10 g/24 h	15 g/24 h	20 g/24 h	OCR-002
N	63	17	40	18	75
Mean (SD)	9 (9.5)	9 (8.9)	12 (9.6)	11 (8.5)	11 (9.1)
Median	8	10	10	10	10
Minimum, maximum	-15, 24	-6, 24	-11, 24	-2, 24	-11, 24
p-value, OCR-002 vs.placebo[a]		0.750	0.585	0.226	0.342

ITT = intent-to-treat; MO-log = modified orientation log; SD = standard deviation.
[a]2-sided p-values comparing OCR-002 and placebo for continuous results based on Wilcoxon Rank-Sum test; 2-sided p-values for categorical results based on the Chi-Square Test.

Other Efficacy Analyses of Interest

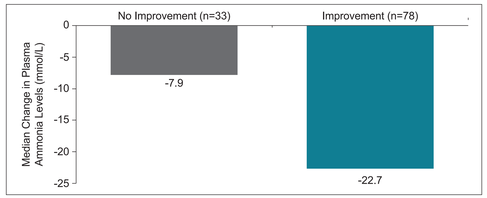
- The physician's overall evaluation of the change in degree of HE since the patient began study drug infusion was "better" for 61% of all OCR-002 patients and 49% of placebo patients (p=0.026).
- Response (time to clinical improvement at 48 hours) rate was higher with OCR-002 vs placebo (p=0.026).
- Ammonia level at screening correlates with severity of HE (p=0.003) (**Table 7**).

Table 7. Mean Ammonia Levels at Screening by HE Severity

HEST Score	Mean Ammonia Levels at Screening (µmol/L)
2	90
3	100
4	143

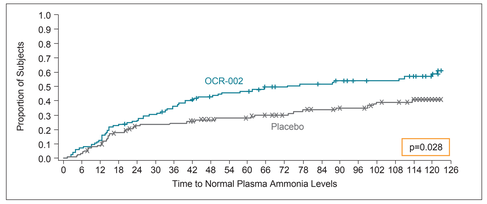
- Reduction in plasma ammonia levels correlated with clinical improvement (p=0.009) (**Figure 6**).

Figure 6. Plasma Ammonia Levels and Clinical Outcome at 48 Hours



- Median change in plasma ammonia levels was -7.9 µmol/L for no improvement (n=33) and -22.7 µmol/L among those with improvement (n=78).
- OCR-002 normalized and reduces ammonia levels faster than placebo (p=0.028) (**Figure 7**).

Figure 7.



Safety and Tolerability

- The incidence of adverse events (AEs) was comparable between treatment groups (**Table 8**). No significant differences were observed between placebo and OCR-002, 2-sided Fisher's Exact Test.

Table 8. Incidence of Adverse Events Occurring in >3% of Patients With OCR-002 (Safety Population)

	Number (%) of Patients				
		OCR-002 (Dose, g/24 h)			
	Placebo (n=113)	10 g (n=29)	15 g (n=59)	20 g (n=26)	All (n=114)
Any adverse event	79 (71)	20 (69)	42 (71)	18 (69)	80 (70)
Drug-related AEs	14 (13)	5 (17)	10 (17)	3 (12)	18 (16)
Serious AEs	33 (29)	10 (34)	13 (22)	6 (23)	29 (25)
Discontinuation for AEs	9 (8)	3 (10)	4 (7)	0	7 (6)
Most common AEs					
Hepatic encephalopathy	11 (10)	5 (17)	11 (19)	5 (19)	21 (18)
Anemia	8 (7)	5 (17)	6 (10)	3 (12)	14 (12)
Hypokalemia	8 (7)	3 (10)	4 (7)	2 (8)	9 (8)
Urinary tract infection	4 (4)	2 (7)	3 (5)	3 (12)	8 (7)
Pyrexia	8 (7)	1 (3)	3 (5)	2 (8)	6 (5)
Hypophosphatemia	9 (8)	2 (7)	2 (3)	1 (4)	5 (4)
Hypotension	4 (4)	1 (3)	3 (5)	1 (4)	5 (4)
Nausea	4 (4)	2 (7)	2 (3)	1 (4)	5 (4)
Hypomagnesemia	4 (4)	1 (3)	3 (5)	0	4 (4)
Sepsis	5 (4)	1 (3)	2 (3)	1 (4)	4 (4)
Acute renal failure	6 (5)	1 (3)	0	2 (8)	3 (3)
Ascites	5 (4)	1 (3)	0	2 (8)	3 (3)

- No significant or notable differences were observed between treatment groups for treatment-emergent clinical laboratory values, vital signs or ECG changes through the 3 h post-end-of-infusion assessment.

Summary of Results

- Treatment groups were comparable for baseline characteristics.
- PK data showed PAA steady state reached in 3 days and a clear separation of doses.
- Trend for improved time to clinical improvement (primary endpoint) with OCR-002 and faster improvement in HE, i.e., time to improvement was significantly shorter with OCR-002 (p=0.034) among those with confirmed elevated ammonia level at baseline.
- Response (time to clinical improvement at 48 hours) rate was higher with OCR-002 vs. placebo (p=0.026).
- Time to complete response to Stage 0/1 was faster with OCR-002 vs placebo, although not significant, but the responder rate increased as the dose increased.
- The cumulative proportion of responders for Clinical Improvement was higher with OCR-002 than with placebo, but the difference was not statistically significant.
- Dose separation was demonstrated, but the design of the study may have led to under dosing at lower doses especially 10 g, missing the therapeutic range.
- Change from baseline in MO-log appears to have a dose-response trend but does not demonstrate statistical significance.
- The physician's overall evaluation of the change in degree of HE since the patient began study drug infusion was "better" for 61% of all OCR-002 patients and 49% of placebo patients (p=0.026).
- Good correlation was observed for ammonia and clinical response.
  - Ammonia level at screening correlates with severity of HE (p=0.003)
  - Significantly greater reduction in ammonia (p=0.009) among those with a response vs. non response
  - OCR-002 reduced and normalized ammonia faster than placebo (p=0.028)
- Safety/tolerability comparable to placebo + SOC
- Importantly, these effects were observed even though OCR-002 was added to SOC, which consisted primarily of lactulose and/or rifaximin.

Conclusions

- **This study demonstrated the efficacy of OCR-002 in cirrhotic patients hospitalized with HE and the potential to improve patient outcomes.**
- **The study confirmed the MOA of OCR-002 as an ammonia scavenger.**
- **Rapid ammonia reduction by OCR-002 greater than placebo was demonstrated and has been reported to lead to faster improvement in HE.[10]**
- **The data support further study of OCR-002 as a new treatment option for patients hospitalized with overt HE.**

References

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