Geographic Differences for Patients Enrolled in STOP-HE: A Randomized, Phase 2 Study of OCR-002 for Hepatic Encephalopathy

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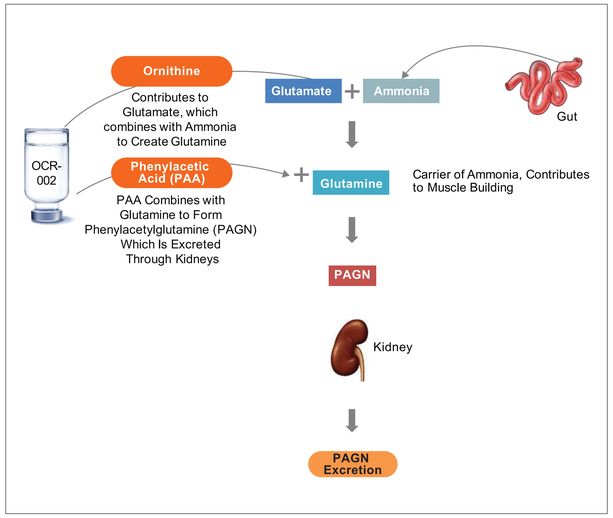
Introduction

- A major complication of liver cirrhosis is hepatic encephalopathy (HE), which is associated with increased morbidity and mortality and greater use of health care resources (Vilstrup et al, 2014; Elwir and Rahimi, 2017).
- 30% to 40% of cirrhotic patients will experience overt HE (OHE) at some time in the course of their disease, and recurrent episodes of OHE are common within 6 months of an initial OHE event (Vilstrup et al, 2014).
- The standard of care includes lactulose and rifaximin, but their use may be limited by the need for oral administration and frequent dosing as well as side effects (Liu et al, 2015), and rifaximin is not approved for acute overt HE indication in either NA or ROW.
- LOLA is approved in a limited number of European and Asian countries, but not in the U.S. for the treatment of hyperammonemia.
- OCR-002 (ornithine phenylacetate) is an ammonia scavenger that provides a novel mechanism to lower plasma ammonia levels independent of gut action (Romero-Gomez et al, 2015; Aldridge et al, 2015) (**Figure 1**).
- Previous studies with OCR-002 in cirrhotic patients with gastrointestinal (GI) bleeding demonstrated reductions in plasma ammonia levels, which were significant in patients with the Child-Pugh Class C (Ventura-Cots et al, 2016).
- STOP-HE was an international Phase 2b study that demonstrated the efficacy, safety, and tolerability of OCR-002 in patients hospitalized with OHE.

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



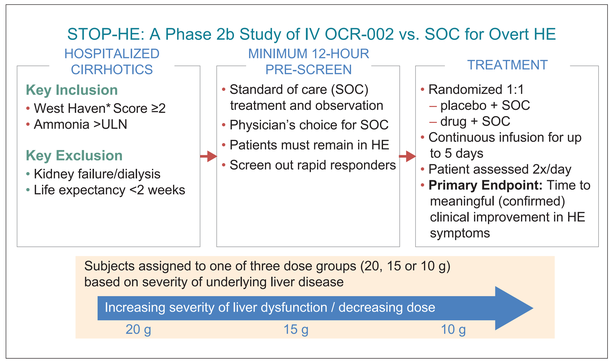
Objective

- The aim of this ancillary analysis was to assess geographic differences in the enrolled patient population and treatment, and their influence on clinical outcomes.

Methods

- Double-blind, randomized, placebo-controlled study of OCR-002 in patients hospitalized with cirrhosis, an HE Staging Tool Score ≥2, and Screening plasma ammonia level >ULN (**Figure 2**)

Figure 2. Study Design for STOP-HE



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

- After prescreening on standard of care (SOC), patients were randomized to treatment for 5 days with:
  - SOC + placebo
  - SOC + OCR-002 10, 15 or 20 g infused over 24 hours
    - Dose of OCR-002 was based on severity of underlying liver disease
- Primary endpoint was time to meaningful clinical improvement
- For this analysis, patients from North American (NA, n=130) and Rest-of-World (ROW, n=101) were compared to determine differences in:
  - Baseline characteristics
    - Including baseline use of concomitant medications
  - Inciting factors for precipitating an OHE event
  - SOC during hospitalization
  - Outcomes
    - Median time (h) to clinically meaningful improvement
    - Median time (h) in hospital

Results

- 231 patients were randomized to OCR-002 (n=116) or placebo (n=115).

Baseline Characteristics

- Significant differences were observed for NA vs. ROW for some baseline characteristics, including gender, MELD score, serum creatinine, and NASH as an etiology of cirrhosis (**Table 1**).

Table 1. Baseline characteristics

	North America (N=130)	Rest of World (N=101)	p-value[b]
Age, years[a]	60 ± 9.1	58 ± 10.2	0.175
Male, n (%)	77 (59%)	73 (72%)	0.039
Body mass index, kg/m[2a]	29.4 ± 7.3	27.9 ± 6.4	0.069
Child-Pugh Score, n (%)			0.668
A	1 (<1)	2 (2)	
B	36 (28)	30 (30)	
C	93 (72)	69 (68)	
MELD Score[a]	20 ± 6.8	18 ± 5.9	0.007
Serum creatinine (mg/dL)[a]	1.3 ± 0.5	1.1 ± 0.6	0.004
Serum creatinine (mg/dL), n (%)			<0.001
0 – <1	43 (33)	60 (59)	
1 – <2	70 (54)	29 (29)	
2 – <3	14 (11)	8 (8)	
HEST Stage, n (%)			0.150
2	72 (55)	68 (67)	
3	48 (37)	29 (29)	
4	10 (8)	4 (4)	
Etiology of cirrhosis, n (%)			0.203
Alcohol	50 (38)	43 (43)	
Hepatitis C	29 (22)	22 (22)	
Non-alcoholic steatohepatitis	32 (25)	15 (15)	
Other	18 (15)	18 (18)	

[a]Mean ± standard deviation.
[b]2-sided comparisons of OCR-002 and placebo for continuous results based on the Wilcoxon Rank-Sum test; 2-sided for categorical results based on the Chi-Square Test.

Use of Medications to Treat HE Prior to Study Drug Administration (Table 2)

- Rifaximin was used by 135 (58.4%) patients. Of these, 92 patients (68%) were in NA vs. 43 patients (32%) ROW, a 2-fold greater use of rifaximin was observed in NA vs. ROW.
- Lactulose was used by 173 (74.9%) patients of these 95 patients (55%) were in NA vs. 78 patients (45%) ROW).
- While the frequency of use was similar between regions, an approximately 2-fold greater amount of lactulose was observed in NA vs. ROW.
- Use within region was similar between OCR-002 and placebo arms.

Table 2. Baseline use of medications for HE

	North America			Rest of World		
	Total N=130	OCR-002 N=66	Placebo N=64	Total N=101	OCR-002 N=50	Placebo N=51
Lactulose, mL/d	n=95	n=49	n=46	n=78	n=42	n=36
Mean (SD)	176.4 (152.2)	176.6 (181.1)	176.1 (115.9)	80.2 (51.2)	78.6 (54.2)	82.1 (48.3)
Median	120.0	120.0	180.0	60.0	60.0	75.0
Rifaximin, mg/d	n=92	n=47	n=45	n=43	n=25	n=18
Mean (SD)	1081 (152)	1077 (160)	1086 (144)	1007 (256)	1066 (209)	925 (296)
Median	1100	1100	1100	1100	1200	1100

Precipitating Factors for OHE

- Precipitating factors for OHE differed significantly between NA and ROW for poor compliance with lactulose, dehydration, TIPS, and renal impairment (**Table 3**).

Table 3. Etiology of inciting factor that precipitated OHE

Etiology of Precipitating Factor Precipitating OHE	Number (%) of Patients		p-value
	North America (N=130)	Rest of World (N=101)	
Bacterial infection	21 (16)	8 (8)	0.061
Poor compliance with lactulose	25 (19)	3 (3)	<0.001
Dehydration	8 (6)	17 (17)	0.010
Transjugular intrahepatic portosystemic shunt (TIPS)	5 (4)	11 (11)	0.036
Constipation	6 (5)	9 (9)	0.189
Esophageal/Gastric variceal bleeding	4 (3)	7 (7)	0.172
Renal impairment	8 (6)	1 (<1)	0.044
Sepsis	4 (3)	3 (3)	0.963
Spontaneous bacterial peritonitis	2 (2)	4 (4)	0.251

Use of Standard of Care to Treat HE

- Concomitant SOC medications used during the study were consistently distributed between treatment groups (**Table 4**).

Table 4. Concomitant SOC medications

	OCR-002 (n=116)	Placebo (n=115)
Lactulose	31 (27%)	38 (34%)
LOLA	3 (3%)	4 (4%)
Rifaximin	25 (22%)	29 (26%)

- Median time to clinical improvement with OCR-002 was lower in NA vs. ROW, but the difference was not significant (**Table 5**).
  - Patients in NA were more severely ill (higher MELD score)

Table 5. Outcome for primary endpoint by NA vs. ROW

	North America N=130			Rest of World N=101		
	OCR-002	PBO	Median Difference (95% CI)	OCR-002	PBO	Median Difference (95% CI)
Median time to clinically meaningful improvement (h)	41	62	-20.6 (-54, 8) p=0.552	67	70	-5.2 (-61, 27) p=0.149

p-value from log rank test.

Summary

- Significant differences in baseline characteristics were observed between NA and ROW clinical sites.
- The etiology of inciting factors for OHE differed significantly between NA and ROW clinical sites, including poor compliance with lactulose, dehydration, TIPS, and renal impairment.
- Marked differences were observed in the use of SOC between NA and ROW clinical sites.
- The average daily dose of lactulose used in NA was double the dose used in ROW.
- OCR-002 resulted in a trend with shorter median time to clinical improvement at clinical sites in NA vs. ROW.

Conclusions

- **In STOP-HE, differences were observed between patients enrolled in NA and ROW for baseline characteristics, severity of liver disease and use of SOC treatments.**
- **Geographic differences could be attributed to differences in management strategies for HE, differences in the use of concomitant medications, differences in intestinal microbiota or other as yet unexplained causes.**
- **Further study is needed to explore these differences more thoroughly.**
- **Geographic differences should be considered when designing clinical trials in patients with HE in order to avoid any bias.**

References

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