A Phase 2 study of OCE-205, a novel, selective vasopressin receptor mixed agonist-antagonist: Positive proof-of-concept established in subjects with cirrhosis and hepatorenal syndrome–acute kidney injury (HRS-AKI)

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INTRODUCTION

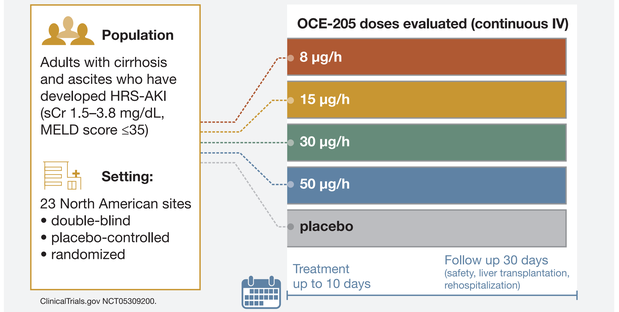
- OCE-205 is a mixed agonist-antagonist selective for the vasopressin 1A (V_{1A}) receptor, with no vasopressin 2 (V_2) receptor activity across a wide therapeutic range. It is being developed for the treatment of hepatorenal syndrome–acute kidney injury (HRS-AKI)

AIM

- Conduct dose-escalation (part 1) of a Phase 2 study to assess the efficacy, pharmacokinetics (PK), and safety of OCE-205 in patients with cirrhosis and ascites complicated by HRS-AKI

METHODS

Figure 1. Study Design



Endpoints included safety, pharmacokinetics, biomarkers and clinical outcomes

Primary:
- Clinical improvement: sCR <1.5 mg/dL on 2 consecutive days*

Secondary:
- Absolute change in sCr
- % of complete responders: sCr <1.5 mg/dL at the end of treatment*#

Exploratory:
- Change in mean arterial pressure (MAP)
- Ascites severity
- % of partial responders

*For participants entering the study with sCr ≤1.8 mg/dL, sCr needed to decrease to <1.5 mg/dL and have ≥0.3 mg/dL reduction from baseline;
#OR, if historical baseline was available, sCr at the end of treatment was within 0.3 mg/dL of historical baseline and less than the trial baseline
Partial Response: ≥30% reduction in sCr from treatment start baseline to end of treatment AND did not meet either criteria for complete response

RESULTS

- The patient group studied was representative of the broader population with HRS-AKI (**Table 1**)

Table 1. Study Baseline and Demographic Characteristics

	OCE-205 (n=37)	Placebo (n=10)
Age, years; mean (SD)	57.8 (10.0)	53.1 (6.5)
Male, %	48.6	80.0
Etiology, n (%)		
NAFLD/MASH	11 (29.7)	3 (30.0)
Alcohol	19 (51.4)	6 (60.0)
Serum creatinine, mg/dL; mean (SD)	2.6 (0.7)	2.3 (0.6)
MELD score; mean (SD)	28.5 (5.3)	25.8 (4.2)
Total bilirubin, mg/dL; mean (SD)	6.1 (5.4)	4.4 (3.7)

Pharmacokinetic Results

- PK of OCE-205 was dose proportional over the range tested (**Table 2**)
- Total body clearance was similar between patients with HRS-AKI and healthy individuals

Table 2. OCE-205 Pharmacokinetic Results, N=36

	OCE-205
Mean C_{SS}, ng/mL; for 8 µg/h to 50 µg/h groups	0.73–4.76
$t_{1/2}$, h; range	2.2–2.5
Mean clearance, L/h; for 8 µg/h to 50 µg/h groups	11.9–13.8
ED_{90}, µg/h	8

Abbreviations

AE, adverse event; bpm, beats per minute; C_{SS}, concentration at steady state; ED_{90}, 90% of the effective dose; HR, heart rate; HRS-AKI, hepatorenal syndrome-acute kidney injury; IV, intravenous; MAP, mean arterial pressure; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; NS, not significant; PK, pharmacokinetics; sCr, serum creatinine; SD, standard deviation; SUSAR, suspected unexpected serious adverse reaction; $t_{1/2}$, half-life; TEAE, treatment-emergent adverse event; V_{1A}, vasopressin type 1A receptor; V_2, vasopressin type 2 receptor

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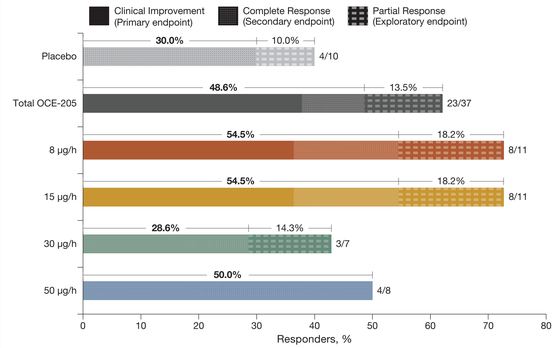
Clinical Efficacy Results

- Clinical improvement was seen in 48.6% of patients receiving OCE-205 vs 30% with placebo (NS)
- Complete response (secondary endpoint) was 54.5%, 54.5%, 28.6%, and 50.0% in the OCE-205 8, 15, 30, and 50 µg/h cohorts, respectively, vs 30% for placebo (**Figure 2**)

Figure 2. Clinical Treatment Benefit Following OCE-205 Infusion

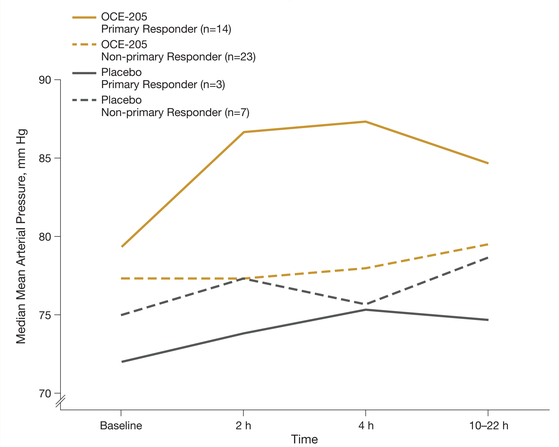


n/N at the end of each bar denote the cumulative number of participants in each treatment group that had any response. Bolded percentages above the bars indicate the percentage of participants in each treatment group that had a complete response.

Pharmacodynamic Results

- In patients receiving OCE-205, mean MAP increased ≥5 mm Hg at 2 and 4 h after infusion (**Figure 3**)

Figure 3. MAP by Responder Status for Primary Endpoint. MAP showed a rapid increase in responders following infusion of OCE-205



Safety Results

- No events of ischemia or related events of pulmonary edema, fluid overload, or cardiac failure reported in patients receiving OCE-205 (**Table 3**)
- Drug-related adverse events (AEs) occurred in 7 (18.9%) patients receiving OCE-205
- Drug-related bradycardia (HR <60 bpm) occurred in 6 (16.2%) patients receiving OCE-205; none required intervention

Table 3. Adverse Events, Safety Population

Patients, n (%)	Total OCE-205 (n=37)	Placebo (n=10)
Any TEAE	34 (91.9)	8 (80.0)
TEAE of special interest*	11 (29.7)	1 (10.0)
Serious TEAE up to 30 days post treatment, no SUSARs	21 (56.8)	4 (40.0)
AE resulting in death	9 (24.3)	1 (10.0)
TEAE leading to study discontinuation	5 (13.5)	1 (10.0)
System Organ Classes with most commonly reported preferred term		
Gastrointestinal disorders	16 (43.2)	5 (50.0)
Metabolism and nutrition disorders	16 (43.2)	2 (20.0)
General disorders and administration site conditions	12 (32.4)	3 (30.0)
Cardiac disorders	11 (29.7)	0
Respiratory, thoracic and mediastinal disorders	11 (29.7)	3 (30.0)
Hepatobiliary disorders	10 (27.0)	0
Renal and urinary disorders	10 (27.0)	3 (30.0)
TEAE occurring in ≥10% of patients receiving OCE-205, by preferred term		
Diarrhea	4 (10.8)	0
Bradycardia	8 (21.6)	0
Hepatic cirrhosis	5 (13.5)	0
Acute kidney injury	4 (10.8)	1 (10.0)

TEAE: a treatment-emergent adverse event was an adverse event that began, or a pre-existing adverse event that worsened, after receiving the study drug
*TEAEs of special interest included: ischemia, hypoxia, cardiac failure, and bradycardia

CONCLUSIONS

- OCE-205 was well tolerated, with no evidence of excessive vasoconstriction, no ischemic AEs, and no related events of pulmonary edema or serious infections, at any dose level
- Based on PK, no dose adjustment is expected in this population with HRS-AKI
- OCE-205 had a predictable, capped maximal efficacy that demonstrated reversal of HRS-AKI in more patients than placebo
- OCE-205 carries great promise to become a novel HRS-AKI therapy, with a favorable risk/benefit profile

Disclosures

DG, NK, SK, NL, KP, DR, and PZ report no conflicts of interest. ASA is a consultant to Ocelot Bio, Mallinckrodt Pharmaceuticals, Sequana Medical, and Mortic Bio. RB is a consultant to and receives research funding from Ocelot Bio and Mallinckrodt Pharmaceuticals, and is a consultant to eGenesis, AbbVie, Intercept, Gilead, Regeneron, and Salix. GC is a consultant to Ocelot Bio and Retro. PYK is a consultant to Mallinckrodt, and received institutional research support from Ocelot Bio. NTP has received research support from Ocelot Bio, Salix, Grifols, Gilead, DURECT, Intercept, and Cytosorbents. RSR and KS have received research support from Ocelot Bio. AS reports stock options in GENFIT, Akarna, Tiziana, DURECT, Inversago, and Galmed; serving as a consultant to AstraZeneca, Salix, Tobira, Takeda, Janssen, Gilead, Terns, Bird Rock Bio, Merck, Valeant, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, HemoShear, Novartis, Novo Nordisk, Pfizer, 89 bio, Regeneron, Alnylam, Akero, Tern, HistoIndex, Corcept, Poxel, PathAI, and GENFIT; institutional research support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, AstraZeneca, Mallinckrodt, and Novartis; and royalties from Elsevier and UptoDate. DS is a consultant to Biovie, Mallinckrodt, Evivie, and Resolution Therapeutics. LS serves on the speaker's bureau for Gilead, AbbVie, and Intercept; is a consultant or advisor to Intercept, GSK, and Madrigal; and received institutional research support from DURECT, Ocelot Bio, and Renal2River. HEV reports research support from Ocelot Bio, Renal2River, Sequana, Takeda, and Kezar; and serves as a consultant to Mallinckrodt. DB is a consultant to Ocelot Bio, Inc. LK and SR were employees of Ocelot Bio, Inc. at the time of the study. FW is a consultant to and has received institutional research support from Ocelot Bio.

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