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ORIGINAL RESEARCH ARTICLE

OCE-205, A Novel, Selective Vasopressin Receptor Mixed Agonist-Antagonist: Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics from a Phase 1 Study in Healthy Volunteers

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Abstract

Background OCE-205, a novel, selective vasopressin V1a receptor mixed agonist/antagonist with no V2 receptor activity, may treat the portal hypertension-related complications of end-stage liver disease with an improved therapeutic profile over currently utilized nonselective full-agonist vasopressin analogs.

Objectives This Phase 1, double-blind, placebo-controlled, within-dose-group randomized trial investigated the safety, tolerability, and pharmacokinetic/pharmacodynamic profiles of OCE-205 in healthy adults.

Methods Subjects received a single intravenous dose of OCE-205 0.1, 0.3, 0.45, 0.6, or 0.9 mg, or placebo infused over 6 h. Safety and tolerability were assessed, and blood samples were obtained for pharmacokinetic analyses. Sixty-four subjects were randomized and treated.

Results Area under the concentration–time curve (AUC) and maximum plasma concentrations (C_{max}) were approximately dose-proportional across doses from 0.1 to 0.9 mg. OCE-205 terminal half-life was ~ 1.5 h. Diastolic, and to a lesser extent systolic, blood pressure increased in all OCE-205 dose groups; pulse rate decreased. Overall changes in mean arterial pressure were similar to changes in diastolic blood pressure. Absolute changes in cardiac output, by echocardiogram, were somewhat dose-dependent, with mean reductions of 3–12% after the 0.9 mg dose, and individual reductions ≤ 20 to 25% across all doses. The most frequent adverse events were abdominal pain, abnormal gastrointestinal sounds, and diarrhea, with no reported cases of mesenteric ischemia. Adverse events were generally mild or moderate in severity.

Conclusion OCE-205 was safe and well tolerated, with a pharmacodynamic profile achieving submaximal partial agonism consistent with mixed agonism-antagonism of the V1a receptor. OCE-205 shows promise as a treatment for some complications of end-stage liver disease.

1 Introduction

Systemic hemodynamic complications, including portal hypertension and reflex splanchnic arteriolar vasodilatation, are hallmarks of decompensated cirrhosis. In decompensated cirrhosis, these hemodynamic changes can lead to systemic complications, including hepatorenal syndrome–acute kidney injury (HRS-AKI), which, if left untreated, has a mortality rate approaching 90% and a median duration of survival of weeks to months [1–7]. Treated promptly, however, HRS-AKI is potentially reversible. Current HRS-AKI treatment paradigms focus on normalizing the deranged systemic hemodynamics associated with decompensated cirrhosis to restore renal perfusion and, thus, function. Reversal of HRS-AKI is typically measured by restoring serum creatinine (sCr) to within 0.3 mg/dL of the baseline level prior to the development of HRS-AKI. Achieving HRS-AKI reversal has been shown to correlate with raising mean arterial pressure (MAP) by 10–20 mmHg from baseline at presentation [8].

Current International Club of Ascites (ICA) recommendations for the treatment of HRS-AKI center on the expansion of blood volume with albumin and the short-term use of systemic vasoconstrictors to reverse renal dysfunction, with the long-term goal of stabilizing patients until they can undergo liver transplantation [9, 10]. Terlipressin is a synthetic vasopressin analog that has been used outside the USA for more than 10 years. In September 2022, terlipressin was approved by the US Food and Drug Administration (FDA) to treat adults with HRS with rapid reduction in kidney function (patients with sCr < 5 mg/dL). Terlipressin

Extended author information available on the last page of the article

Key Points

Because of its unique mixed agonism/antagonism without V2 receptor activity, OCE-205, a novel, selective vasopressin V1a receptor, may treat portal hypertension-related complications of end-stage liver disease with an improved therapeutic profile over currently utilized nonselective full-agonist vasopressin analogs.

OCE-205 was safe and well tolerated, with a pharmacodynamic profile achieving submaximal partial agonism consistent with mixed agonism-antagonism of the V1a receptor.

OCE-205 shows promise as a treatment for some complications of end-stage liver disease.

is essentially an inactive prodrug; it is lysine vasopressin (LVP) that has full activity at both vasopressin (V)2 and V1a receptors that drives the observed pharmacology. While recommended for the treatment of HRS-AKI, terlipressin poses a serious risk of tissue hypoperfusion and potential ischemia, likely due to full agonism at the vasopressin V1a receptor [11–13]. Terlipressin is also associated with fluid overload with life-threatening respiratory failure, particularly in very ill patients with hypoxemia, due to its stimulation of V2 receptors leading to sodium and water retention [14–17].

OCE-205 is a novel vasoconstrictor in clinical development that selectively targets the V1a receptor as a mixed agonist-antagonist. It does so via a unique molecular design comprising two domains: one that can bind the V1a receptor as an agonist, and another that binds it as an antagonist [18]. As proposed by Zhu and colleagues in 1996 [19], a single molecule possessing both agonist and antagonist properties would functionally act as a partial agonist. The design of OCE-205 as a dual-acting, mixed agonist-antagonist prevents the full activation of V1a-mediated vasoconstrictive effects that drive safety concerns with terlipressin [18, 20]. In ex vivo human blood vessels and in vivo animal models, OCE-205 achieves the desired level of systemic vasoconstriction and increases in MAP that correlate with HRS-AKI reversal [20]. Furthermore, in animal models of cirrhosis, OCE-205 has been shown to reduce portal pressure, increase vascular resistance, and improve renal function [21, 22]. At therapeutic concentrations, OCE-205 is selective for the V1a receptor and does not activate the vasopressin V2 receptor, thus avoiding undesired sodium and water retention caused by other agents.

This study was designed to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of intravenous (IV) OCE-205 administered to healthy subjects.

2 Methods

2.1 Ethical Considerations

This study was conducted at one site in the USA (New Orleans Center for Clinical Research, Knoxville, TN, USA) between September 2014 and March 2015. The protocol and informed consent forms for this study were reviewed by the institutional review board (Crescent City IRB, New Orleans, LA, USA) and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. All participants gave their written informed consent before any study-related procedures.

2.2 Study Design

This was a double-blind, placebo-controlled, within-dose-group randomized trial investigating the safety, tolerability, and pharmacokinetics/pharmacodynamics of OCE-205 administered as an IV infusion. A 3-week screening period ensured that participants met study requirements before entering the dosing phase.

2.3 Participants

Healthy adults aged 18–45 years with a body mass index (BMI) of 18.5–32.0 kg/m^2, inclusive, with no history of cardiovascular conditions were selected for participation in this study. Subjects were included if they were healthy based on medical history, physical examination, 12-lead electrocardiogram (ECG), blood pressure, and clinical laboratory testing; and had no history of any chronic liver disease or clinically significant diseases of the pulmonary, renal, gastrointestinal, cardiovascular, musculoskeletal, or gynecological systems. Individuals were excluded if they were pregnant or breastfeeding; positive for HIV, hepatitis C virus, or hepatitis B virus; or had a history of clinically significant psychiatric, immunological, endocrine, or metabolic diseases. Participants were required to have a negative urine drug screen and breath alcohol test and to have smoked fewer than 7 nicotine cigarettes per week in the 6 months preceding study start.

2.4 Randomization and Treatment Regimen

All participants were randomized to active treatment or placebo according to a computer-generated randomization list. At each dose level, the first 2 participants to be infused were

randomized to receive either OCE-205 or placebo, with a minimum observation period of 24 h. If no safety concerns arose, then the remaining participants in that dose group were randomized and treated in a staggered dose manner. Dose escalation was terminated if one or more predefined stopping criteria, as confirmed by a second measurement, were met in ≥ 2 participants on active treatment. These stopping criteria included a systolic blood pressure (SBP) of ≥ 180 mmHg or that had increased by ≥ 50% from baseline; diastolic blood pressure (DBP) ≥ 105 mmHg; MAP ≥ 130 mmHg; reduction of cardiac output by ≥ 25% (echocardiogram); or any signs or symptoms of hypertensive crisis.

OCE-205 or placebo was administered as a 6-h, continuous IV infusion for a total dose of 0.1, 0.3, 0.45, 0.6, or 0.9 mg, not sooner than 2 h after a standardized breakfast. Based on data from an earlier study (Data on File, Ocelot Bio), selection of the escalating doses was based on administration of 0.3 mg as a 6-h IV infusion that resulted in maximum plasma concentrations (C_{max}) of ~ 6 ng/mL, which was considered in the therapeutic range. In addition to OCE-205 and placebo, 1 liter of 5% dextrose solution was administered because food and water intake was restricted during the IV infusion. No concomitant medication was allowed, except necessary treatment for adverse events (AEs), paracetamol, cromoglycate, and oral contraceptives according to label.

2.5 Pharmacokinetics

Blood samples to measure plasma concentrations of OCE-205 were collected pre-dose and from 0.5 through 24 h after start of infusion, for a total of 14 samples. Concentrations of OCE-205 in human plasma were determined by protein precipitation followed by online solid phase extraction and liquid chromatography with tandem mass spectrometric detection. The lower limit of quantification (LLOQ) of the method was 0.100 ng/mL over a range of concentrations from 0.100 to 20.0 ng/mL. Precision was ≤ 6.8% and bias ranged from − 0.9 to 5.6%. Pharmacokinetic parameters (AUC from zero to time infinity [AUC_{0-inf}], C_{max}, time of C_{max} [T_{max}], total systemic clearance [CL], terminal phase elimination half-life [$t_{z½}$], volume of distribution at steady state [V_{ss}], and renal clearance [CL_R]) were calculated via noncompartmental analysis using Phoenix WinNonlin® (Certara, Princeton, NJ, USA). AUC was calculated using the linear trapezoidal model.

2.6 Bioanalytical Assay

Plasma concentrations of OCE-205 were determined by protein precipitation followed by online solid phase extraction and liquid chromatography with tandem mass spectrometric detection. The method was qualified at York Bioanalytical Solutions (YBS study number YBG/129). The LLOQ was 0.100 ng/mL for each analyte, using a sample aliquot volume of 100 µL. The concentrations of OCE-205 in calibration standards were 0.100, 0.200, 1.00, 2.50, 5.00, 10.0, 18.0, and 20.0 ng/mL. For OCE-205, the overall precision for the QC samples at the low (0.300 ng/mL), medium (8.0 ng/mL), and high (16 ng/mL) concentrations was ≤ 6.8%. The overall bias observed was between − 0.9% and 5.6%.

2.7 Safety and Pharmacodynamics

Adverse events were collected and recorded according to System Organ Class (SOC) and Medical Dictionary of Regulatory Activities (MedDRA) Preferred Terms. Adverse events of special interest included peripheral ischemia, increased blood pressure, and decreased cardiac output. Systolic and diastolic BP, pulse, body temperature, and respiratory rate were assessed at screening, every 30 min from pre-dose to 8 h after start of infusion, and on Day 2. Blood pressure was measured after the participant had been in the supine position for ≥ 5 min.

A 12-lead ECG was recorded at screening, Day − 1, pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 h after start of the IV infusion. Parameters, including heart rate, PR interval, RR, QRS, QT, and QTcF (i.e., QT correction according to the Fridericia formula), were assessed. The Investigator or a designate evaluated whether the ECG was normal or abnormal, and whether any abnormality was clinically significant. Cardiac output was assessed by echocardiogram pre-dose and 1, 2, 3, 4, 5, 6, 8, and 24 h after start of the IV infusion on Day 1.

Blood samples were collected for safety evaluations of clinical chemistry at screening on Day − 1, pre-dose, and 1, 2, 4, 6, 8, 12, and 24 h after the start of IV administration of OCE-205. Blood samples for hematology and hemostasis were collected at screening, on Day − 1, and 6, 12, and 24 h after the start of IV administration of OCE-205. Samples for analysis of venous blood gases (O_2 and CO_2) and lactate were collected pre-dose and 1, 2, 4, 6, 8, 12, and 24 h after the start of infusion. Urinary output was recorded pre-dose and over the course of 24 h, divided into collection periods of 0–4, 4–8, 8–12, and 12–24 h after the start of the infusion. Urine samples for safety evaluation of urinalysis parameters were collected at screening on Day − 1, pre-dose, and at the collecting periods.

2.8 Statistical Analysis

No formal sample size calculations were performed for this Phase 1 study. Six participants receiving active treatment and 2 receiving placebo in each dose panel were considered sufficient for the purposes of this study

to provide adequate information about the safety and pharmacokinetic/pharmacodynamic parameters at each dose level.

The full analysis set (FAS) comprised data from all dosed participants and was used for presentation of compliance and all baseline characteristics; the safety population comprised all treated participants and was analyzed according to actual treatment received. The per-protocol (PP) set comprised data from all dosed subjects and excluded subjects with major protocol violations. The PP set was used for pharmacokinetic and pharmacodynamic endpoints. The statistical analyses included descriptive statistics, reflecting the exploratory nature of the study. Data were presented by dose group, and data for participants receiving placebo are presented pooled across groups. Continuous data were summarized by dose using mean, standard deviation, median, minimum, and maximum. Pharmacokinetic parameters were presented by minimum, maximum, geometric or harmonic mean, and percent coefficient of variation (%CV) based on untransformed data for geometric mean (for AUC and C_{max}). Dose proportionality for C_{max} and $AUC_{0–inf}$ was determined from the model: log(parameter) = log(alpha) + beta × log/(dose) and reported as the estimate and 95% confidence interval (CI).

3 Results

3.1 Participants

Of 85 subjects screened, 64 healthy adults were randomly assigned to and received OCE-205 ($n = 48$) or placebo ($n = 16$). All participants on active treatment in the five dose groups completed the study. Demographics and clinical characteristics at baseline were generally well balanced between the study groups (Table 1). Overall, 32 women and 32 men aged between 18 and 45 years were included. Body weight ranged from 54 to 106 kg, and BMI from 21.4 to 32.0 kg/m^2. Two subjects were excluded for major protocol violations. The IV infusion was stopped early in 1 subject in the 0.1 mg group prior to completion of the infusion and in 1 subject in the 0.6 mg group for IV infiltration; these 2 subjects were not included in the PP population.

3.2 Pharmacokinetic Endpoints

Pharmacokinetic analyses were based on the PP dataset. After IV administration, exposure, as measured by AUC and C_{max}, was approximately dose proportional over the dose range from 0.1 to 0.9 mg (Fig. 1). For C_{max}, the dose-proportionality estimate was 1.061 (95% CI 0.988, 1.134) and for $AUC_{0–inf}$ the estimate was 1.048 (95% CI 0.973, 1.123).

Table 2 summarizes PK parameters for OCE-205 after IV infusion. The $t_{z½}$ was slightly longer in the 0.6- and 0.9-mg dose groups, at 1.5 and 1.7 h, compared with the other dose groups. The T_{max} was between 5 and 6 h in all dose groups, and the $t_{½}$ of OCE-205 was ~ 1.5 h. Clearance and V_{ss} were approximately 13 L/h and 15–22 L, respectively.

3.3 Pharmacodynamic Endpoints

OCE-205 administration led to consistent increases (range 12–14 mmHg) in MAP. The percent change in MAP is presented in Fig. 2. An increase in DBP, and to some extent SBP, accompanied by a reduced pulse rate, was observed for participants on active treatments in all dose groups (Table 3). Diastolic blood pressure increased during the IV infusion in response to all five doses of OCE-205 to reach a plateau after ~ 2 h; subsequent to the end of infusion, DBP returned to near-baseline values within 2 h. The effect of OCE-205 on SBP was less pronounced in absolute as well as relative terms compared with DBP. A reversible decrease in pulse rate was observed after the IV infusion; at the end of infusion, pulse rate rapidly returned to baseline.

3.4 Safety

Altogether, 94 treatment-emergent adverse events (TEAEs) occurred in 35 of the 48 participants on active treatment, and 8 TEAEs occurred in 5 of the 16 participants on placebo after IV infusion. Of these, 87 of the TEAEs reported by 34 participants on active treatment and 6 of the TEAEs reported in 3 participants on placebo were regarded as adverse drug reactions—i.e., assessed as reasonably possibly related to treatment. Most AEs related to treatment were generally mild or moderate in severity. The most frequent related TEAEs (≥ 10%) were abdominal pain, abnormal gastrointestinal sounds, and diarrhea (Table 4), with no reported cases of mesenteric ischemia. One related AE of bradycardia in 1 participant in the 0.1-mg dose group was judged as severe. No other serious AEs occurred, and no AE led to death or study discontinuation.

No dose-related trends or treatment-related changes in ECGs were observed. Absolute changes in cardiac output showed mean reductions of 3–12% after the 0.9 mg IV dose, and individual reductions ≤ 20 to 25% across all doses. The decrease in cardiac output was secondary to a decreased heart rate, as no changes were observed in stroke volume. No apparent dose-related trends or changes in clinical chemistry, hematology, or urine volume, and no clinically significant abnormal urinalysis values, were observed. No dose-related trends for mean values of venous blood gases, including lactate, PCO_2, or PO_2, were apparent. The absence of any apparent dose-related effect can probably be attributed to

Table 1 Baseline characteristics of study participants

Characteristic	0.1 mg (n = 6)	0.3 mg (n = 6)	0.45 mg (n = 12)	0.6 mg (n = 12)	0.9 mg (n = 12)	Placebo (n = 16)	Total (N = 64)
Sex, n (%)							
Female	4 (67)	4 (67)	6 (50)	6 (50)	6 (50)	6 (38)	32 (50)
Male	2 (33)	2 (33)	6 (50)	6 (50)	6 (50)	10 (63)	32 (50)
Age (years)							
Mean (SD)	25.0 (3.5)	29.7 (9.6)	31.3 (7.5)	34.0 (5.0)	29.5 (6.9)	32.1 (6.8)	30.9 (6.9)
Median (range)	25.0 (21–30)	31.0 (18–44)	29.0 (23–45)	32.5 (29–45)	29.0 (20–43)	32.0 (19–43)	30.0 (18–45)
Height (m)							
Mean (SD)	1.66 (0.1)	1.61 (0.1)	1.68 (0.1)	1.72 (0.1)	1.71 (0.1)	1.71 (0.1)	1.69 (0.1)
Median (range)	1.64 (1.59–1.77)	1.59 (1.48–1.78)	1.66 (1.57–1.85)	1.72 (1.58–1.93)	1.71 (1.62–1.83)	1.72 (1.45–1.94)	1.69 (1.45–1.94)
Weight (kg)							
Mean (SD)	73.8 (10.3)	70.5 (15.9)	77.7 (9.6)	81.3 (13.6)	79.8 (11.1)	81.0 (12.5)	78.5 (12.1)
Median (range)	75.1 (60.8–85.3)	66.3 (54.1–95.0)	78.5 (60.1–98.9)	80.9 (56.5–106)	79.2 (62.4–99.8)	81.8 (65.0–105)	78.7 (54.1–106)
BMI (kg/m^2)							
Mean (SD)	26.9 (3.7)	26.7 (2.1)	27.4 (2.7)	27.5 (3.5)	27.0 (2.8)	27.7 (3.1)	27.3 (2.9)
Median (range)	25.3 (23.0–31.7)	26.5 (24.7–30.0)	27.9 (23.7–31.7)	28.3 (22.1–32.0)	26.7 (22.4–31.4)	27.6 (21.4–31.8)	27.4 (21.4–32.0)
Race, n (%)							
Asian	0	1 (16.7)	0	0	0	0	1 (1.6)
Black or African American	0	1 (16.7)	2 (16.7)	2 (18.2)	3 (25.0)	8 (50.0)	16 (25.4)
White	6 (100.0)	4 (66.7)	10 (83.3)	9 (81.8)	9 (75.0)	8 (50.0)	46 (73.0)
Missing	0	0	0	1 (8.3)	0	0	1 (1.6)
Hispanic or Latino, n (%)	1 (16.7)	0	1 (8.3)	1 (8.3)	0	1 (6.3)	4 (6.3)

BMI body mass index, *SD* standard deviation

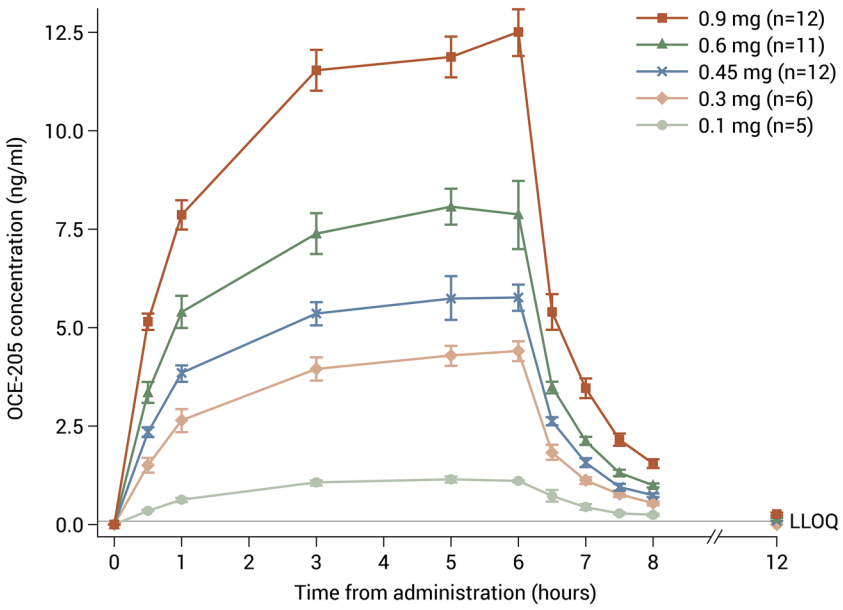

Fig. 1 Time course of OCE-205 concentration after intravenous infusion. *LLOQ* lower limit of quantitation. Values are mean ± standard error

Table 2 Pharmacokinetic parameters for OCE-205 after 6-h intravenous infusion

Parameter	0.1 mg (n = 5)	0.3 mg (n = 6)	0.45 mg (n = 12)	0.6 mg (n = 11)	0.9 mg (n = 12)
AUC_{0-inf} (h·ng/mL)					
Geometric mean (%CV)	6.96 (14)	24.6 (14)	34.1 (15)	46.5 (21)	71.8 (15)
Min; max	6.16; 8.73	20.4; 30.3	25.7; 43.0	29.1; 66.8	55.8; 95.3
C_{max} (ng/mL)					
Geometric mean (%CV)	1.18 (10)	4.45 (15)	6.20 (15)	8.32 (18)	12.7 (16)
Min; max	1.09; 1.39	3.55; 5.30	4.76; 7.83	5.66; 11.7	9.29; 16.5
T_{max} (h)					
Median	5.0	5.5	5.0	6.0	6.0
Min; max	5.0; 6.0	3.0; 6.0	3.0; 6.0	3.0; 6.0	3.0; 6.0
$t_{½}$ (h)					
Harmonic mean	1.2	1.2	1.3	1.5	1.7
Min; max	0.9; 1.7	1.0; 1.7	0.8; 1.7	1.3; 1.9	1.1; 3.2
Total clearance (L/h)					
Geometric mean (%CV)	14.4 (14)	12.2 (15)	13.2 (15)	12.9 (22)	12.5 (15)
Min; max	11.5; 16.2	9.9; 14.7	10.5; 17.5	9.0; 20.6	9.4; 16.1
Renal clearance (L/h)[a]					
Geometric mean (%CV)	0.87 (9)	0.66 (15)	0.84 (41)	0.93 (26)	0.89 (39)
Min; max	0.78; 0.92	0.52; 0.76	0.34; 1.23	0.56; 1.31	0.49; 1.92
V_{ss} (L)					
Geometric mean (%CV)	21.7 (10)	14.5 (30)	15.2 (21)	15.4 (33)	15.3 (15)
Min; max	19.6; 25.0	9.0; 19.2	10.5; 22.3	10.7; 32.3	12.7; 19.3

AUC area under the concentration–time curve from time 0 to infinity, C_{max} maximum plasma concentration, *CV* coefficient of variation, *max* maximum, *min* minimum, $t_{½}$ terminal half-life, T_{max} time of C_{max}, V_{ss} volume of distribution at steady state

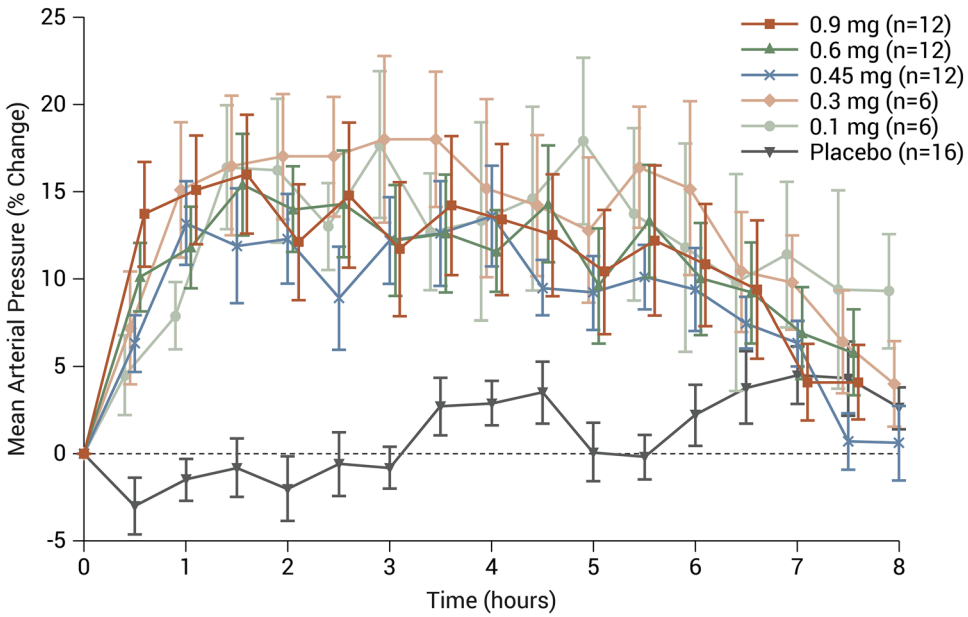

Fig. 2 Mean (SD) arterial pressure after intravenous infusion. Mean arterial pressure data were measured every 30 min after administration, but are plotted offset on the *x*-axis for clarity of presentation

administration of single doses to each subject and the variability in responses.

4 Discussion

In this Phase 1 study with 64 healthy subjects, OCE-205 showed pharmacokinetic/pharmacodynamic effects

Table 3 Maximal absolute mean changes (relative to baseline) in vital sign parameters during IV infusion of OCE-205

Parameter	0.1 mg (n = 5)[a]	0.3 mg (n = 6)	0.45 mg (n = 12)	0.6 mg (n = 12)	0.9 mg (n = 12)
DBP, mmHg (%)	15 (25%)	16 (24%)	12 (17%)	13 (19%)	12 (19%)
SBP, mmHg (%)	13 (13%)	12 (11%)	12 (11%)	12 (11%)	13 (13%)
Mean arterial pressure, mmHg (%)	13 (18%)	14 (18%)	12 (14%)	13 (15%)	12 (16%)
Pulse rate, beats/min (%)	− 17 (25%)	− 17 (21%)	− 17 (23%)	− 13 (19%)	− 14 (21%)

[a]The IV infusion in 1 subject in the 0.1 mg group was discontinued early, and data for vital signs were not available

DBP diastolic blood pressure, *IV* intravenous, *SBP* systolic blood pressure

consistent with a mixed selective V1a agonist-antagonist. Exposure (C_{max} and AUC_{0-inf}) was proportional to the infusion rate, suggesting dose-independent total body clearance over the dosing range of 0.1–0.9 mg/6 h (5–150 µg/h). OCE-205 displayed PK characteristics consistent with other peptides and proteins with high total body clearance, low volume of distribution, and short half-life.

OCE-205, given as a single IV infusion of up to 0.9 mg over 6 h, was safe and well tolerated in healthy subjects aged 18–45 years. The main concerns prior to this first-in-human study were cardiac, ischemic, and pulmonary AEs, none of which were noted in this Phase 1 study. No dose-related trends or treatment-related changes in ECG parameters occurred, and reductions in cardiac output were secondary to decreased heart rate, as no changes were observed in stroke volume. The lack of pulmonary AEs is important, as use of the current recommended treatment for HRS-AKI, terlipressin, is associated with an increased risk of respiratory compromise [23, 24]. The overall safety and tolerability profile of OCE-205 in healthy subjects is promising.

OCE-205 administration led to predictable increases in MAP, ranging from 12 to 14 mmHg. These results were consistent with that of a V1a selective partial agonist. Since OCE-205 achieves a degree of vasoconstriction less than the maximal degree of vasoconstriction achievable with full V1a receptor activation, it is expected to have a lower risk of excessive vasoconstriction-driven AEs compared with terlipressin, which is a full agonist of this receptor. All doses of OCE-205 produced the same effects on blood pressure. Thus, potential HRS-AKI–induced alterations in OCE-205 pharmacokinetics might be expected to have little consequence on the blood pressure effects of OCE-205. However, in such patients, this would only be true if the PD mechanisms and relationships follow those seen in healthy participants, and this will be examined in ongoing studies.

Limitations of this study include the use of healthy subjects with an upper age limit of 45 years and the short duration of dosing (6 h). Also, we did not stratify randomization by sex, which could have confounded findings, although studies with other vasopressin analogs have found not differences in response related to sex.

Given the promising Phase 1 results from this study of OCE-205 in healthy subjects, a Phase 2, multicenter, randomized, placebo-controlled, double-blind, adaptive dose-ranging study is currently ongoing in adults diagnosed with ascites who have developed HRS-AKI (NCT05309200). In this study, participants are randomized into five treatment arms, including one placebo arm and four active drug arms [IV infusion] (placebo and 8, 15, 30, or 50 µg/h). The primary outcome of this study is treatment time to serum creatinine value of < 1.5 mg/dL on 2 consecutive days. Secondary outcome measures include total body clearance of OCE-205, elimination half-life, volume of distribution of OCE-205, change and percentage change in rate of MAP increase, change and percent change in pulse rate, and change in serum creatinine concentration.

Table 4 Related treatment-emergent adverse events occurring in ≥ 10% in total active group, by System Organ Class and Preferred Term

Patients reporting, n (%)	0.1 mg (n = 6)	0.3 mg (n = 6)	0.45 mg (n = 12)	0.6 mg (n = 12)	0.9 mg (n = 12)	Placebo (n = 16)	Total active (N = 48)
Any adverse event	2 (33)	3 (50)	9 (75)	8 (67)	12 (100)	3 (19)	34 (71)
Gastrointestinal disorders							
Abdominal pain	1 (17)	3 (50)	6 (50)	5 (42)	11 (92)	1 (6)	26 (54)
Gastrointestinal sounds, abnormal	1 (17)	3 (50)	7 (58)	2 (17)	7 (58)	0	20 (42)
Diarrhea	0	1 (17)	4 (33)	3 (25)	8 (67)	0	16 (33)

5 Conclusions

These findings suggest that OCE-205, at therapeutic doses, is safe and well tolerated in healthy subjects. The data support that the dual agonist/antagonist structure behaves as a functional partial agonist at vasopressin V1a receptors, thus making it an ideal candidate for further development as a potential treatment for certain portal hypertensive complications of end-stage liver disease, such as HRS-AKI and resistant or refractory ascites.

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Declarations

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Conflict of interest Stan Bukofzer and Geoff Harris are founders of Ocelot Bio, Inc; Stan Bukofzer, Geoff Harris, and William R. Ravis are consultants/advisors to Ocelot Bio, Inc. Yu Bagger was an employee of Ferring Pharmaceuticals A/S at the time of the study.

Availability of data and material Data archiving is not mandated, but data will be made available upon a reasonable request to the corresponding author.

Ethics approval This study was conducted at one site in the USA (New Orleans Center for Clinical Research, Knoxville, TN) between September 2014 and March 2015. The protocol and informed consent forms for this study were reviewed by the institutional review board (Crescent City IRB, New Orleans, LA) and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements.

Consent to participate All participants gave their written informed consent before any study-related procedures.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions Conceptualization: GH; Methodology: GH; Formal analysis: WRR and GH; Investigation: YB; Data curation: YB and GH; Writing—original draft preparation: SB; Writing—review and editing: All authors; Funding acquisition: SB; Supervision: GH and SB; Project administration: SB.

References

1. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(2):1014–48. https://doi.org/10.1002/hep.31884.
2. Gines A, Escorsell A, Gines P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology. 1993;105(1):229–36. https://doi.org/10.1016/0016-5085(93)90031-7.
3. Gines P, Sola E, Angeli P, Wong F, Nadim MK, Kamath P. Hepatorenal syndrome. Nat Rev Dis Primers. 2018;4(1):23. https://doi.org/10.1038/s41572-018-0022-7.
4. Harper D, Chandler B. Splanchnic circulation. BJA Educ. 2016;16:66–71.
5. Moller S, Bendtsen F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis. Liver Int. 2018;38(4):570–80. https://doi.org/10.1111/liv.13589.
6. Smith A, Baumgartner K, Positis C. Cirrhosis: diagnosis and management. Am Fam Physician. 2019;100:759–70.
7. Tellez L, Guerrero A. Management of liver decompensation in advanced liver disease (renal impairment), liver failure, adrenal insufficiency, cardiopulmonary complications). Clin Drug Investig. 2022;42(Suppl 1):15–23. https://doi.org/10.1007/s40261-022-01149-3.
8. Velez JCQ, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. Am J Kidney Dis. 2011;58(6):928–38. https://doi.org/10.1053/j.ajkd.2011.07.017.
9. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015;64(4):531–7. https://doi.org/10.1053/j.ajkd.2011.07.017.
10. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. J Hepatol. 2019;71(4):811–22.
11. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology. 2016;150(7):1579-89 e1572. https://doi.org/10.1053/j.gastro.2016.02.026.
12. Donnellan F, Cullen G, Hegarty JE, McCormick PA. Ischaemic complications of glypressin in liver disease: a case series. Br J Clin Pharmacol. 2007;64(4):550–2. https://doi.org/10.1111/j.1365-2125.2007.02921.x.
13. Sarma P, Mukthesh G, Singh RS, et al. Terlipressin-induced ischemic complications: a systematic review of published case reports. J Pharmacol Pharmacother. 2018;9(2):76–85. https://doi.org/10.4103/jpp.JPP_23_18.
14. Griffin BR, Liu KD, Teixeira JP. Critical care nephrology: core curriculum 2020. Am J Kidney Dis. 2020;75(3):435–52. https://doi.org/10.1053/j.ajkd.2019.10.010.
15. Messmer AS, Zingg C, Muller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid overload and mortality in adult critical care patients—a systematic review and meta-analysis of observational

studies. Crit Care Med. 2020;48(12):1862–70. https://doi.org/10.1097/CCM.0000000000004617.
16. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med. 2004;35(12):159–69. https://doi.org/10.1056/NEJMra032401.
17. Wong F, Pappas SC, Reddy KR, et al. Terlipressin use and respiratory failure in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure. Aliment Pharmacol Ther. 2022;56(8):1284–93. https://doi.org/10.1111/apt.17195.
18. Croston G, Cable E, Toy J, et al. Selective partial agonism of vasopressin 1a receptors in vitro by OCE-205. J Pharmacol Exp Ther. 2023;14(1):54–61. https://doi.org/10.1177/0976500X231175220.
19. Zhu BT. Rational design of receptor partial agonists and possible mechanisms of receptor partial activation: a theory. J Theor Biol. 1996;181:273–91. https://doi.org/10.1006/jtbi.1996.0130.
20. Bukofzer S, Harris G, Cable EE. OCE-205 in rats and non-human primates: pharmacokinetic and pharmacodynamic analysis. Curr Res Pharmacol Drug Discov. 2023;5:100163. https://doi.org/10.1016/j.crphar.2023.100163.
21. Bukofzer S, Harris G, Song S, Cable EE. OCE-205, a selective V1a partial agonist, reduces portal pressure without excess peripheral effects in two rat models of cirrhosis. J Exp Pharmacol. 2023;15:279–90. https://doi.org/10.2147/JEP.S416673.
22. Bukofzer S, Cable E, Fernandez G, et al. Partial vasopressin 1a receptor agonism reduces portal hypertension and hyperaldosteronism, thereby inducing a powerful diuretic effect and natriuretic effect in cirrhotic rats with ascites. Biomed Pharmacother. 2023;165: 115116. https://doi.org/10.1016/j.biopha.2023.115116.
23. Allegretti AS, Subramanian RM, Francoz C, Olson JC, Cardenas A. Respiratory events with terlipressin and albumin in hepatorenal syndrome: a review and clinical guidance. Liver Int. 2022;42(10):2124–30. https://doi.org/10.1111/liv.15367.
24. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021;384:818–28. https://doi.org/10.1056/NEJMoa2008290.

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