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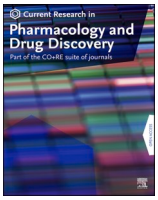

OCE-205 in rats and non-human primates: Pharmacokinetic and pharmacodynamic analysis

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ABSTRACT

Treatment for complications associated with the hemodynamic consequences of decompensated cirrhosis remains suboptimal. Terlipressin, the latest pharmacological management of hepatorenal syndrome–acute kidney injury (HRS-AKI), targets the vasopressin system but has serious side effects. OCE-205 is a novel peptide designed to target the vasopressin receptor system as a mixed V1a agonist/antagonist, resulting in effective partial agonism without V2 agonism. We examined the *in vivo* pharmacokinetic/pharmacodynamic properties of OCE-205 in healthy rats and cynomolgus monkeys. OCE-205 was administered by IV or SC bolus injection; arginine vasopressin (AVP) or terlipressin were comparators. After IV OCE-205 administration in rats, mean plasma concentration decreased in a mostly linear manner to 2 mg/mL after 120 min, and for SC administration, slowly decreased to ~50 ng/mL after 300 min. Compared with pre-test values, arterial blood pressure values significantly increased after all OCE-205 doses tested. For monkeys, the concentration after IV OCE-205 administration was mostly linear to 5 ng/mL after 180 min, and for SC administration, ~3 ng/mL after 480 min. Subcutaneous OCE-205 administration increased mean arterial pressure (MAP) versus baseline, with ΔMAP in OCE-205–treated animals marked and long-lasting while terlipressin induced an increase from baseline in MAP, with negligible ΔMAP, on average, by 150 min after administration in all groups. AVP, but not OCE-205, significantly increased blood lactate concentrations. OCE-205 was well tolerated in adult male rats and cynomolgus monkeys following single-dose bolus administration. The preclinical results of OCE-205, with its demonstrated V1a selective partial agonist activity and potentially tolerable safety profile, suggest its potential utility for treatment of the cardiovascular complications of cirrhosis.

Institutional protocol number: Procedures were approved by the Ferring Research Institute (FRI) Institutional Animal Care and Use Committee (IACUC) on November 27, 2006 under protocol FRI 06-011, and by the Sinclair Research Center IACUC under protocol S11177.

1. Introduction

Decompensated cirrhosis and the associated serious hemodynamic complications remain an area unmet need for patients. Systemic hemodynamic complications are typical of portal hypertension (PHT) as a result of cirrhosis (Tellez and Guerrero, 2022; Biggins et al., 2021; Smith et al., 2019; Moller and Bendtsen, 2018). The onset of decompensated cirrhosis leads to vasodilation of the splanchnic arteries, reduction in systemic vascular resistance, lower effective arterial blood volume, and reduced arterial pressure (Ginès et al., 2018). With lower perfusion pressure, the kidney activates the renin-angiotensin-aldosterone system leading to subsequent retention of sodium and water (Ginès et al., 2018; Harper and Chandler, 2015). The reduced perfusion pressure, combined with intrarenal vasoconstriction, leads to renal hypoperfusion and if severe enough, the development of hepatorenal syndrome–acute kidney injury (HRS-AKI). (Ginès et al., 2018; Harper and Chandler, 2015).

HRS-AKI treatment aims to restore renal function with a therapeutic goal of liver transplantation (European Association for the Study of the Liver, 2018). Therapy aims to restore the intravascular volume with albumin while restricting fluids and, if needed, administering systemic vasoconstrictors to restore normal systemic vascular resistance and increase blood pressure. Historically, HRS-AKI has been treated with either single-agent or a combination of midodrine (an α-adrenergic

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Abbreviations

AKI	acute kidney injury
AUC	area under the concentration–time curve
AVP	arginine vasopressin
CL/F	apparent total body clearance
DBP	diastolic blood pressure
EC50	half maximal effective concentration
F_{sc}	fraction of the dosed substance reaching system circulation following administration by subcutaneous dose route (SC bioavailability)
GFR	glomerular filtration rate
HRS	hepatorenal syndrome
LVP	lysine vasopressin
MANOVA	multivariate analysis of variance
MAP	mean arterial pressure
MBP	mean blood pressure
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	portal pressure
SBF	skin blood flow
SBP	systolic blood pressure
$t_{½}$;Elim	elimination half-life
$t_{½}$;Term	terminal half-life
V	vasopressin
V_c	initial apparent volume of the central compartment
V_{ss}	volume of distribution at steady state

agonist) and octreotide (a vasoconstrictor that mimics somatostatin) (Karwa and Woodis, 2009; Israelsen et al., 2017), or in some instances with norepinephrine and, most recently, with terlipressin, or N-[N-(N-glycylglycyl) glycyl]-8-L-lysinevasopressin (triglycyl-LVP). Norepinephrine and midodrine, as α-adrenergic agonists, may have limited clinical and therapeutic efficacy (Karwa and Woodis, 2009; Angeli et al., 1998; Smythe et al., 1952). The former agents have limited efficacy, while norepinephrine requires a central venous line for administration, which is typically in an intensive care unit (European Association for the Study of the Liver, 2018). More recently, vasopressin agonists have been studied. Arginine vasopressin (AVP), a key hormonal regulator of osmotic balance, is mostly synthesized in the hypothalamus and released by the posterior pituitary gland (Treschan and Peters, 2006). The V2 receptor mediates the principal function of vasopressin and leads to water retention upon activation (Treschan and Peters, 2006; Barberis et al., 1998; Koshimizu et al., 2012). Vasopressin can activate the V1a receptor at high physiologic and pharmacologic concentrations and causes systemic vasoconstriction (Treschan and Peters, 2006). Additionally, vasopressin acts on the V1b receptor, which can stimulate corticotropin secretion, also leading to water retention (Albert et al., 1955).

Terlipressin was recently approved by the US Food and Drug Administration in September 2022 to treat adults with HRS with rapid reduction in kidney function (TERLIVAZ, 2022; U.S. Food & Drug Administration, 2022). Triglycyl-LVP is a prodrug of lysine vasopressin (LVP, the porcine version of AVP) and has activity at the V1a, V1b, and V2 receptors (Jamil et al., 2018; Colson et al., 2016; Ouattara et al., 2005; Henderson and Byron, 2007). Its active metabolite, LVP, is a full V1a agonist that also maximally activates the V2 receptor at therapeutic concentrations (Jamil et al., 2018).

Triglycl-LVP (terlipressin), though recommended by multiple societies as first-line treatment for HRS-AKI (Biggins et al., 2021; European Association for the Study of the Liver, 2018), can cause clinically significant adverse effects, such as tissue hypoperfusion and ischemia, due to its vasoconstrictive effects—likely due to LVP's full agonism at V1a receptor (Donnellan et al., 2007; Sarma et al., 2018; Boyer et al., 2016)—and fluid overload and respiratory failure through V2 receptor stimulation, which can lead to sodium and water retention (Colson et al., 2016; Krag et al., 2008; Messmer et al., 2020; Schrier and Wang, 2004; Griffin et al., 2020).

OCE-205 offers an improved approach by selectively targeting the V1a receptors with submaximal activity and avoiding activity at the V2 receptor. The molecule was constructed based on a theory from 1996, that a single molecule possessing both agonist and antagonist properties would then act functionally as a partial agonist (Zhu, 1996). OCE-205 is a novel peptide designed to target the vasopressin receptor system as a mixed agonist/antagonist for the V1a receptor, resulting in effective partial agonism. The activity at human V1a receptors plateaus at ~50% maximum possible effect (EC_{50} for human V1a = 0.70 nM), with little to no activity at human V2 receptors at clinically relevant concentrations (Croston et al., 2023). Thus, unlike other AVP analogs, OCE-205 should not cause water retention due to V2 activation and should result in the desired vasoconstrictive effect for treating complications related to cirrhotic PHT (e.g., HRS-AKI), with fewer unwanted effects, by modulating disease pathophysiology. Herein, we examined the *in vivo* pharmacokinetic/pharmacodynamic (PK/PD) properties of OCE-205 in healthy rats and cynomolgus monkeys, including arterial pressure parameters, skin blood flow, blood lactate concentrations, and vital signs.

2. Experimental procedures

2.1. Animal use

Housing conditions, animal care facilities, and all experiments were maintained in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Research Council. Procedures were approved by the Ferring Research Institute (FRI) Institutional Animal Care and Use Committee (IACUC) on November 27, 2006 under protocol FRI 06-011, and by the Sinclair Research Center IACUC under protocol S11177. Additionally, all experiments were performed in compliance with the ARRIVE guidelines.

2.2. Experimental methods: Pharmacokinetics in rats

Rat models are the most common animal model of end-stage liver disease (Claria and Jimenez, 2005) and were used as a model to assess PK/PD of OCE-205. The studies were each performed using four adult male Sprague Dawley rats housed in a controlled environment with free access to food and water for ≥3 days before experimentation. OCE-205 ([Phe2,Dab(Lys(Lys(Ac)-[Ala6,Glu9]))8]VT) was dissolved in 5% mannitol and administered ≤2 h after IV and SC administration of formulation in rats for both studies (see **Supplemental Methods** for further details).

2.3. Experimental methods: Pharmacodynamics in rats

2.3.1. Skin blood flow and blood lactate

This study was performed over multiple experiments using a total of 48 adult male Wistar rats. Animals were housed in a controlled environment with free access to food and water for ≥2 days before experimentation. Compounds were dissolved in 2.5% dextrose and 0.45% sodium chloride on the day of the study, at concentrations allowing administration of the desired dose at an infusion rate of 20 μL/kg/min (0.15–150 pmoL/μL). Compounds were infused via an IV catheter at six sequentially increasing doses. A group of vehicle-treated animals received vehicle throughout the study and data were reported from

intervals timed analogously with the dose–response in compound-treated animals.

Briefly, on the day of experimentation animals were anesthetized and instrumented. A tracheostomy was performed to allow assisted respiration and three catheters were placed. Laser Doppler probes were positioned on a shaved portion of the animal's lower abdominal skin for blood-flow measurements. Ventilation was initiated, and baseline readings for the primary parameter of skin blood flow (SBF) were recorded. Readings for the secondary parameters were also recorded: blood lactate concentration, mean arterial pressure (MAP), and blood pH. Data collection was performed continuously for SBF and MAP using NOTOCORD-hem™ (Instem), and blood samples were taken at each compound dose and immediately analyzed using an i-STAT® meter (Fig. 1).

After the final dose administration, animals were euthanized and a final SBF measurement was recorded to detect any signal from the flow probe after the animal's heart stopped beating to control for a signal not attributed to blood flow. Animal body temperature, pulse, and ventilation adequacy were monitored throughout the procedure.

2.3.2. Vitals

The study was performed using six adult male Sprague Dawley rats, aged ~11 weeks. The pressure catheter was a polyurethane tubing that extended out of the device body and was inserted into the lower abdominal aorta. A postoperative injection of analgesia (flunixin, 5 mg per animal; Finadyne®, Schering-Plough) was given once immediately after implantation, and once at an interval of 24 h. The surgical wounds were disinfected with povidone iodine (Vétédine®, Vetoquinol SA) for 4 consecutive days. After surgery, the animals recovered for ~2 weeks before first study treatment (day 0).

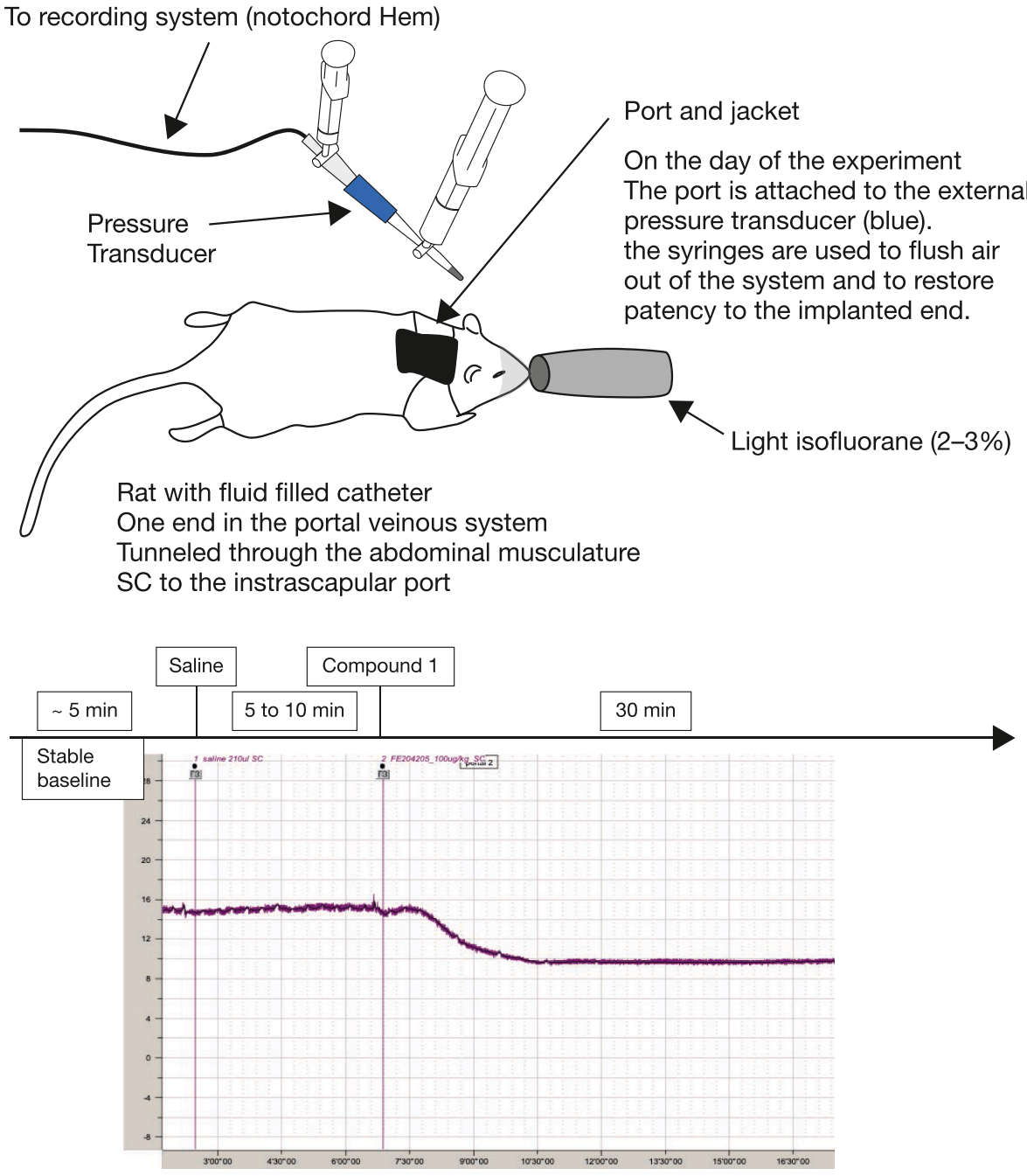

Fig. 1. Experimental set-up.

Animals were allocated at random using a Latin-square design and treated according to the schedule in Supplemental Table 1. Telemetric system and other details are described in the **Supplemental Information**.

2.4. Experimental methods: Pharmacokinetics and pharmacodynamics in monkeys (n=3)

Cynomolgus monkeys have a close phylogeny to humans, and thus these non-human primates represent an important model for assessing parameters such as PK/PD (Cauvin et al., 2015; Phillips et al., 2014). The studies of IV and SC OCE-205 administration were each performed using three adult male cynomolgus monkeys. For both studies, OCE-205 was dissolved in saline (0.9% NaCl) and administered within 2 h post formulation. Clinical observations were made before and after dosing. The in-life portion of the studies was performed at Sinclair Research Center, LLC (Auxvasse, MO). See **Supplemental Methods** for full details.

2.5. Experimental methods: Pharmacodynamics in monkeys, OCE-205 versus terlipressin (n=6)

The in-life portion of the study was performed at the European Research Biology Center (ERBC; Baugy, France) over multiple dosing sessions using six non-naive adult male cynomolgus monkeys. Animals were previously (3–4 weeks before study start) instrumented with indwelling pressure telemetry devices and trained to be restrained in chairs. Animals had access to food and drinking water *ad libitum*.

Test items were dissolved in water (OCE-205) or saline (0.9% NaCl; terlipressin) at a maximum stock concentration of 40 mg/mL and stored at −15 °C. Stock solutions were diluted in saline on the day of administration. Animals with indwelling pressure telemetry devices were trained to be restrained in chairs for 8-h periods.

2.6. Data analysis

PK and PD data were analyzed according to normal practices. Full details for data analysis can be found in the **Supplemental Methods**.

3. Results

3.1. PK characterization of OCE-205 in rats after IV and SC administration

Plasma concentration–time profiles are shown in Fig. 2. For IV administration, mean plasma concentration decreased in a mostly linear manner from ~800 ng/mL to 2 ng/mL after 120 min. For SC administration, the mean (SD) plasma concentration normalized to a dose of 1.0 mg/kg (n=4). The mean normalized plasma concentration of OCE-205 was initially ~100 ng/mL, increased to ~300 ng/mL after 30 min, and slowly decreased to ~50 ng/mL after 300 min.

PK parameters of OCE-205 after IV and SC bolus administration are shown in Table 1. The average values for V_c, V_{ss}, $t_{½}$, and CL from four animals at a nominal dose of 0.10 mg/kg were 104 mL/kg, 164 mL/kg, 19 min, and 10 mL/min/kg for those with IV administration. The following parameters resulted from SC administration of OCE-205 (n=4, nominal dose of 1.0 mg/kg): T_{max} 35 min; $t_{½Term}$ 113 min; AUC_{∞}/unit dose 59,965 min ng/mL per mg/kg; CL/F 19 mL/min/kg; and F_{sc} 59%.

OCE-205 was well tolerated in adult male rats following single-dose IV bolus administration (cassette dosing). It was also well tolerated via the SC bolus administration via parallel individual administration.

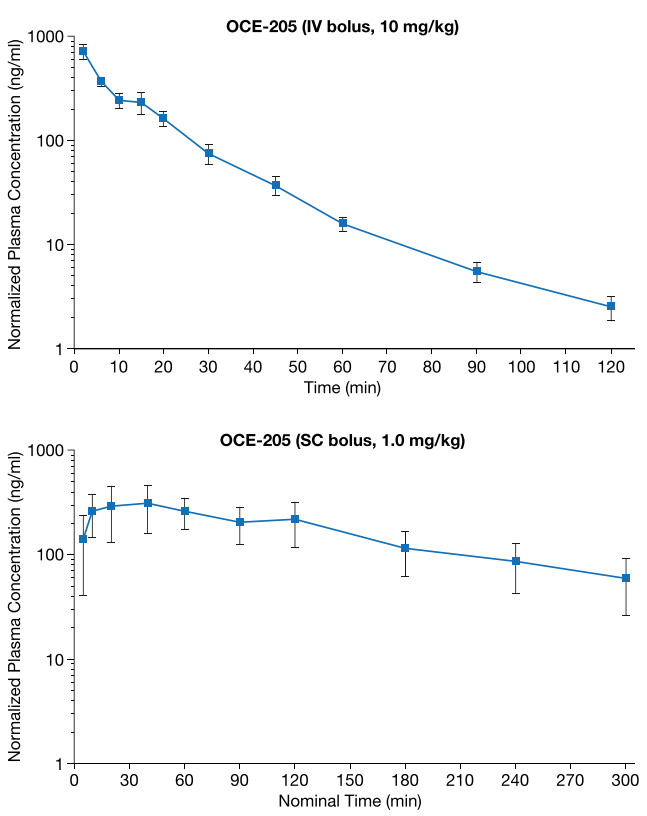

Fig. 2. Plasma concentration–time profile of OCE-205 following IV bolus (A) or SC bolus (B) in adult male rats
Abbreviations: SC, subcutaneous; IV, intravenous.

Table 1
Pharmacokinetic parameters of OCE-205 following IV bolus or SC bolus in adult male rats.

Pharmacokinetic parameter	Mean (SD)
Intravenous bolus	
V_c, mL/kg	104 (29)
V_{ss}, mL/kg	164 (21)
$t_{½Elim}$, min	19 (3)
CL, mL/min/kg	10 (1)
Subcutaneous bolus	
C_{max} per unit dose, ng/mL per mg/kg	345 (116)
T_{max}, min	35 (19)
$t_{½Term}$, min	113 (31)
AUC_{∞} per unit dose, min·ng/mL per mg/kg	59,965 (29,227)
CL/F, mL/min/kg	19 (7)
F_{sc}, %	59 (29)

CL, clearance; CL/F, apparent total body clearance; F_{sc}, fraction of the dosed substance reaching system circulation following administration by subcutaneous dose route (SC bioavailability); $t_{½Elim}$, elimination half-life; $t_{½Term}$, terminal half-life; V_c, initial apparent volume of the central compartment; V_{ss}, volume of distribution at steady state.

3.2. PD characterization of OCE-205 in rats after IV and SC administration

3.2.1. Skin blood flow

IV administration is shown in Fig. 3. SBF showed dose-related decreases after IV administration of OCE-205 and AVP (Fig. 3A). E_{max} (95% CI) for OCE-205 and AVP were 38.6% (34.6–42.7) and 91.8% (85.5–98.0), respectively. ED_{50} (95% CI) for OCE-205 and AVP were 25.2 pmoL/kg/min (15.1–35.4) and 12.6 pmoL/kg/min (9.18–16.0), respectively. The greatest percent change (SEM) from baseline in skin flow was −42.1% (3.9%) and −89.5% (1.9%) for OCE-205 (n=11) and

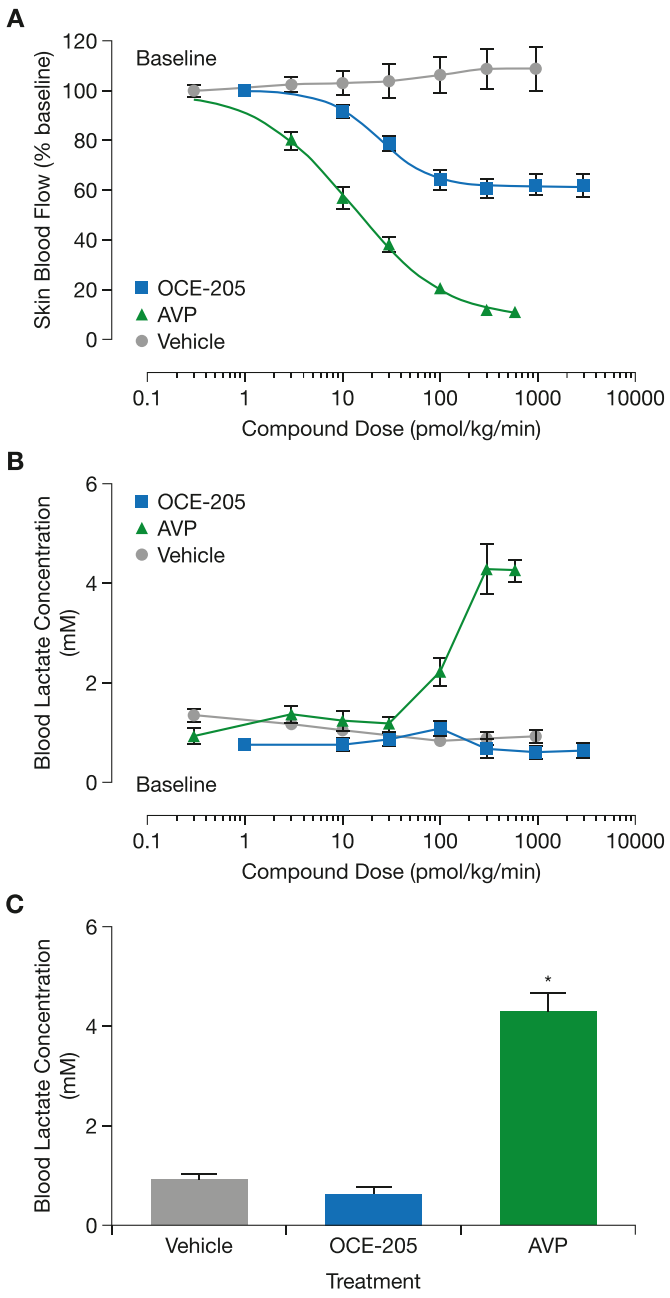

Fig. 3. Dose–response of OCE-205, AVP and vehicle on skin blood flow (A) and blood lactate concentration (B) during IV infusion in rats, and comparison of blood lactate concentration at the highest dose tested (C)
Abbreviations: AVP, arginine vasopressin.

AVP (n=13), respectively.

3.2.2. *Blood lactate*

Dose–response of blood lactate concentrations is shown in Fig. 3B. Mean (SEM) blood lactate concentrations did not increase after OCE-205 (n=11) administration, with doses ranging from 10 pmoL/kg/min to 3000 pmoL/kg/min. Mean (SEM) blood lactate concentrations increased after AVP administration (n=13), starting from 1.34 mM (0.18) at 3 pmoL/kg/min to 4.27 mM (0.39) at 600 pmoL/kg/min.

At the highest doses tested, blood lactate concentrations after AVP administration were significantly elevated compared with OCE-205 and vehicle ($p<0.05$; Fig. 3C).

3.2.3. *Arterial blood pressure*

SC administration was tested at four doses (n=6 each at 0.1, 0.6, 4.0, and 20 mg/kg; Fig. 4). Compared with pre-test values, there was a statistically significant increase in arterial blood pressure values (mean, systolic, and diastolic [MBP/SBP/DBP] components) in all the SC OCE-205–treated groups up to 4 h (at the 0.1 mg/kg dose), up to 6 h (at the 0.6 and 4.0 mg/kg doses), and up to 24 h (20 mg/kg; Fig. 4A–C). For each component of arterial blood pressure, the amplitude of increase was similar. The time of occurrence and amplitude of maximum increase

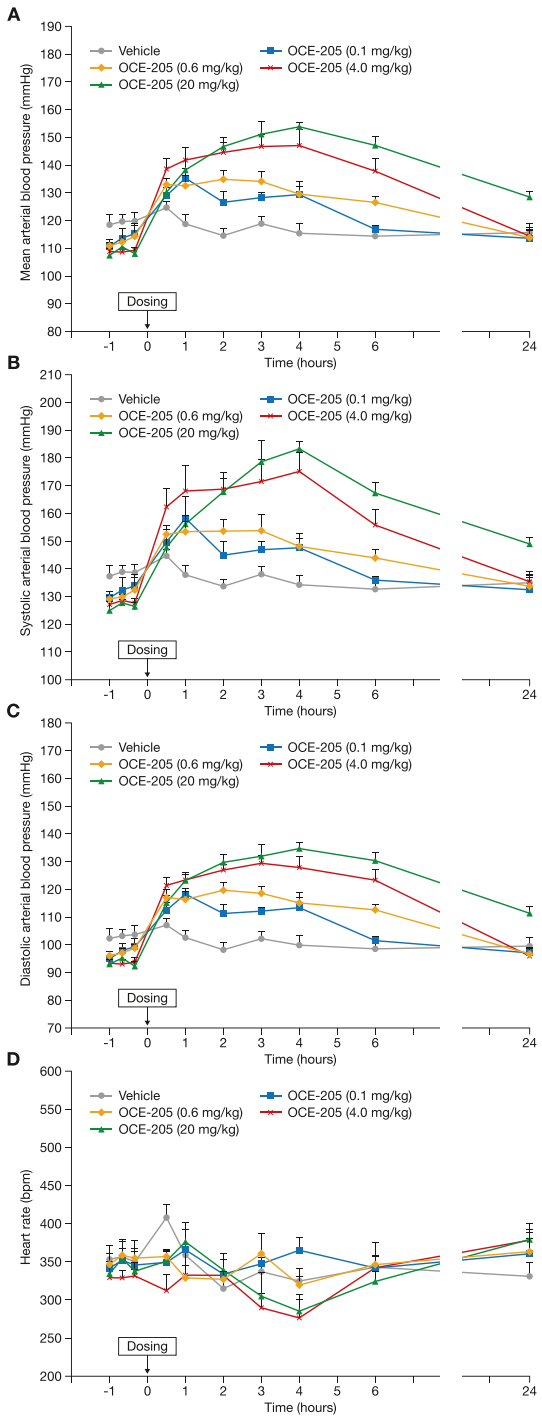

Fig. 4. Effects on mean arterial blood pressure (A), systolic arterial blood pressure (B), diastolic arterial blood pressure (C), and heart rate (D) following SC administration of OCE-205 in rats
Abbreviations: bpm, beats per minute; SC, subcutaneous.

in blood pressure were both dependent on the dose of OCE-205. Specifically, compared with the respective mean pre-test values for the mean arterial blood pressure component, the maximum increase was +22 mmHg at 1 and 2 h after administration of 0.1 and 0.6 mg/kg, respectively; +38 mmHg at 3 and 4 h after a dose of 4 mg/kg; and +46 mmHg at 4 h after the 20 mg/kg dose. At the 24-h time point, there was still a ~18% elevation of all blood pressure components. For the highest dose level (20 mg/kg), arterial blood pressure values did not return to pre-test values by the end of the evaluation period.

3.2.4. Heart rate

A slight decrease in heart rate was observed following SC administration of OCE-205 at 3 and 4 h with the 4.0 (291 and 278 bpm, respectively) and 20 (306 and 285 bpm, respectively) mg/kg dose levels (n=6 each) compared with the control group (338 and 326 bpm [n=6 each]; Fig. 4D).

3.2.5. Safety/tolerability

For safety considerations, no deaths occurred following SC administration in the control or OCE-205 treated animals. There was a local reaction at the injection site in three of the six males treated with dose levels of 4 and 20 mg/kg of OCE-205. The reaction was described as redness, skin irritation, erythema, or scab. Four treatments with different dose levels of OCE-205, up to 20 mg/kg, did not influence bodyweight gain.

3.3. PK characterization of OCE-205 in monkeys after IV and SC administration

Following IV administration, the mean (SD) plasma concentration normalized to a dose of 0.05 mg/kg (Fig. 5A). The decrease was mostly linear from ~500 to 5 ng/mL after 180 min (n=3). For SC administration, the plasma concentration normalized to a dose of 0.50 mg/kg (n=3). As shown in Fig. 5B, the mean normalized plasma concentration of OCE-205 was initially ~300 ng/mL, increased to ~400 ng/mL after 15 min, and slowly decreased to ~3 ng/mL after 480 min.

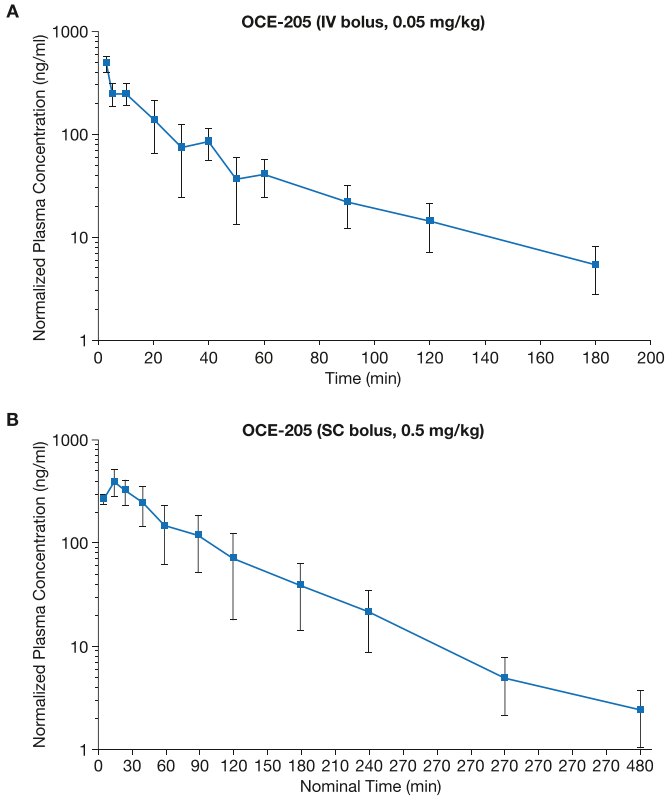

Fig. 5. Plasma concentration–time profile of OCE-205 following IV bolus (A) or SC bolus (B) in adult male monkeys
Abbreviations: IV, intravenous; SC subcutaneous.

The PK parameters of OCE-205 after IV/SC bolus administration are shown in Table 2. For IV administration at a nominal dose of 0.05 mg/kg (n=4), V_c was 45 mL/kg, V_{ss} was 153 mL/kg, $t_{½Elim}$ was 44 min, and CL was 4.6 mL/min/kg. For the three animals at a nominal dose of 0.5 mg/kg, the respective PK parameters from SC injection were as follows for C_{max}, T_{max}, $t_{½Term}$, AUC_{∞}/unit dose, CL/F, and F_{sc},: 801 ng/mL per mg/kg; 12 min; 70 min; 60,864 min ng/mL per mg/kg; 19 mL/min/kg; and 30%.

3.4. PD characterization of OCE-205 (SC) in monkeys

In these animals, blood lactate concentrations were variable and not notably increased at 15, 40, 90, 180, or 360 min post dose relative to concentrations measured prior to OCE-205 SC administration. The predose average blood lactate concentration was 2.8 mM (± 0.9) and from 15 to 360 min ranged from 2.0 (±−1.0) to 3.9 (±−0.4) mM.

The SC administration of OCE-205 is illustrated in Fig. 6. OCE-205 showed an increase from baseline in MAP (Fig. 6A), with the maximum, on average, similar across treatment groups and occurring at 5–15 min after administration. For 0.01, 0.05, and 0.5 mg/kg, the respective maximum Δ MAP values were 36.1 ± 2.1, 34.9 ± 1.1, and 41.6 ± 6.5 mmHg. Compared with vehicle-treated animals (vehicle SC: maximum Δ MAP = 25.9 ± 1.6 mmHg at 5 min after dosing), Δ MAP in OCE-205–treated animals was marked and long-lasting. The increases from baseline that were above 20 mmHg were sustained for an average of 150, 75, and 300 min after administration in the 0.01, 0.05, and 0.5 mg/kg treatment groups, respectively.

Between 30 min and 5 h after administration, the average increase in MAP were as follows for 0.01, 0.05, and 0.5 mg/kg groups: 20.6, 18.4, and 24.8 mmHg, respectively. For comparison, average increase in MAP was only 0.8 mmHg in the vehicle (SC)-treated animals. Markedly, Δ MAP was maintained above 14 mmHg, on average, throughout the 8 h of measurement in the 0.5 mg/kg OCE-205 treatment group.

Compared to vehicle-treated animals, Δ MAP was statistically different from 5 to 420 min after administration in the 0.5 mg/kg OCE-205 group. For the 0.01 and 0.05 mg/kg OCE-205 groups, Δ MAP was statistically different versus vehicle-treated animals from 15 to 240 min and 15 to 210 min after administration, respectively.

Terlipressin induced an increase from baseline in MAP with the maximum, on average, occurring at 5–30 min after administration across treatment groups (Fig. 6B). The following were maximum MAP

Table 2
Pharmacokinetic parameters of OCE-205 following IV bolus or SC bolus in adult male monkeys.

Pharmacokinetic parameter	Mean (SD)
Intravenous bolus	
V_c, mL/kg	45 (23)
V_{ss}, mL/kg	153 (42)
$t_{½Elim}$, min	44 (5)
CL, mL/min/kg	4.6 (1.8)
Subcutaneous bolus	
C_{max} per unit dose, ng/mL per mg/kg	801 (220)
T_{max}, min	12 (6)
$t_{½Term}$, min	70 (4)
AUC_{∞} per unit dose, min·ng/mL per mg/kg	60,864 (25,980)
CL/F, mL/min/kg	19 (11)
F_{sc}, %	30 (21)

CL, clearance; CL/F, apparent total body clearance; F_{sc}, fraction of the dosed substance reaching system circulation following administration by subcutaneous dose route (SC bioavailability); $t_{½Elim}$, elimination half-life; $t_{½Term}$, terminal half-life; V_c, initial apparent volume of the central compartment; V_{ss}, volume of distribution at steady state.

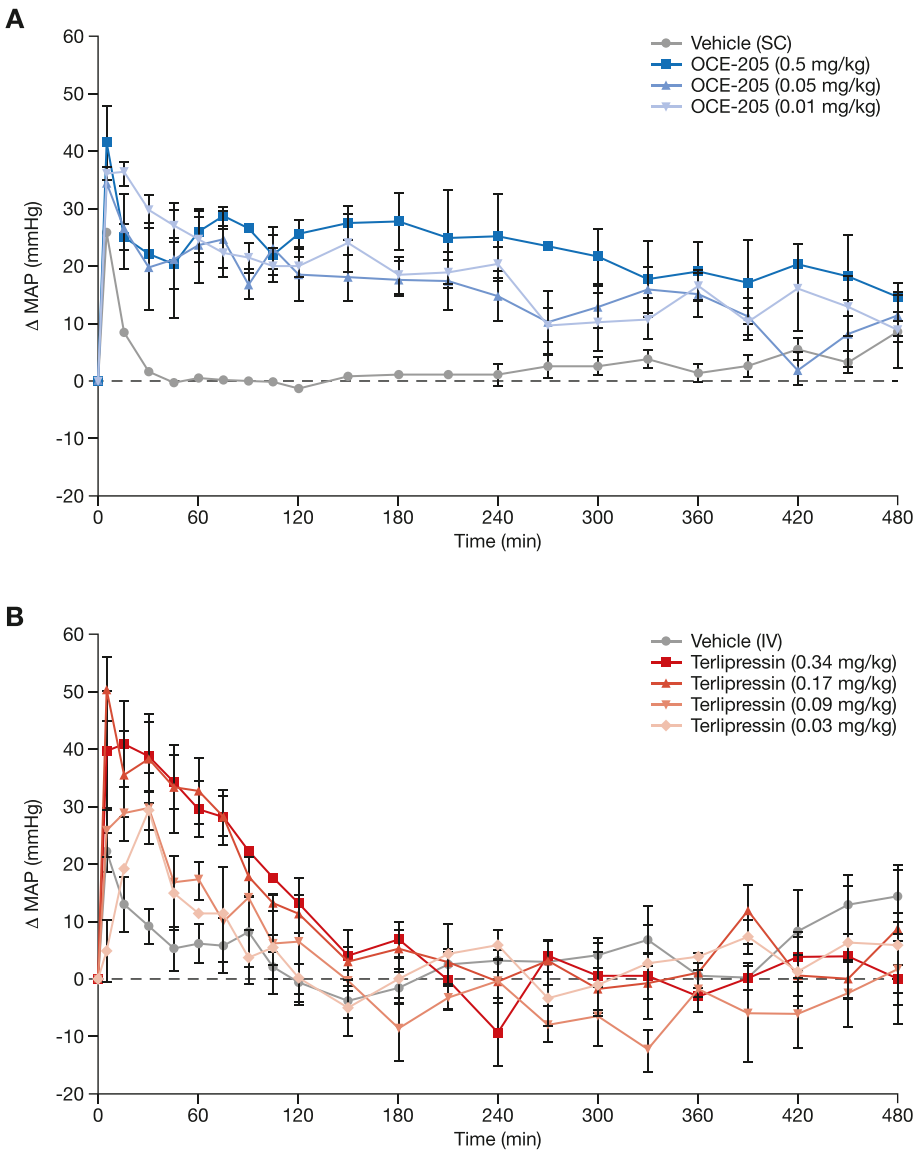

Fig. 6. Change from baseline in mean arterial pressure following OCE-205 (A) or terlipressin (B) administration in adult male monkeys
Abbreviations: IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous.

values for doses 0.03, 0.09, 0.17, and 0.34 mg/kg: 29.6 ± 3.6, 29.9 ± 6.2, 50.8 ± 5.6, and 41.2 ± 7.5 mmHg, respectively. IV vehicle-treated animals showed a maximum Δ MAP of 22.2 ± 3.5 mmHg at 5 min after dosing. Compared to vehicle-treated animals, MAP increases from baseline above 20 mmHg, on average, were not sustained past 30, 30, 75, or 90 min after administration in the 0.03, 0.09, 0.17, and 0.34 mg/kg treatment groups, respectively. Between 30 min and 5 h, the average increase in MAP was 6.0, 5.8, 14.6, and 14.7 mmHg as the dose increased in treatment groups, respectively; vehicle-treated animals increased by 3.5 mmHg. The ΔMAP was negligible, on average, by 150 min (2.5 h) after administration in all terlipressin treatment groups.

For each animal and dosing session, the pre-dose values of systolic, diastolic, and mean arterial pressures, heart rate, and body temperature were within the normal range of values generally observed per ERBC validation data. When video recordings from each dosing session were reviewed, no clinical signs were observed upon treatment administration or during the 3 h after administration.

4. Discussion

OCE-205 is a mixed V1a agonist/antagonist that functionally acts like a selective partial agonist at the V1a receptor. This provides the desired therapeutic splanchnic vasoconstriction, while theoretically minimizing the incidence of adverse effects that exist with existing mixed, full V1a/V2 receptor agonists. Our study showed that OCE-205 demonstrated V1a receptor activity at all tested dosages and that all doses were well tolerated in healthy rats and monkeys after both IV and SC bolus dosing. OCE-205 treated animals showed increased MAP, which was sustained over time; this was accompanied by a modest decrease in heart rate, which plateaued within the ranges tested (dose given at this level would achieve this biology). Changes in SBP and DBP mirror overall changes in MAP.

OCE-205 demonstrated a differentiated pharmacologic profile in this study. This profile was reinforced in healthy animals, with MAP increases not driven by differential changes in SBP versus DBP. As increases in serum lactate levels are a clinical marker for anaerobic metabolism and tissue hypoxia (Bakker et al., 2013), they can be used as a surrogate marker for the development of severe vasoconstriction and tissue ischemia. In this study, OCE-205 had no effect on blood lactate levels, regardless of dose up to the maximum dose tested, while AVP significantly elevated blood lactate levels. Furthermore, these data showed that both OCE-205 and AVP were effective in reducing the SBF

in anesthetized rats; however, AVP was a potent *full* agonist, whereas OCE-205 acted as a potent and *partial* agonist, with an approximately maximal decrease of 40% from baseline.

Non-human primates may be a more accurate model of human PD than Sprague Dawley rats (Phillips et al., 2014). Under controlled experimental conditions using conscious, telemetered animals trained to be chair restrained, treatment of adult male cynomolgus monkeys with OCE-205 or terlipressin resulted in increases in MAP in this study. A single SC bolus administration of OCE-205 at doses between 0.01 and 0.5 mg/kg caused significant increases in arterial pressure in non-human primates that at higher doses was sustained for a prolonged period of time. In contrast, a single IV bolus administration of terlipressin at doses between 0.03 and 0.34 mg/kg produced transient effects on MAP and at the higher doses tested produced significantly higher maximal MAP than OCE-205.

OCE-205 was designed as a selective V1a partial agonist using an agonist and an antagonist moiety in a single molecule to achieve effective partial agonism, demonstrating a differentiated pharmacologic profile. This novel molecular design is believed to bind to the receptor in either orientation, with each molecule binding only one receptor at a time. Binding of the agonist domain to V1a receptors drives the desired vasoconstrictive effect, while binding of the antagonist domain in a competitive manner would prevent maximal activation of the V1a receptor pool. Cell-based functional assays of OCE-205 provide support for this partial agonism, with no activity at the human or rat V2 receptor (Croston et al., 2023).

The selective partial agonist mechanism of action is further supported by the PK/PD observed in this study. In rats, the observed terminal half-life ($t_{½Term}$) of OCE-205 after SC administration (113 min) was greater than the IV elimination half-life ($t_{½Elim}$; 19 min in rats), and the bioavailability after SC dosing was 59%. The clearance of OCE-205 was similar to the glomerular filtration rate (GFR; 5–15 mL/min/kg) in male Sprague Dawley rats (Prasad et al., 1988; Radin et al., 1986). Furthermore, AVP showed potent *full* V1a agonism, whereas OCE-205 acted as a potent and *partial* V1a agonist in the SBF assay (Fig. 3). Similar results were also observed in non-human primates, where the clearance of OCE-205 was similar to the GFR (2–4 mL/min/kg) in cynomolgus monkeys after IV administration (Tahara et al., 2006; Lin et al., 2003). The observed $t_{½Term}$ of OCE-205 after SC administration (70 min) was greater than the IV $t_{½Elim}$ (44 min) in monkeys, and the bioavailability after SC dosing was 30%. In non-human primates, the increases in arterial pressure after OCE-205 administration were sustained over time and accompanied by measurable decreases in heart rate. Similar maximal increases from baseline in MAP were observed across OCE-205 treatment groups spanning a 50-fold dose range, which might represent the maximal effect on arterial pressure for this V1a receptor partial agonist. However, the doses of terlipressin administered in this study led to significantly higher maximal change in MAP with a shorter duration of elevation compared to OCE-205, with maximal increases from baseline in MAP occurring at 5–30 min across treatment groups that were negligible by 150 min (2.5 h) after administration.

4.1. Tolerability of OCE-205

A single SC administration of OCE-205 to conscious rats was well tolerated at all dose levels. Study animals showed a slight diminution in heart rate at 3 and 4 h following SC administration of OCE-205, at dose levels of 4 and 20 mg/kg. This change in heart rate is likely treatment related, because bradycardia is an expected reaction to a peripheral vasoconstriction. This decrease in heart rate was not associated with any adverse events and, at this level, would not likely be clinically significant. OCE-205 treatment also induced a dose-related increase in arterial blood pressure. In non-human primates, no apparent OCE-205–related effect on body temperature was noted, and OCE-205 was well tolerated following single-dose SC and IV bolus administrations.

Although the data generated in these studies were preclinical in nature, no concerns were identified that would preclude assessing OCE-205 in humans. Specifically with cynomolgus monkeys, variations in their regional origins can affect pharmacologic response (e.g., hematology and clinical chemistry); however, given their close resemblance to human physiology, they are the most commonly used primate species in preclinical toxicology studies (Cauvin et al., 2015).

4.2. Future implications

The preclinical results of OCE-205, with its demonstrated V1a selective partial agonist activity and encouraging tolerable safety profile, suggest its potential utility for the treatment of the cardiovascular complications of cirrhosis. Initial data from a phase 1 study of healthy human participants revealed PK/PD effects that were consistent with a mixed agonist/antagonist mechanism, alongside predictable increases in MAP (Bagger et al., 2023). Favorable outcomes from preclinical and clinical studies support further progression to a phase 2 trial of OCE-205 treatment for patients with cirrhosis and ascites who developed HRS-AKI (NCT05309200).

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CRediT authorship contribution statement

Stan Bukofzer: Writing – original draft, Writing – review & editing, Supervision, Project administration. **Geoff Harris:** Conceptualization, Formal analysis, Writing – review & editing, Supervision, Project administration. **Edward E. Cable:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

SB, the founding Chief Scientific and Medical Officer of Ocelot Bio, Inc., now serves as a strategic advisor to the company. GH is a founder of and consultant to Ocelot Bio, Inc. EC and GH were employees of Ferring Research Institute Inc., at the time of the study.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crphar.2023.100163.

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