# Multicenter, Randomized Phase 2B Study to Evaluate the Efficacy, Safety and Tolerability of OCR-002 (ornithine phenylacetate) in Hospitalized Patients with Cirrhosis and Associated Hyperammonemia with an Episode of Hepatic Encephalopathy (STOP-HE Study)

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The primary objective of this study is the following:**To evaluate the efficacy of OCR-002 for treatment of an acute hepatic encephalopathyepisode in cirrhotic patients requiring hospitalization**To evaluate the safety and tolerability of OCR-002 in...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Encephalopathies |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON42053

**Source**
ToetsingOnline

**Brief title**
STOP-HE study

### Condition

- Encephalopathies

**Synonym**
neuropsychiatric abnormalities in patients with liver dysfunction/Brain dysfunction directly

due to liver dysfunction

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Ocera Therapeutics
**Source(s) of monetary or material Support:** Pharmaceutical industry

## Intervention

**Keyword:** cirrhosis, hepatic encephalopathy, hyperammonemia, OCR-002

## Outcome measures

### Primary outcome

The primary objective of this study is the following:

**To evaluate the efficacy of OCR-002 for treatment of an acute hepatic

encephalopathy

episode in cirrhotic patients requiring hospitalization

**To evaluate the safety and tolerability of OCR-002 in hospitalized cirrhotic

patients with

an acute episode of hepatic encephalopathy

### Secondary outcome

The secondary objectives include the following:

**To confirm the pharmacokinetic (PK) profile of OCR-002 in this patient

population

**To assess the kinetics of reduction of plasma ammonia with OCR-002 and

excretion of

phenylacetylglutamine (PAGN) in urine

# Study description

**Background summary**

Hyperammonemia and Associated Hepatic encephalopathy
Hepatic encephalopathy (HE) is the most common complication of cirrhosis; it has a significant negative effect on survival even after liver transplantation (Bustamante 1999) and is associated with irreversible impairment in cognitive function (Garcia-Martinez 2011). An estimated 60*70% of cirrhotic patients have at least subtle signs of neurocognitive impairment, and HE is the principal diagnosis in hospitalized patients. Overt HE has a prevalence of approximately 30% in the cirrhotic population, and accounts for about 150,000 hospitalizations annually in the United States (Al Sibae 2009).
HE is a neuropsychiatric disorder that occurs when gut-derived toxins, primarily ammonia, bypass a failing liver that would normally detoxify such agents, enter the circulation, and then cross the blood-brain barrier, resulting in impairment of neurotransmission and central nervous system (CNS) function. HE can arise in the setting of acute liver failure, chronic progressive liver disease resulting in cirrhosis, or as a result of portocaval shunting in the absence of any true liver disease. The severity of HE correlates with elevated ammonia levels (Ong 2003, Bernal 2007), supporting the need for novel, safe, and effective ammonia-lowering therapies to treat as well as to prevent episodes of HE.
Ammonia is generated in the intestines from nitrogenous compounds from the diet, deamination of glutamine by glutaminase, and metabolism of nitrogenous substances by colonic flora. In normal circumstances, most ammonia is metabolized to urea in the liver. Portal-systemic shunts and liver failure cause a rise in blood ammonia that may affect brain function by inducing several disturbances in astrocytes; these may impair mitochondria and the glutamate-glutamine trafficking between neurons and astrocytes. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine. The kidney has also an important role in determining blood ammonia by excreting urea in the urine (Cordoba and Minguez, 2008).
In healthy people, ammonia is produced mostly from ingested protein, as well as endogenous protein catabolism in skeletal muscle. Protein digestion is not 100% efficient, and even though most protein is absorbed as amino acids, some amino acids remain unabsorbed within the lumen of the gut and reach the colon. Certain colonic bacteria, mainly coliforms and anaerobes, convert ingested amino acids into ammonia. The ammonia is then absorbed, and approximately 90% of it enters the portal circulation and is brought to the liver where it gets converted to urea via the urea cycle and excreted in urine. Only about 10% of absorbed ammonia normally bypasses the liver and is metabolized by peripheral tissues, including kidney, heart, and brain (Meijer 1990). Liver failure is the most common cause of elevated ammonia, and can result from numerous conditions from cirrhosis to inborn genetic disorders such as urea cycle disorders.

In patients with inherited deficiencies of the urea cycle, the liver partially compensates by converting ammonia and glutamate into glutamine, an action catalyzed by the enzyme glutamine synthetase. This is an incomplete response to the problem, as glutamine is converted back to glutamate and ammonia in other organs via glutaminase.
In patients with cirrhosis, arterial ammonia concentrations can be increased 2* 3 fold. Patients are at risk of developing multifactorial disturbances in neuropsychiatric and neurocognitive function: the chronic elevation in circulating ammonia induces brain swelling as well as multiple alterations in neurotransmitter function, including increases in gamma-aminobutyric acid, endogenous benzodiazepine-like compounds, endogenous opioids, and pro-inflammatory cytokines; and decreases in serotonergic neurotransmitters and endogenous antioxidants (Al Sibae 2009). Additionally, the peripheral immune system communicates with the brain in response to infection and inflammation. Astrocytes and microglial cells release cytokines in response to injury or inflammation (Prakesh and Mullen, 2010). Findings from studies in rats have indicated that the rise in blood levels of tumor necrosis factor (TNF) that occurs during inflammation stimulates glial cells to secrete the cytokines interleukin(IL)-1 and IL-6. TNF also compromises the endothelial blood*brain barrier and IL-1* affects the integrity of the glial side of the blood-brain barrier. Both TNF and IL-6 enhance fluid-phase permeability of isolated brain endothelial cells in vitro, and TNF also increases the diffusion of ammonia into astrocytes (Prakesh and Mullen, 2010). These effects accentuate and contribute to manifestations of hepatic encephalopathy.
Cirrhotic patients with HE often suffer sleep-wake abnormalities, cognitive changes, and impaired motor function that impact their day-to-day lives and can become severe enough to lead to coma and require hospitalization. Acute or overt HE (HE episode resulting in hospitalization) affects about 150,000 patients per year in the United States, and there are no FDA-approved effective parenteral treatments. The current standard of care in HE treatment focuses on reducing ammonia uptake from the gastrointestinal (GI) tract and treating the precipitating factor. In patients hospitalized with HE, a reversible precipitating factor is identified in approximately 50% of cases. These factors include GI bleeding, infection, dehydration, electrolyte disturbances, an increase in dietary protein load, and use of sedative-hypnotic drugs.

Dietary protein restriction had long been advocated as a strategy to reduce circulating ammonia in these patients. However, recent data have shown that this strategy is not effective in preventing HE and may harm these patients by making them more prone to muscle wasting (Cordoba 2004). Pharmacological approaches include non-absorbed disaccharides (e.g. lactulose) and antibiotics, (e.g. neomycin, rifaximin), which reduce ammonia production in the GI tract. These strategies have been shown to be effective in preventing recurrent episodes of HE, but not in the acute care of hospitalized cirrhotic patients with HE (Bass 2010, Als-Nielsen 2004). L-ornithine L-aspartate (LOLA) is available as an IV product in Europe and Asia and has shown to benefit patients by trapping circulating ammonia in the form of glutamine (Kircheis 1997),

although benefit in acute liver failure was not demonstrable (Acharya et al., 2009). Phenylacetate (PAA) and its prodrug phenylbutyrate have been used successfully to reduce ammonia in patients with genetic urea cycle disorders as these patients have very high circulating glutamine levels. The approach of using only PAA or phenylbutyrate to reduce high ammonia loads is not expected to work as effectively in patients with chronic liver disease, because these patients typically have lower circulating glutamine levels (reduced expression of glutamine synthetase), although recent data of oral prophylaxis to prevent recurrent hepatic encephalopathy with glycerol phenylbutyrate have shown promising results (Rockey et al., 2012). Additionally, the risk of chronic treatment and sustained glutamine depletion in cirrhotic patients with already poor lean muscle mass remains a concern.

OCR-002 (ornithine phenylacetate) in the form of the phenylacetate (PAA) salt of L-ornithine (ORN) is a single new chemical entity that allows for alternative pathways for the excretion of ammonia in the setting of cirrhosis potentially producing an enhanced effect on elimination of ammonia (Jalan 2007). ORN stimulates the activity of glutamine synthetase, inducing body muscle to trap circulating ammonia in the form of glutamine, which is a non-toxic carrier of ammonia. Glutamine is then conjugated with PAA to form phenylacetylglutamine (PAGN), which is excreted in urine. This strategy prevents the eventual recirculation and degradation of glutamine by glutaminase and avoids re-formation of ammonia.
Because OCR-002 works simultaneously on stimulation of glutamine production (via ORN) and glutamine conjugation and excretion (via PAA), this approach is expected to be effective in removing circulating ammonia.
L-ornithine is a precursor for glutamate production and reduces ammonia via inducing glutamine production in muscle. In chronic liver diseases, increasing glutamine production has not proven to be a durable ammonia-reducing strategy due to the glutaminase enzyme back converting glutamine into the component parts of glutamate and ammonia.

OCR-002 is the phenylacetate salt of L-ornithine, providing both L ornithine (ORN) and phenylacetate (PAA). PAA covalently binds glutamine via enzymatic conjugation and prevents it from being back converted into glutamate and ammonia. OCR-002 thus allows for alternative pathways for the efficient excretion of ammonia.
OCR-002 has been granted orphan drug status by the United States (US) Food and Drug Administration (FDA) and was granted fast track designation for the treatment of hyperammonaemia and resultant hepatic encephalopathy.
1.2 Rationale for the Investigational Use of OCR-002 in HE

Rationale for Dose Selection
Ocera Therapeutics Inc. (Palo Alto, CA) has conducted two clinical trials evaluating safety, tolerability and pharmacokinetics in healthy volunteers (n=48) and stable cirrhotic patients (n=43) (OCR-002 HV201 and OCR-002 HE201) [Total patients dosed with OCR-002 was 77].

Clinical study OCR-002 HV201 was designed as a randomized, placebo-controlled, dose-ranging study, evaluating doses (IV infusion) of 1, 3, 10, 20 and 30g administered over 4h, and 30, 40 and 60g administered over 24h in healthy subjects. Following a single ascending dose phase, a multiple ascending dose phase (5 days of consecutive administration) for doses of 1, 3, 10 and 20g administered over 4h was assessed. Clinical study OCR-002 HE201 was designed as a randomized, placebo-controlled dose ranging study, evaluating doses (IV infusion) of 1, 3, 10, 20 and 40g administered over 4h and 10, 20 and 40g administered over 24h in stable cirrhotic patients.

Key findings from both studies are summarized as follows:
* There were no deaths, SAE or AE discontinuations.
* Dose-related increases in the incidence and severity of adverse events was observed.
* Commonly occurring adverse events that appeared to be related to dose and phenylacetate Cmax included dizziness, somnolence, headache, nausea/vomiting and tinnitus.
* There was no evidence to suggest that AEs increased or new AEs occur with multiple dosing.
* With respect to blood pressure, there were no apparent trends from placebo with respect to mean changes from baseline; however at dose levels *20g/4h, several subjects experienced clinically significant orthostatic hypotension (this is probably not relevant to current dosing paradigm [24h continuous infusion] as the effect was noted at 6 times planned infusion rate).
* 24h Holter monitor recording identified dose and exposure-related increases in mean heart rate at infusion rates of 2.5g/h and higher (* 3-fold higher rate than the proposed highest dose in current study). In healthy volunteers, these effects were accompanied by modest effects on ventricular repolarization as measured by QTcF, however were confounded by the inability of the Fridericia formula to appropriately correct for increases in heart rate. The increase in heart rate was also demonstrated in cirrhotic patients at infusion rates > 2.5g/h (more than 3-fold higher rate than proposed highest dose in current study). Importantly, no associated effects on ventricular repolarization as measured by QTcF were recorded in this population.
* 20g administered over 4 hours was the maximum tolerated dose (MTD). Doses of 10g/4h (2.5g/h) and below were well tolerated in both study populations. For 24-hour infusions, 40g administered over 24 hours was the MTD.
* There were no clinically significant abnormal laboratory parameters and no patient had any clinically significant changes in physical examination findings or mean change in body weight between baseline and follow up.
* Doses higher than 10g/4h were associated with adverse effects that appear related to phenylacetate plasma concentrations (Cmax). Thus slower 24-hour infusions were considered optimal for the present study.
* A slower infusion rate (24hr-infusion) avoids Cmax related adverse effects while providing similar waste nitrogen excretion as measured by urinary output of PAGN. 40g administered over 24 hours was the MTD for continuous infusion, and in the current study the highest planned dose level (20g/24h) is half of

this MTD.

Both 10g/24h and 20 g/24h as a continuous infusion of 0.417 g/h (or 0.833 g/h), were well tolerated in the HE-201 (compensated cirrhosis) study. The OCR-002 dose of 10g/24h has also been well tolerated in open-label Part A of the study reported by Cordoba and colleagues (Ventura-Cots, ISHEN 2012) in 10 patients without hepatic encephalopathy who had cirrhosis and acute gastrointestinal bleeding (7 Child-Pugh A; 3 Child-Pugh B) with a salutary effect on ammonia, and no intolerance or safety issues. Preliminary blinded safety data from the double-blind, placebo-controlled portion of this study (Part B of OP-GIB) in 17 patients including Child-Pugh A, B, C cirrhotics with upper gastrointestinal bleeding receiving an OCR-002 dose of 10g/24h for 5 days has shown a benign safety profile to date.

However, in the setting of Study OCR002-HE209 wherein patients are hospitalized with acute overt hepatic encephalopathy utilization of higher dose levels than 10 g/24h OCR-002 seems necessary to provide potential benefit. Newly available pharmacokinetic data from OP-GIB Part A and Part B (currently in aggregate n=21 patients) indicated that average plasma phenylacetate exposure (Cave) was substantially below that achieved with glycerol phenylbutyrate (RavictiTM) at the dosage (6.6 g twice daily) employed in their seminal HALT-HE study which showed statistically significant reduction in HE episodes via the same mechanism of action, ammonia reduction via urinary PAGN elimination (Ghabril 2013; Rockey 2014). Specifically, in the OP-GIB study plasma PAA Cave was 30 µg/mL (mean), which is more than 3-fold lower.
OCR-002 has a molar ratio of ornithine to phenylacetate of 1:1, which given the nearly identical molecular weight for ornithine and phenylacetate means that 10 g of OCR-002 contains 5 g of phenylacetate, and 20 g of OCR-002 contains 10 g of phenylacetate. Essentially the above OP-GIB PK results confer a need to provide OCR-002 dosages in the range of 20 g/24h to achieve the anticipated optimal effect on hepatic encephalopathy. This dose is well within the MTD delineated above for OCR-002, and would provide a phenylacetate dosage (10 g/24h) which is within the approved labeling in terms of phenylacetate content for intravenous Ammonul®(sodium phenylacetate, sodium benzoate for urea cycle disorders), in the range of the RavictiTM dosage employed for the HALT-HE study which demonstrated efficacy in prevention of HE episodes, and less than that employed in oncology studies wherein phenylacetate infusions were maintained for 14 days (Thibault 1995; Chang 1999). Further details are provided below.
The recommended adult dose of Ammonul® (sodium phenylacetate and sodium benzoate intravenous injection for urea cycle disorders) is 5.5 g/m2 infused over 1.5 to 2 hours as a loading dose followed by 5.5 g/m2 infused over 24 hours as the maintenance dose. With an estimated average body surface area (BSA) of 1.73 m2 for adults, the dose for sodium phenylacetate in Ammonul® given in the first day is approximately 19 g (16.4 g phenylacetate), nearly double the phenylacetate content at the highest dose level in the current Protocol OCR002-HE209. Similarly, the currently prescribed maximum total daily dose for RavictiTM (glycerol phenylbutyrate, GPB) for urea cycle disorders is

17.5 mL, which is equivalent to approximately 17.9 g of phenylbutyrate (PBA), and equivalent to approximately 14.8 g of phenylacetate (PAA) per day based on direct molecular weight conversion.
In the HALT-HE clinical trial of RavictiTM as HE prophylaxis in patients with cirrhosis and a prior history of HE, a 6 mL twice daily dose of GPB was found to significantly reduce the proportion of patients with an HE event, correlating with significant reduction of plasma ammonia levels from baseline (Rockey 2014). This dose of 6 mL of RavictiTM twice daily translates to approximately 12.2 g PBA dose per day, and 10.2 g PAA dose per day assuming complete bioavailability. This is essentially the same PAA content as the highest dose level of OCR-002 (20 g/24h) proposed in Study OCR002-HE209.
As mentioned above, pharmacokinetic data from Study OP-GIB obtained to date show that plasma exposure to phenylacetate following OCR-002 administration at 10 g/24h is substantially lower than that observed following administration of RavictiTM or Ammonul® at doses prescribed in the product labels or in relevant literature as summarized in the table in section 1.2 of the protocol. We interpret this finding to be the result of a lower phenylacetate dosage (5 g) with OCR-002 (infused at 10 g/24h) than provided with either RavictiTM or Ammonul® and the fact that OCR-002 is administered as a slow continuous infusion without a loading dose.

The summary of the data (Table 1 protocol section 1.2) shows that plasma PAA exposure following administration of OCR-002 at a rate of 10g/24h was substantially lower than after Ammonul® or RavictiTM administration, even after PAA dose normalization. It is well documented that PAA disposition follows non-linear kinetics, with saturable conjugation of PAA with glutamine to form phenylacetylglutamine (PAGN). The IV loading dose of Ammonul® and an oral dose of RavictiTM would be expected to yield initial higher plasma PAA concentrations due to potential saturation of the conjugation pathway than an equivalent phenylacetate dose administered as a constant slow infusion. The total body clearance (CL) of PAA after OCR-002 administration in the OP-GIB study was apparently much higher than that after Ammonul® administration, suggesting that the OCR-002 (PAA) dosing rate may not be high enough at 10 g/24h (5g/24h PAA) to maintain efficient conjugation of PAA with glutamine to form PAGN. This is shown by the lower plasma PAGN concentrations observed after OCR-002 administration in Study OP-GIB (mean Cave: 19.2 *g/mL) as compared to RavictiTM (mean Cave: 46.3 *g/mL) (Ghabril 2013). Thus it was considered necessary in Study OCR002-HE209 to consider a dose of OCR-002 of 20 g/24h (10 g PAA) as the highest dose level.

Furthermore, the OCR-002 dosage for each patient will be predicated upon dose level adjustment per severity of liver impairment. By analogy with pharmacokinetic data in the RavictiTM 2013 product label summarizing hepatic impairment studies in patients without overt encephalopathy, participants in the current study with greater degrees of hepatic synthetic and portal impairment will receive lower dosages of OCR-002, specifically 15 g/24h and 10 g/24h, respectively, because (per the RavictiTM label) Child-Pugh class B and C

cirrhotics showed a progressive increase (about 30%) in PAA plasma exposure when compared to Child-Pugh class A. Given the decades-long experience with intravenous phenylacetate in various clinical settings (urea cycle disorders, oncology trials) and available OCR-002 data to date, this dose level adjustment by extrapolation is not undertaken because of any observed medical or clinical issue but rather to assure a considered, conservative, and temperate approach and to provide objective reassurance regarding dosing of medically delicate hospitalized patients with greater degrees of hepatic impairment in this specific context.

Notably, Thibault et al. (1994) previously described PAA kinetics in cancer patients and suggested a threshold for CNS effects of PAA of >500 µg/mL. This level of PAA concentration is approximately 10-fold higher than the mean PAA concentrations observed when administering 10g OCR-002 over 24h, and well above that observed at 20 g/24h. The liver is not the primary organ responsible for metabolism of phenylacetic acid to PAGN since renal tissue metabolic activity accounts for the highest percentage of phenyl CoA-acyltransferase activity with the ratio of renal to liver metabolism of approximately 3:1. Additionally, in preclinical models of acute liver failure (ALF) (anhepatic porcine model) OCR-002 was effective in lowering ammonia levels and was metabolized even in the absence of a liver (Ytrebo et al., 2009).

These data taken together combined with the a priori OCR-002 dose level adjustment predicated on hepatic synthetic and portal impairment point score at entry provide a strong level of assurance that an appropriate benefit/risk will be maintained for participating patients hospitalized with hepatic encephalopathy in acute need of intervention. The Independent Data Monitoring Committee will review pharmacokinetic data as delineated in Section 3 and are empowered to provide dose level adjustment while the study is ongoing as outlined in Section 5.6 in the case of over-exposure or suboptimal dosage.

**Study objective**

The primary objective of this study is the following:
**To evaluate the efficacy of OCR-002 for treatment of an acute hepatic encephalopathy
episode in cirrhotic patients requiring hospitalization
**To evaluate the safety and tolerability of OCR-002 in hospitalized cirrhotic patients with
an acute episode of hepatic encephalopathy

The secondary objectives include the following:
**To confirm the pharmacokinetic (PK) profile of OCR-002 in this patient population
**To assess the kinetics of reduction of plasma ammonia with OCR-002 and excretion of

phenylacetylglutamine (PAGN) in urine

**Study design**

This is a Phase 2B, multicenter, randomized, double-blind, placebo-controlled study evaluating OCR-002 administered via continuous 24-h intravenous (IV) infusion to hospitalized patients with cirrhosis, hyperammonemia, and an acute episode of hepatic encephalopathy Stage 2-4, inclusive (Appendix A, Hepatic Encephalopathy Staging Tool). A total of approximately 140 unique patients (± 10%) will be stratified at time of randomization by 1) model for end-stage liver disease (MELD) score (less than or equal to 30 versus > 30), and 2) Hepatic Encephalopathy Staging Tool (Stage 2 versus Stage 3/4) using an interactive voice/web-response randomization system. A third stratification (in North America) will group investigational centers into two categories as follows: liver transplantation centers performing * 70 transplants per year, and liver transplantation centers performing < 70 transplants per year or centers not performing liver transplantation. Outside of North America stratification will be employed with the same MELD and Hepatic Encephalopathy Staging Tool thresholds delineated above. Patients will be randomized (1:1) to OCR-002 or placebo given as a continuous infusion for 5 days which will be administered on top of standard of care inclusive of lactulose/lactitol per usual institutional practice. Breakthrough HE occurring during prophylaxis with rifaximin for * 1 week duration is allowed (de novo treatment of HE episode with rifaximin is not allowed). There is no protocol stipulation for in-hospital location of participating patients who may be hospitalized for instance in the intensive care unit, step-down unit, hospital floor etc, according to medical condition and usual clinical triage. Patients can be discharged from hospital if medically appropriate before 5 days (120 hours) of continuous infusion is completed. For patients remaining in hospital for standard of care safety/efficacy is assessed 24-hours post end-of-last-infusion, for patients subsequently discharged during the follow-up period an additional evaluation is performed immediately prior to discharge, and all patients have a follow-up visit scheduled 2 weeks after cessation of IV infusion of study drug (Study Day 19). Assessments of hepatic encephalopathy, specifically the Hepatic Encephalopathy Staging Tool, Glasgow Coma Scale, and modified orientation log will be evaluated by specifically trained investigators, subinvestigators, nurse practitioners, or physician*s assistants. The Physician Overall Treatment Evaluation of Hepatic Encephalopathy and Physician Ranked Assessments (specific items) performed in the time interval between end-of-final-infusion and 3 hours post end-of-final-infusion must be performed by a physician, and must be the same assessor as the Screening or Baseline evaluator so that the ranking relative to pretreatment status (same, better, worse) will be accurate. OCR-002 or matching placebo will be infused IV for 5 days (500 mL/24h at a rate of 20.8 mL/h); study drug dosage will be predicated upon Baseline calculation of hepatic synthetic and portal

elements (depicted below). The interactive voice/web-response randomization system will also autocalculate the Child-Pugh score for patients based on the entries for hepatic encephalopathy stage (Appendix A) plus the hepatic synthetic and portal elements of Child-Pugh tabulated below (for consistency of measure).

Parameter Points (circle patient*s status for each item then total all 4 items below)

1
2
3
Ascites
None Mild/Moderate (diuretic-responsive) Tense (diuretic-refractory)
Total bilirubin (mg/dL) < 2 (< 34 µmol/L) 2-3 (34-51 µmol/L) > 3 (> 51 µmol/L)
Albumin (g/dL) > 3.5 (> 35 g/L) 2.8-3.5 (28-35 g/L) < 2.8 (< 28 g/L)
PT (sec prolonged) or INR < 4
4-6 > 6
<
1.7

1.7-2.3
> 2.3
Patient Total Score (all 4 items added together)

For 4-6 points using the above scoring system the OCR-002 dose will be 20 g/24h (0.833 g/h); for 7-9 points 15 g/24h (0.625 g/h); and for 10-12 points 10 g/24h (0.417 g/h). The unblinded pharmacist will adjust study drug concentration in the infusate (40 mg/mL, 30 mg/mL, or 20 mg/mL for 4-6 points, 7-9 points, and 10-12 points, respectively) per instructions from the interactive voice/web response randomization system so that 500 mL infused at a continuous rate over 24 hours (20.8 mL/h) will provide the appropriate dosage by level of hepatic decompensation. This approach is intended for best dose level assignment which is related to the above tabulated elements of liver function and is congruent with the level of cognition in the PK population used in common practice for dosage considerations. Dosing may be stopped at any time for safety or tolerability reasons.
Blood and urine will be collected frequently for PK assessments beginning at baseline and continuing throughout the dosing period, up to 3 hours following cessation of dosing (end-of-final infusion).
For all patients HE will be assessed by the Hepatic Encephalopathy Staging Tool (Appendix A), Glasgow Coma Scale, and modified orientation log prior to the start of infusion, twice daily (7 a.m. and 5 p.m. with a ± 1 hour window) during infusion and 3 hours post end-of-infusion, and Day 19.

An Independent Data Monitoring Committee will conduct a review of safety data monthly for each of the first 3 months of the study, every 2 months for the next 6 months and every 3 months thereafter until study completion (unless no new data); the review will also include assessment of survival, and an analysis of survival between arms may be performed if 10 or more deaths have occurred. Additionally following recruitment of at least 6-10 patients, PK data will be reviewed monthly on an ongoing basis by a third party expert pharmacokineticist; individual patient PK data will be blinded and not be shared with personnel involved in study conduct in order to assure that the study blind is maintained. As PK data are generated on a monthly basis during the trial, the PK findings of the third party expert pharmacokineticist will be reviewed in conjunction with safety by the Data Monitoring Committee (see above).
An interim analysis of the primary efficacy endpoint will be conducted after the first 37 endpoints are observed to assess the sample size and power of the study, including the impact of censoring due to liver transplant or death. The Haybittle procedure will be utilized for purpose of declaring a statistically significant difference between treatment groups using alpha=0.001, thereby preserving the remaining alpha (0.049) for the end of treatment analysis (Haybittle 1971). The interim analysis will be prepared by a third party statistical group, shared with the Independent Data Monitoring Committee, and may also include PK/pharmacodynamic (PD) analyses. Summary outputs will not unblind treatment assignment at the individual patient level.

**Intervention**

Patients will be randomized 1:1 in one of the following treatment arms (70 patients per arm):

-treatment with OCR-002+standard of care
-treatment with placebo+ standard of care

Administration of OCR-002 or placebo will last for up to 5 days (120 hours) with brief assessments through 3 hours after the end of the final intravenous infusion (nominal day 6/7), and for those patients still in the hospital, an assessment 24 hours after the end of the final intravenous infusion. Additionally there is a follow-up visit 14 days after the last study drug infusion (nominal Day 19). Thus total study participation lasts for about 19 days, though most assessments are within 6/7 days.

**Study burden and risks**

Patients will be randomized 1:1 in one of the following treatment arms (70 patients per arm):

-treatment with OCR-002+standard of care

-treatment with placebo+ standard of care

Administration of OCR-002 or placebo will last for up to 5 days (120 hours) with brief assessments through 3 hours after the end of the final intravenous infusion (nominal day 6/7), and for those patients still in the hospital, an assessment 24 hours after the end of the final intravenous infusion. Additionally there is a follow-up visit 14 days after the last study drug infusion (nominal Day 19). Thus total study participation lasts for about 19 days, though most assessments are within 6/7 days.

Screening/baseline:
vital signs (blood pressure, pulse rate, respiratory rate, and body temperature); height and weight; brief examinations of mental functioning to assess orientation (Modified Orientation Log), investigator (physician) evaluation of awareness and responsiveness (Hepatic Encephalopathy Staging Tool), and alertness (Glasgow Coma Scale); physical and neurological (nervous system) examination; a review of medical history and medications; and laboratory evaluations performed for kidney function, liver function, hematology, chemistry including blood ammonia measurement, blood alcohol at screen, pregnancy test in women, analysis of urine and urine drug screen. 12-lead electrocardiograms (ECGs) to measure the electrical activity of your heart will be performed. A blood and urine sample will be drawn as a reference for study drug concentrations during infusion right before starting the study drug (active or placebo).

Treatment Period:
Study drug intravenous infusion lasts up to 5 days (120 hours) for full dosing but may be shorter if hospital discharge is planned earlier. Two times on each day of study drug infusion vital signs and brief examinations of mental functioning will be performed as described above, and a sample from the vein for blood ammonia measurement will be drawn. Each day of infusion 12-lead ECGs will be performed and there will be complete collection of all urine for metabolites of study drug (which measures how your body disposes of study drug). Each day of study drug infusion laboratory evaluations will be performed of kidney function, liver function, hematology, chemistry, analysis of urine, and blood collected for plasma concentration of study drug metabolites. Physical and neurological (nervous system) exam and review of medications will also be done daily. These assessments will all be performed at the time of hospital discharge if this occurs before Day 6/7. For patients who are still in the hospital 24 hours after the end of the last study drug infusion, laboratory evaluations will be performed of kidney function, liver function, hematology, chemistry, analysis of urine, physical and neurological (nervous system) exam, vital signs, brief examinations of mental functioning will be performed as described above, and review of medications will be done. Monitoring for any possible adverse effects will continuously be done during the Treatment Period.

Follow-up Visit:

If a patient is discharged from hospital during the follow-up period an additional evaluation will be performed immediately prior to discharge (brief examinations of mental functioning as described above and review of medications). A follow-up visit will be conducted for all patients who complete the full course of treatment or who do not complete the full course of treatment but remain in the study and will be done approximately 14 days after the end of the final (last) infusion (19 days after admission into the study). At this visit review of current medications and brief examinations of mental functioning will be performed as described above.

Taking the study drug may involve unknown risks to a pregnant woman, an unborn baby or a nursing infant. If the patient is pregnant or is breastfeeding a child, this patient cannot take part in this study. If the patient is a woman who could become pregnant, the serum (blood) pregnancy test must be negative at the time of Screening for the study. The patient should not become pregnant nor breastfeed a baby while taking part in this study because the active drug in this study might affect and involve risks to a pregnant woman, unborn child, or a baby in ways that are currently not foreseeable.

If the patient agrees to take part in this study, there may not be direct benefits. The researchers cannot guarantee that the patient will benefit from participation in this research.

There may possibly be other side effects that are unknown at this time 9for adverse events, please see section E9).

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

* 18*75 years with HE admitted to hospital (eg, via emergency department or direct admission, etc);* Evidence of/known cirrhosis * The diagnosis of liver cirrhosis will be based on clinical, radiological, or histological criteria;* Hospitalized with an acute episode of hepatic encephalopathy as complication of cirrhosis;* Venous ammonia greater than the upper limit of normal at Screening;* Acute HE episode defined by Stage * 2 (Hepatic Encephalopathy Staging Tool, Appendix A) at both Screening and baseline (pre-randomization). At the end of a prerequisite minimum 12-hour interval from hospital HE diagnosis to start of Screening patients must still be clearly overtly encephalopathic and during the Screening/Baseline Period have no improvement (decrease in Hepatic Encephalopathy Stage). During the 12-hour pre-Screening period in order to qualify the patient must consistently manifest hepatic encephalopathy that is clearly overt and equivalent to at least Stage 2 using the Hepatic Encephalopathy Staging Tool (Appendix A). ;* Patients with transjugular intrahepatic portosystemic shunt (TIPS) are allowed ;* Women of child-bearing potential must have negative serum pregnancy test

## Exclusion criteria

* Not expected to survive 2 weeks (note patients with malignancy, e.g. hepatocellular carcinoma, exceeding this life expectancy may enroll);* Type 1 hepatorenal syndrome characterized by rapidly progressive reduction in renal function as defined by a doubling of the initial serum creatinine to a level > 3 mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level <20 mL/min in less than 2 weeks.;* Hyponatremia (sodium <125 mmol/L);* Renal failure with serum creatinine > 3 mg/dL (265.2 µmol/L) or need for hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration at Screening;* New York Heart Association (NYHA) Class 3 or 4 congestive heart failure or overt clinical signs of congestive heart failure;* Patients requiring mechanical ventilation may enroll if they are electively intubated only for airway protection (to prevent aspiration) due to severe HE and

do not require ongoing sedation. Transitory intubation with sedation for specific procedure/intervention anticipated to be < 24 hours is allowed. The following ventilator settings would exclude a patient: (a) fraction of inspired oxygen (FiO2) > 0.5 (> 50% oxygen); (b) positive end-expiratory pressure (PEEP) > 10 cm H2O (water). The intent is to exclude patients requiring intubation for respiratory failure or severe pneumonia. Note continuous positive airway pressure (CPAP) is allowed.;* Any prior stroke with cognitive sequelae;* Acute alcoholic hepatitis (current hospital admission);* Schizophrenia, dementia, or other severe psychiatric disorders that would interfere with evaluation of hepatic encephalopathy;* Presentation to hospital with acute alcohol or drug intoxication (patients with alcoholic liver disease/cirrhosis due to alcohol are allowed). Inebriated patients and those with acute effects of alcohol at presentation, by immediate prior history, overall clinical evaluation, or blood alcohol level * 1.6 g/L (0.16% w/v, 160 mg/dL, 34.74 mmol/L) are excluded. Patients with symptoms of serious alcohol withdrawal at either Screening or Baseline are excluded.;* Patients with gastrointestinal bleeding may enroll. However, active upper gastrointestinal bleeding at the time of enrollment that has not been addressed by definitive endoscopic treatment or appropriate medical therapy and remains uncontrolled (requiring > 2 units packed red blood cells per day on a continuing ongoing basis) will exclude a patient; patients whom the physician considers likely to die of gastrointestinal bleeding should be excluded. Those with bleeding from portal hypertensive gastropathy may enroll provided they are within above confines.;* Hemodynamic instability, defined as a mean arterial pressure of <60 mm Hg and/or evidence of poor organ perfusion or the use of more than one (1) vasopressor to support blood pressure. Terlipressin, vasopressin (and analogs), and octreotide (and somatostatin analogs) are allowed to address complex vascular dynamic issues specific to this population (eg, variceal bleeding, renal perfusion). However, if more than one (1) vasopressor is being given for hemodynamic support of unstable mean arterial pressure (ie, implying shock and sequelae) this makes the patient ineligible. ;* Corrected QT interval calculated using Fridericia*s formula (QTcF) > 500 msec at screening ;* Concomitant administration of drugs known to interfere with renal excretion of phenylacetylglutamine (PAGN), such as probenecid. Use of L-ornithine L-aspartate and neomycin during study is prohibited.;* MARS (molecular adsorbent recirculation system) use is prohibited ;* Receiving or will receive sodium benzoate, Ammonul®, sodium phenylbutyrate (Buphenyl®) or glycerol phenylbutyrate (RavictiTM).;* Participation in another interventional, investigational experimental device or novel drug clinical trial within 30 days prior to admission. Trials of established medications (not for HE) or new techniques must be reviewed case-by-case by the Medical Monitor. Observational studies are allowed.;* Patient is listed as high priority candidate for liver transplantation *Status 1* per United Network for Organ Sharing (UNOS) definition or for whom the investigator anticipates imminent liver transplantation within 5 days;* Prior transplant recipient (solid organ, bone marrow, or stem cell);* Irreversible brain damage, massive aspiration pneumonia, non-hepatic-encephalopathy causes for altered mental status;* Known or suspected hypersensitivity or allergic reaction to ornithine (ORN), phenylacetate (PAA), or any of the components of OCR 002;* Pregnancy or breastfeeding

## Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 27-06-2016 |
| Enrollment: | 7 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | OCR-002 |
| Generic name: | ornithine phenylacetate |

# Ethics review

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|---|---|
| Approved WMO Date: | 16-09-2014 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 18-03-2015 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 17-06-2015 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 24-06-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 04-11-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 09-11-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 01-02-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 11-03-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-005412-10-NL |
| ClinicalTrials.gov | NCT01966419 |
| CCMO | NL50464.068.14 |