Clinical Study Protocol

A Phase 2a Study to Evaluate the Safety and Tolerability of OCR-002 (ornithine phenylacetate) in the Treatment of Patients with Acute Liver Failure/Severe Acute Liver Injury (STOP-ALF)

Protocol Number: ALFSG-OCR-002
IND Number: 113534

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Ocera Therapeutics, Inc.

Sponsor of IND:
William M. Lee, MD
for the Acute Liver Failure Study Group

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Investigator Statement of Agreement

I agree to:

Implement and conduct this study diligently and in strict compliance with the protocol, the Principles of Good Clinical Practice, and all applicable laws and regulations.

Maintain all information supplied by Ocera Therapeutics, Inc. (Ocera) in confidence and, when this information is submitted to an Institutional Review Board (IRB) or any other group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

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Principal Investigator **Date**

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Printed Name of Investigator

_____

Institution

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACLD	acute on chronic liver disease
AE	adverse event
ALFSG	Acute Liver Failure Study Group
ALF	acute liver failure
ALI	acute liver injury
ALT	alanine aminotransferase (= serum glutamic pyruvic transaminase, SGPT)
ANA	antinuclear antibody
ASMA	anti-smooth muscle AB
AST	aspartate aminotransferase (= serum glutamic oxaloacetic transaminase, SGO
ATN	acute renal tubular necrosis
AUC	area under the concentration–time curve
AUC0-last	area under the concentration–time curve from the time of dosing (Time 0) to the time of the last measureable concentration
CAH	chronic autoimmune hepatitis
Cmax	observed maximum concentration
CMV	cytomegalovirus
Cr	creatinine
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CVVH	continuous veno-venous hemofiltration
dL	Deciliter
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDTA	edetic acid (ethylenediaminetetraacetic acid)
FDA	Food and Drug Administration
g	grams
GCP	Good Clinical Practice
h/hrs	hour/hours

Abbreviation	Definition
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HDV	Hepatitis delta virus
HE	hepatic encephalopathy
Hg	mercury
HSV	Herpes simplex virus
ICF	Informed consent form
ICH	International Conference on Harmonization
ICP	intracranial pressure
IgG	Immunoglobulin G
IgM	Immunoglobulin M (antibody)
ICU	Intensive Care Unit
IND	Investigational new drug
IMM	Internal Medical Monitor
INR	International Normalized Ratio (for prothrombin time)
IRB	Institutional Review Board
IU/L	international unit per liter
IV	Intravenous
K3+EDTA	tri-potassium edetic acid (ethylenediaminetetraacetic acid)
LAR	legally authorized representative
LKMA	anti-liver-kidney microsome antibody
µL	Microliter
µmol/L	micromole per liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mm	millimeter

Abbreviation	Definition
msec	millisecond
MSM	Medical Safety Monitor
MOO	Manual of Operations
NAC	*N*-acetylcysteine
ng	nasogastric
OCR-002	ornithine phenylacetate
O-log	Orientation Log
PAGN	Phenylacetylglutamine
PCR	polymerase chain reaction (viral diagnostic test)
PD	Pharmacodynamic
PK	Pharmacokinetic
Qt Interval	time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
RNA	ribonucleic acid
SAE	serious adverse event
SAR	suspect Adverse Reaction
SDCC	Statistical and Data Coordinating Center
SOP	standard operating procedure
SRC	Safety Review Committee
T0	Treatment Day 1 - Time “0”
T1/2	half-life
ULN	upper limit normal
US	United States
X	Times

2 PROTOCOL SYNOPSIS

Protocol Number/Title	ALFSG-OCR-002: A Phase 2a Study to Evaluate the Safety and Tolerability of OCR-002 (ornithine phenylacetate) in the Treatment of Patients with Acute Liver Failure/Severe Acute Liver Injury (STOP-ALF)
Phase	Phase 2a
Objectives	Primary Objectives: To evaluate the safety and tolerability of OCR-002 in patients with acute liver failure/severe acute liver injury Secondary Objectives: To evaluate the steady state pharmacokinetic and pharmacodynamic profile of OCR-002 in patients with minimal renal dysfunction using urinary PAGN as a surrogate marker To evaluate the effect of OCR-002 on ammonia levels in patients with acute liver failure/severe acute liver injury To evaluate the effect of OCR-002 on neurological function in patients with acute liver failure/severe acute liver injury
Study Chair	William M. Lee, MD, UT Southwestern Medical Center, Dallas, TX
Co-Principal Investigators	Robert J. Fontana, MD, University of Michigan, Ann Arbor, MI R. Todd Stravitz, MD, VCU Medical Center, Richmond, VA
Investigative Sites	Approximately 6-12 investigative sites in the United States
Study Design	This is a Phase 2a, multi-center, open-label study, conducted in two cohorts of patients diagnosed with acute liver failure/severe acute liver injury (ALF/ALI) who meet inclusion/exclusion criteria. Cohort 1 is defined as patients with ALF/ALI with minimal renal dysfunction at the time of enrollment (defined as a serum creatinine ≤1.5 mg/dL and mean arterial pressure of >65 mm Hg). Cohort 2 is defined as patients with ALF/ALI with compromised renal function (defined as a serum creatinine >1.5 mg/dL and <10 mg/dL with mean arterial pressure of >65 mm Hg). Informed consent will be obtained from the patient and/or patient's legally authorized representative (LAR) or family member as defined in 21CFR50.3(m). All patients will receive medical care for acute liver failure/severe acute liver injury according to the institution's standards of care. Standard of care may include, but is not limited to, administration of *N*-acetylcysteine and consideration for orthotopic liver transplantation. Up to 36 evaluable patients will be enrolled. An evaluable patient is one who has received an infusion of OCR-002 for at least 72 hours. It is expected that not every enrolled patient will be treated for at least 72 hours due to transplant, death or early hospital discharge. Due to this, we anticipate 25% of the enrolled population will fail to reach evaluable status. Therefore, we plan to enroll up to 50 patients in order

Study Design Continued	to obtain 36 evaluable patients. Dosing with OCR-002 may be initiated immediately after obtaining signed informed consent; or, up to 32 h after obtaining consent should the time be necessary to complete any pre-study drug initiation requirements and/or to provide a time frame for study drug administration. Baseline is immediately prior to the start of the initial infusion. At Treatment Day 1 - Time "0" (T0) and after baseline measurements, patients enrolled at Dose Levels 1 through 3 will receive an initial infusion rate of OCR-002. Dose will be escalated to a maximum dose of 10g/24h infusion as indicated herein. Patients receiving Dose Level 4 will receive the full 20 gm/24 hour dose level from initiation of infusion for a maximum time of 120 hours with no further dose escalation, provided the dose level is well tolerated with no noteworthy side effects. Titration of dose will depend on evidence of safety and tolerability (refer to Treatment section below). Patients may have an IV catheter inserted as a safer and easier method for obtaining repeated blood sampling and a separate IV for the infusion. Blood samples for measurement of plasma ornithine, phenylacetate and PAGN concentrations will be collected at multiple time-points during the infusion period, at the Completion of the Last Infusion and up to 24 hours Following the Completion of the Last Infusion. Urine will be collected at specific intervals to determine the amount of PAGN excreted. Patients will be assessed for safety and tolerability of OCR-002 as well as pharmacokinetic and pharmacodynamic variables during the infusion period, at the Completion of the Last Infusion and 24 hours Following the Completion of the Last Infusion. Data on clinical outcomes will also be collected during the study period. Safety data will be reviewed by a Safety Review Committee (SRC) operating under an approved charter and made up of three ALFSG clinicians who are independent of the participating clinical sites and a clinical pharmacologist with experience in PK and clinical trials. Throughout the trial, the SRC will review all safety data at regular intervals, and the FDA will receive annual IND reports. Supportive Care Inotropic support may be used to maintain mean arterial pressure above 65 mm Hg in patients who are hypotensive either before or after enrollment. Dialysis or continuous veno-venous hemofiltration (CVVH), endotracheal intubation and mechanical ventilation will be considered as indicated. Cerebral edema will be managed post-enrollment with mannitol or hypertonic saline per local institutional practices. Antibiotic therapy may be initiated and modified as required. In patients who have intracranial pressure (ICP) monitors placed, ICP, cerebral perfusion pressure and mean arterial pressure will be recorded continuously and reported hourly.
Study Drug	OCR-002 (ornithine phenylacetate) Supplied to the Investigator by Ocera Therapeutics, Inc., Durham, NC
Treatment	Patients enrolled in Dose Levels 1 through 3 will receive an initial infusion at the lowest dose level. The infusion will be escalated in two dosing levels, provided the previous dose level is well-tolerated with no noteworthy side effects. If a patient

Treatment Continued	experiences CTCAE grade 1 or 2 adverse reactions or intolerance to the assigned dose, the investigator may choose to titrate back to the lower tolerated dose and closely monitor the patient. The infusion rate and dose may be discontinued if the patient experiences CTCAE grade 3 or higher, or any time at the investigator's discretion. Each dose level between 1 and 3 will be administered to Cohort 1 patients and safety and PK data reviewed, prior to exposing Cohort 2 patients to the study drug and subsequent dosing levels. Dose level 4 will be administered to both Cohort 1 and 2 beginning simultaneously. The dosing levels for Dose Levels 1 through 3 are defined follows: <u>Dose Level 1</u>: Patients will receive the initial infusion of study drug at 0.139 g/h for the first 12 hours (approximately 3.33 g/24h or 6.9 mL/h) and be maintained at this rate for up to 5 days. <u>Dose Level 2</u>: For patients assigned to this dose level, the infusion will be initiated at 0.139 g/h for the first 12 hours (approximately 3.33 g/24h) and increased to 0.277 g/h (approximately 6.65 g/24h or 13.8 mL/h) for the remainder of the treatment period. <u>Dose Level 3</u>: For patients assigned to this dose level, the infusion will be initiated at 0.139 g/h for the first 12 hours (approximately 3.33 g/24h), increased to 0.277 g/h (approximately 6.65 g/24h) for the next 12 hours, and then increased to 0.416 g/h (approximately 10 g/24h or 20.8 mL/h) for the remainder of the treatment period. The dosing level for Dose Level 4 is defined follows: <u>Dose Level 4</u>: For patients in Cohorts 1 and 2, the infusion of OCR-002 will be initiated at 20g/24hr for a maximum time of 120 hours (approximately .83g/h), provided the dose level is well tolerated with no noteworthy side effects. Initiation of each higher dose for patients in Dose Levels 1 through 3 and continuation of study drug administration for patients in Dose Level 4 will occur only if there are no treatment emergent SAEs of CTCAE Grade 4 or higher that are not attributed to acute liver failure in the opinion of the investigator. In all dose levels, if 1 out of the 3 patients within a dose group experiences a treatment emergent SAE of CTCAE Grade 3 that is not attributed to acute liver failure, then an additional patient will be enrolled into that specific dose group. Within a given dose level, if 2 or more patients experience a treatment emergent SAE of CTCAE Grade 3 that is not attributed to acute liver failure in the opinion of the investigator, then dose escalation (Dose Levels 1 through 3) or continuation of study drug administration (Dose Level 4) will stop. Dose escalation or continuous administration also will stop if 1 patient experiences a Grade 4 or higher SAE that is not attributed to acute liver failure in the opinion of the investigator. Otherwise, dose escalation and continuous study drug administration will continue to the maximum tolerated dose and the remaining enrolled patients will be treated at this dose. Further details of dose

Treatment Continued	escalation are provided in the protocol. The Study Treatment listed below occurs in consecutive order. After the completion of each Dose Level (for each Cohort) the SRC will receive a safety report. The first 3 enrolled patients will have minimal renal dysfunction (Cohort 1) and will be treated at Dose Level 1 for up to five days. If patient safety is confirmed, the next 3 enrolled patients will also have minimal renal dysfunction (Cohort 1) and will receive an initial infusion of study drug at 0.139 g/h for the first 12 hours. The dose will be titrated, provided the previous dose level is well-tolerated with no noteworthy side effects, to the maximum dose in Dose Level 2 for 108 hours. Study enrollment will be paused while the SRC reviews the safety and PK data for the first six evaluable Cohort 1 patients. If patient safety is confirmed, the next 3 Cohort 1 patients (minimal renal dysfunction) will receive an initial infusion of study drug at Dose Level 3 for 12 hours. The dose will be titrated to the maximum dose in Dose Level 3, provided previous dose levels are well-tolerated with no noteworthy side effects, to the maximum dose in Dose Level 3 for 96 hours. In parallel with the enrollment of Cohort 1 patients (minimal renal function) at Dose Level 3, three patients with compromised renal function (Cohort 2) will be enrolled and treated at Dose Level 1 for five days. If patient safety is confirmed, three Cohort 2 patients (compromised renal function) may be enrolled and will be treated with an initial infusion at Dose Level 2 for 12 hours. The dose will be titrated, provided the previous dose level is well-tolerated with no noteworthy side effects, to the maximum dose in Dose Level 2 for 108 hours. The SRC will review the safety and PK data for Cohort 1 (minimal renal dysfunction) patients who received the study drug at Dose Level 3 and for Cohort 2 patients (compromised renal function) who received the study drug at Dose Levels 1 and 2 prior to enrolling Cohort 2 patients into Dose Level 3. Once patient safety has been confirmed by the SRC for Cohort 1 patients in Dose Level 3, patients in Cohort 1 can begin to enroll into Dose Level 4 (20g/24hr) and will receive the full dose level from initiation of infusion for a maximum time of 120 hours, provided this dose is well tolerated with no noteworthy side effects. Once safety has been confirmed by the SRC for Cohort 2 patients in Dose Level 3, patients in Cohort 2 can begin to enroll into Dose Level 4 (20g/24hr) and will receive the full dose level from initiation of infusion for a maximum time of 120 hours, provided this is well tolerated with no noteworthy side effects. If a patient experiences CTCAE grade 1 or 2 adverse reactions or intolerance to the assigned dose, the investigator may choose to titrate to a lower dose in 5 gram increments and closely monitor the patient. The infusion rate and dose may be discontinued if the patient experiences CTCAE grade 3 or higher, or any time at the investigator's discretion.
Study	Up to 36 evaluable male and female patients aged 18 to 65 years (have not reached

Population	their 66th birthday) with acute liver failure or severe acute liver injury will participate.
Key Inclusion Criteria	1. Men and women, ages 18-65 (have not reached their 66th birthday). 2. Acute liver failure, defined as the development of coagulopathy (International normalized ratio [INR] ≥1.5) with encephalopathy in a patient with no prior history of liver disease with onset of symptoms within 28 days of the inciting event. Patients may have either a history of acetaminophen overdose (defined as >4 g/day within 7 days of presentation) and/or detectable acetaminophen levels in the serum, with a pattern of liver function tests typical for acetaminophen toxicity (bilirubin < 10 mg/dL and alanine aminotransferase (ALT) ≥1000 IU/L), or a diagnosis of hepatitis A, hepatitis B, drug-induced liver injury, autoimmune hepatitis or indeterminate cause based on standard criteria; refer to Section 6.2.1 for the definitions of standard criteria for these diagnoses. 3. ALI patients may also be enrolled (those meeting the above criteria plus coagulopathy (INR ≥ 2.0) and no evidence of encephalopathy and may provide consent themselves. 4. Written informed consent from the patient or patient's legally authorized representative or family member as defined in 21CFR50.3(m)--if he/she has evidence of encephalopathy (ALF). 5. Ammonia level ≥60 µmol/L at baseline (within 8 hrs prior to infusion start time). 6. Serum creatinine levels as follows: a. Cohort 1: Creatinine ≤1.5 mg/dL; and b. Cohort 2: Creatinine >1.5 mg/dL and < 10mg/dL. 7. Mean arterial pressure of >65 mmHg.
Key Exclusion Criteria	1. History of chronic liver disease 2. Signs of overt cerebral herniation, or uncontrolled intracranial hypertension by ICP monitoring (if applicable) 3. Evidence of Wilson's disease, alcoholic hepatitis, biliary obstruction, ischemic hepatitis, severe acute renal tubular necrosis (ATN) due to shock, or any patient with ongoing hypotension 4. Significant gastrointestinal bleeding (coffee grounds per ng tube and/or melena) 5. Hemodynamic instability, defined by a mean arterial pressure of <65 mmHg 6. Cardiopulmonary complications such as pulmonary edema, aspiration pneumonia, heart failure 7. QT interval of >500msec at baseline ECG 8. Pregnancy 9. History of malignancy that has not been cured or any cancer in remission for less than 1 year. Non-melanoma skin cancers do not preclude participation in the trial. 10. Concomitant administration of drugs known to interfere with renal excretion of phenylacetylglutamine or those medications that may induce hyperammonemia

Key Exclusion Criteria Continued	such as haloperidol, valproic acid and systemic corticosteroids (prohibited during the study). Alternative ammonia modifying agents such as lactulose and rifaximin are not considered standard of care and are prohibited during the study period. 11. Any other health condition that would preclude participation in the study in the judgment of the site principal investigator.
Safety Evaluations	Safety assessments will be performed at: - Specified time points during the infusion periods (0 to up to 120 h) - At the Completion of the Last Infusion and 24 hours Following the Completion of the Last Infusion - End of study During the infusion period, at the Completion of the Last Infusion and 24 hours Following the Completion of the Last Infusion, daily safety assessments will include: abbreviated physical examinations, vital signs (blood pressure, pulse rate, respiration rate, and body temperature), clinical laboratory tests (hematology and serum chemistry), 12-lead ECGs, and reported and observed adverse events. At the Day 30 follow up visit, safety assessments (physical, vitals, hematology/chemistry) including serious adverse events data will be collected.
Exploratory Efficacy Evaluations	Ammonia concentrations will be collected during the infusion period, at the Completion of the Last Infusion, 24 hours Following the Completion of the Last Infusion and at the Day 30 post treatment period. Neurological assessments measured by the Glasgow Coma Scale and the West Haven Criteria will be done every 12 or 24 hours during the entire infusion period. Orientation log (O- log) assessment will also be undertaken in all patients at these time points.
Concomitant Medications and Therapy	All patients will receive or have received, intravenous *N*-acetylcysteine (NAC) for acetaminophen toxicity. Third generation cephalosporins, hypertonic saline and/or mannitol are permitted. The use of hypothermia therapy is prohibited during the study.
Safety Analysis	All adverse events will be summarized by body system, preferred MedDRA term and cohort. Data listings and summaries of severity, relation to treatment and expectedness will be provided by cohort.
Statistical Considerations	This study is not powered to determine statistical significance. Descriptive statistics will be used to evaluate safety, exploratory efficacy data, PK and PD.

3 INTRODUCTION AND BACKGROUND

3.1 Introduction

Acute liver failure (ALF) is a rare disorder affecting an estimated 2000 patients annually in the United States (US). Hepatotoxicity related to the use of acetaminophen is the most common etiology of ALF in the US (1).

Acute liver failure is the result of massive damage to previously normal liver parenchyma with resultant loss of liver function. As the hepatocyte function is lost, the liver loses its ability to synthesize proteins and extract circulating toxins. The two cardinal signs of ALF, coagulopathy and encephalopathy, represent the loss of the ability to synthesize clotting factors and to remove ammonia, respectively.

Acute liver failure often affects young people and carries a very high mortality. Only 45% of patients with ALF will spontaneously recover. Of the remaining 55%, 30% will die and 25% will undergo an emergency liver transplantation. Emergency liver transplantation in this setting has a 90% 1-month survival rate and a 70% 1-year survival rate. Mortality in ALF can be due to a variety of factors, including sepsis and multi-organ system failure, but cerebral edema due to increased ammonia resulting in intracranial hypertension and brainstem herniation is one of the most common causes of death, accounting for 30% of the mortality in this population (2).

There is strong experimental and clinical rationale for the use of ammonia-lowering therapies in ALF. Ammonia is normally produced in the gut and transformed by the liver into urea. As the liver fails, ammonia increases in the systemic circulation and enters into the brain. The result of a rapid rise in ammonia in the cerebral circulation is hepatic encephalopathy (HE), a reversible neuropsychiatric condition that ranges in severity from mild impairment in attention, to delirium, coma and death. A particular concern regarding HE in ALF is that ammonia level increases tend to be very rapid. This rapid rise in ammonia does not provide sufficient time for brain cells to compensate, with the end result being astrocyte swelling with increased intracranial pressure (ICP) and ultimately, death due to brain herniation. An arterial ammonia level above 150 μM has been shown to correlate with a poor prognosis, and is almost universally indicative of increased intracranial pressure (3).

Cerebral edema in patients with ALF results from overloading brain astrocytes with ammonia. Astrocytes utilize the same mechanism as skeletal muscle to detoxify ammonia (*i.e.*, amidation of glutamate to glutamine via glutamine synthetase). The resulting accumulation of brain glutamine results in impaired astrocyte osmoregulation, astrocyte swelling and cerebral edema (4-6). Astrocytes contain counter-regulatory mechanisms to offset increased intracellular osmotic pressure, but compensate too slowly in the acute situation.

Cortical astrocyte swelling is the most common neuropathological observation in post-mortem brains of ALF patients. Cerebral edema is found in up to 80% of patients who die of ALF and is nearly universal among patients with coma (7).There are clear associations between arterial ammonia levels, uncal herniation, and death in patients with ALF (3,8). There is also clear evidence of these associations in animal models of ALF(9-12).

OCR-002 (L-ornithine·phenylacetate) is an ammonia detoxification agent that works by

eliminating ammonia in the circulation, with the expectation that it will result in a more rapid reduction than current therapies, and a lower incidence of cerebral edema.

3.2 Physical, Chemical, and Biological Characteristics of OCR-002

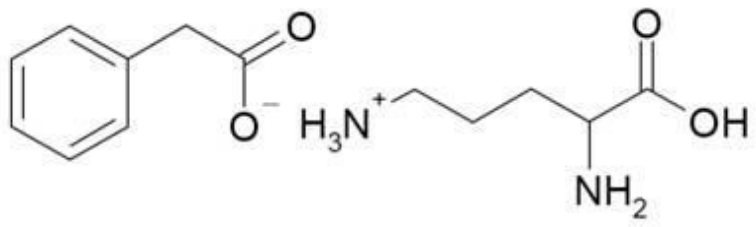
Background information on OCR-002 is summarized below. More detailed information is provided in the Investigator's Brochure.

3.2.1 Chemistry

OCR-002 is an ammonia detoxification agent and has the chemical name L-ornithine·phenylacetate (L-ornithine·benzeneacetate salt (1:1), CAS-RN 952154-79-9). The molecular formula is $C_8H_7O_2 \cdot C_5H_{13}N_2O_2$and OCR-002 has a molecular weight of 268.31 g/mole.

OCR-002 drug substance is a new chemical entity and exists as a single crystalline molecular structure as an ornithine salt ofphenylacetate as shown below:

Figure 1: L-ornithine·phenylacetate



3.2.2 Summary of Nonclinical Safety Data

The nonclinical safety of OCR-002 was evaluated in a comprehensive program of *in vitro* and *in vivo* studies which included evaluation of the potential undesirable pharmacodynamic effects of OCR-002 on physiological functions in relation to exposure in the therapeutic range and above (safety pharmacology core battery), evaluation of the mutagenic and clastogenic potentials of OCR-002 (*in vitro* test battery for genotoxicity), and evaluation of the short- and longer-term functional and morphologic effects associated with OCR-002 exposure in whole animal models (mammalian toxicology program). The results of the OCR-002 toxicology program indicate a low potential for systemic toxicity in humans. Please refer to the OCR-002 Investigator's Brochure for a detailed discussion.

Further evidence of safety is provided by over 20 years of clinical experience with Ammonul® (sodium phenylacetate and sodium benzoate) Injection 10%/10% and Hepa-Merz™ (L-ornithine L-aspartate). The safety profiles of these entities are discussed in the Investigator's Brochure.

3.3 Rationale for the Study and Dose Selection

3.3.1 Rationale for the Study

There is no established medical therapy for ALF (13). Investigational agents such as charcoal

hemoperfusion and administration of prostaglandin E1, which showed early promise, have not been shown to be superior to standard of care when analyzed in randomized controlled studies (14-17). Plasmapheresis and hepatectomy have been suggested as possible "bridges" to liver transplantation but a prospective trial of the former has been presented in abstract form only. Hypothermia has been investigated in a total of only 38 patients with ALF, all from Jalan, *et al* (18), and may be an effective bridge to liver transplantation (19). However, therapeutic hypothermia has considerable potential adverse effects and has never been shown to increase spontaneous (non-transplant) survival. External bio-artificial livers such as the MARS device have been employed, but use of these devices remains experimental, and the preliminary results have been generally disappointing (20).

Treatment strategies focusing on the specific underlying conditions are, for the most part, of little or no use once ALF has occurred. Corticosteroids for fulminant autoimmune hepatitis, chelation therapy for fulminant Wilson's disease, and anti-viral therapies for fulminant hepatitis B have never been shown to be of benefit in the setting of ALF, and supportive care and liver transplantation are the only treatment strategies that can be used in these patients (21-23).

One notable exception to this is the use of *N*-acetylcysteine (NAC) for ALF due to acetaminophen overdose. NAC, a glutathione donor, is the antidote for acute acetaminophen toxicity, and it has been shown to improve outcome in these patients. Importantly, it is most effective if administered within 8-24 hours of the overdose (24), which significantly limits its therapeutic impact. It is mainly of benefit in patients who take an intentional overdose and then present rapidly for medical care. Cases of accidental overdoses often present for medical attention after the effective window for NAC has closed. Similarly, patients taking an intentional overdose who do not seek care often present too late for NAC to be of maximum benefit (25). Recently, a controlled blinded study of NAC has shown evidence that it benefits non-acetaminophen-related ALF if given during early stages of encephalopathy (26).

Thus, for the vast majority of patients with ALF, liver transplantation is the only recognized treatment option. However, some patients cannot be transplanted due to the severity of their disease or a concomitant medical condition, and even patients who are listed may die waiting for a suitable organ to come available. Transplantation is far from an ideal treatment, as short-term survival for patients with ALF is lower than for cirrhosis, with a 90% 1-month survival and 70% one-year survival (27, 28). Transplantation also commits the patient to a lifetime of immune-compromising and toxic anti-rejection medications. Additionally, some neurocognitive sequelae of increased intracranial pressure persist after liver transplantation for ALF.

In summary, therapeutic options in ALF are limited other than supportive care and liver transplantation. NAC is appropriate for early presentations of acetaminophen overdose and possibly is of value in other forms of ALF. Management of fluid status, airway protection and infection control are important, and, for cerebral edema, mannitol or hypertonic saline are used to osmotically draw water from astrocytes, but are temporizing measures (28). Usually, patients with intracranial hypertension who initially respond to mannitol or hypertonic saline die of cerebral herniation if not transplanted in short order.

The above observations provide a strong rationale for using ammonia-lowering therapy in patients with ALF. Lactulose is widely used for this purpose in patients with cirrhosis, but has not been studied systematically in patients with ALF, and may obscure the surgical field at the time of liver transplantation due to gaseous distention of the bowel (28). Poorly absorbable antibiotics such as neomycin or rifaximin have also not been studied, and the former carries considerable risk of nephrotoxicity. A recent randomized, controlled study of L-ornithine L-aspartate (LOLA), a putative ammonia-lowering agent, found no improvement in blood ammonia concentrations or survival in patients with ALF (29). However, the rationale underlying the use of this agent may be flawed, since the compound provides a substrate (ornithine) for the production of glutamate and theoretically may lower ammonia by production of glutamine, but does not provide a route of glutamine elimination from the body. Thus, glutamine persists in the circulation in patients receiving LOLA, and subsequently may be de-amidated back to ammonia and glutamate by gut glutaminases (30).

OCR-002 (ornithine·phenylacetate; OPA) is an ammonia detoxification agent with a better rationale for use in patients with hyperammonemia than LOLA. In contrast to LOLA, OPA not only provides a substrate for the synthesis of glutamate and thus glutamine, but also a route of elimination of glutamine in the urine as phenylacetylglutamine (PAGN) (14). The synergistic effects of L-ornithine and phenylacetate have been documented in validated pharmacology models of liver failure, the devascularized ALF pig and the bile-duct ligated cirrhotic rat (31, 32). In these animal models, reduction of the central target of OPA, ammonia, correlated with improvement in intracranial pressure and frontal brain water, which are associated with HE, as well as morbidity and mortality in humans with ALF. The mechanism supporting elimination of glutamine *via* PAGN in urine has been confirmed in both models and supports the utility of the combination therapy for removal of waste nitrogen (ammonia) from the body. Another important feature of OPA pertains to the ability of PAGN to be dialyzed (33), a critical observation as many patients with ALF develop acute renal failure requiring renal replacement therapy.

Patients with acetaminophen toxicity leading to acute liver injury or liver failure are optimal patients for the planned clinical study for several reasons. First, their liver injury is severe and occurs very rapidly over a prescribed time course, considered hyperacute (< 7 days) in duration. Second, acetaminophen patients comprise a large, relatively homogeneous patient group, are typically young and otherwise healthy. Third and most importantly, they are at the highest risk for elevated ammonia levels and cerebral edema because of their young age and the rapidity of their liver failure. Renal failure can also be observed in this setting, presumed due to a direct effect of the drug on the renal tubular cells, and contributes to hyperammonemia and the risk of cerebral edema. Although the overall recovery rate is quite high after acetaminophen overdose despite the severity of the liver injury, many patients cannot be listed for transplantation because of the psychosocial issues which contributed to the overdose.

In the current protocol, all patients will have been treated with NAC as standard-of-care for acetaminophen toxicity. There are no anticipated interactions between NAC and OCR-002 based on the pharmacology of each compound. All patients who are enrolled will have received appropriate management for acetaminophen toxicity, including N-acetylcysteine either oral or intravenous, prior to study enrollment. In some instances, this will be continued

during, or may overlap with, the study period.

This Phase 2a clinical study is designed to provide data on OCR-002 in patients with ALF/ALI in regard to:

(a) safety and tolerability;

(b) metabolism of the compound to glutamine and phenylacetylglutamine;

(c) its effect on circulating ammonia levels and neurological function in patients with and without impaired renal function after continuous infusion at different infusion rates.

It is anticipated that this early safety and tolerability study, with appropriate PK/PD data, will lead to a development program for the use of OCR-002 in the treatment of hyperammonemia either due to ALF or even more generally, for ACLD.

3.3.2 Rationale for Dose Selection

Ocera Therapeutics, Inc. (Durham, NC) has conducted two clinical trials evaluating safety, tolerability and pharmacokinetics in healthy volunteers (n=48) and stable cirrhotic patients (n=43).

Clinical study OCR-002 HE201 was designed as a randomized, placebo-controlled, dose-ranging study, evaluating doses (i.v. infusion) of 1, 3, 10, 20 and 30g given over 4h, and 30, 40 and 60g given over 24h. Following a single ascending dose phase, a multiple ascending dose phase (5d of consecutive administration) for doses of 1, 3, 10 and 20g given over 4h was assessed. The key findings in this study included:

There were no deaths, SAE or AE discontinuations in the study.

A dose related increase in the incidence and severity of adverse events was observed.

Commonly occurring adverse events that appeared to be related to dose 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 patients experienced clinically significant orthostatic hypotension.

There appeared to be a dose and exposure related increase in mean heart rate starting at a dose level of 10g/4 h and higher. These effects also persisted for longer periods in the higher dose groups.

20g administered over 4 h was the maximum tolerated dose (MTD), however, doses of 10g/4h and below were well tolerated.

24h Holter monitor recording identified a dose-related increase in heart rate accompanied by modest effects on ventricular repolarization as measured by QT. These effects should be interpreted with caution in light of the small sample size and higher heart rates observed in this study.

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 are associated with adverse effects that may be rate and C_{max} related and are likely associated with the non-linear pharmacokinetic profile of phenylacetate above 10 g.

A slower infusion rate (24hr-infusion) avoids C_{max} related adverse effects while providing similar excretion of PAGN.

In aggregate, these studies supported an initial study using a 10g/24 hours dose of OCR-002 as suitable for an early phase study in ALF patients. As STOP-ALF represents the first study of OCR-002 conducted in patients with ALF, the administration of the study drug in three ascending dose levels (Dose Levels 1 through 3) will be implemented as follows and in the protocol for up to 24 evaluable subjects:

The maximum target infusion rate will be 0.42g/h, which is equivalent to 10g administered over 24h.

The infusion rate will be staged for each patient. The initial infusion rate will be 0.14g/h (33% of target dose). The dose will be then increased to 0.28g/h (66% target), and 0.42g/h (100% target) in successive 12h intervals based on a patient safety evaluation by the Investigator.

Patient safety and tolerability at an increased loading dose are supported by the pharmacokinetic data and plasma ammonia levels obtained from the ongoing clinical study Phase 2 OP-GIB conducted in Spain, in which cirrhotic patients with active gastrointestinal hemorrhage receive double-blind treatment, i.e., placebo or OCR-002 at 10 g per 24 hours as a constant intravenous infusion for 5 days.

Ocera began over a year ago a large ongoing trial of OCR-002 in hospitalized patients with cirrhosis and associated hyperammonemia (OCR002-HE209, STOP-HE). In STOP-HE, a placebo-controlled, randomized, double-blind clinical trial designed to evaluate the safety, pharmacokinetics and efficacy of intravenously-administered OCR-002 in resolving neurocognitive symptoms of acute HE in hospitalized cirrhotic patients with elevated ammonia, either OCR-002 or placebo is administered to patients intravenously for up to five days along with standard of care, at doses of 20, 15, or 10 grams over 24 hours based on the patient's degree of liver impairment. In this study, there is no ascending or loading dose being implemented.

Therefore, up to 12 additional evaluable patients will be enrolled at Dose Level 4 as listed below:

Dose Level 4: For patients assigned to this dose level, the infusion will be initiated at the full dose level of 20g/24hr for a maximum time of 120 hours (approximately .83g/h), provided the dose level is well tolerated with no noteworthy side effects.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

To evaluate the safety and tolerability of OCR-002 in patients with acute liver failure/severe acute liver injury.

Hypothesis: Treatment with OCR-002 is safe and tolerable in patients with acute liver failure/acute liver injury.

4.1.2 Secondary Objectives

To evaluate the steady state pharmacokinetic and pharmacodynamic profile of OCR-002 in patients with impaired and minimal renal dysfunction using urinary PAGN as a surrogate marker.

Hypothesis: A dose of 10-20g/24h (0.42-.83g/h) will achieve steady state plasma concentrations within 6-12h with little additional accumulation in the ALI/ALF setting.

To evaluate the effect of OCR-002 on ammonia levels in patients with acute liver failure/severe acute liver injury.

Hypothesis: Treatment with OCR-002 will reduce ammonia levels in patients with ALI/ALF.

To evaluate the effect of OCR-002 on neurological function in patients with acute liver failure/severe acute liver injury.

Hypothesis: Treatment with OCR-002 will improve neurological function in patients with acute liver failure/severe acute liver injury.

4.2 Endpoints

4.2.1 Safety Endpoints

Safety assessments will include: abbreviated physical examinations, vital signs (blood pressure, pulse rate, respiration rate, and body temperature), clinical laboratory tests (hematology and serum chemistry), 12-lead ECGs, and reported and observed adverse events.

4.2.2 Exploratory Efficacy Endpoints

- Ammonia concentrations.
- Neurological assessment will be measured by the Glasgow Coma Scale, the West Haven Criteria, and the Orientation log (O-log) (34).

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is a Phase 2a, multi-center, open-label study, conducted in two cohorts in patients

diagnosed with acute liver failure/severe acute liver injury (ALF/ALI) who meet inclusion/exclusion criteria. The acetaminophen adduct assay will be used as an additional test for equivocal or presumed cases of acetaminophen toxicity, where the history is not substantiated and the assay for acetaminophen itself proves to be negative.

Up to 36 evaluable patients are planned to be enrolled in two cohorts:

Cohort 1 will include patients with ALF/ALI with minimal renal dysfunction at the time of enrollment (defined as serum creatinine ≤1.5mg/dL and mean arterial pressure of >65 mmHg).

Cohort 2 will include patients with ALF/ALI with compromised renal function (defined as a serum creatinine >1.5 mg/dL and <10mg/dL) and mean arterial pressure of >65 mmHg.

Informed consent will be obtained from the patient and/or patient's legally authorized representative or family member [as defined in 21CFR50.3(m)]. All patients will receive medical care for acute liver failure/severe acute liver injury according to the institution's standards of care. Standard of care may include, but is not limited to, administration of NAC and consideration for orthotopic liver transplantation. All patients in Cohort 2 with a serum Cr level of ≥2.0 will be considered for placement on continuous veno-venous hemodialysis (CVVHD) for an appropriate interval as standard of care for this condition.

The initial dose of OCR-002 will be initiated once consent is obtained, all eligibility criteria are confirmed to be met and all baseline measurements have been completed. The infusion may begin after obtaining signed informed consent; or, up to 32 h after obtaining consent should the time be necessary to complete any pre-study drug initiation requirements and/or to provide a time frame for study drug administration.

Treatment Day 1-Time "0" (T0) is the start of the initial infusion. At this time, each patient in Dose Levels 1 through 3 will receive an initial infusion rate of OCR-002; thereafter, up and down titration decisions will be based on patient tolerability, clinical safety assessments (refer to Treatment below), and the patient's status within the assigned dose level. Each dose escalation will be administered to Cohort 1 patients and safety and PK data reviewed and approved by the SRC prior to exposing Cohort 2 patients to the study drug and subsequent dosing levels. A dedicated intravenous infusion line for the study drug is the recommended option.

The SRC will review all safety and PK data for the first six evaluable Cohort 1 patients at Dose Level 1 and at Dose Level 2 to determine if Cohort 2 patients may be enrolled to receive study drug at Dose Level 1.

If patient safety is confirmed, three Cohort 1 patients may be enrolled to receive study drug escalation to Dose Level 3. Concurrent with enrollment of Cohort 1 patients in Dose Level 3, three Cohort 2 patients may be enrolled at Dose Level 1. If patient safety is confirmed for Cohort 2 Dose Level 1, three Cohort 2 patients may be enrolled at Dose Level 2.

Once three Cohort 1 patients complete Dose Level 3, the SRC will review the safety and PK data in both Cohort 1 and Cohort 2 patients. If patient safety is confirmed in both Cohorts and at each dosing level, enrollment will be open to both Cohort 1 and Cohort 2 patients to receive Dose Level 3.

After at least three evaluable Cohort 1 patients complete Dose Level 3 and the data are reviewed by the SRC, Cohort 1 patients may be enrolled to receive study drug at Dose Level 4. Similarly, after at least three evaluable Cohort 2 patients complete Dose Level 3, Cohort 2 patients may be enrolled to receive study drug at Dose Level 4, once the safety and PK data are reviewed and approved by the SRC.

Patients may have an IV catheter inserted for ease of obtaining safety, PK and PD blood sampling. Blood samples for measurement of plasma ornithine, phenylacetate and PAGN concentrations will be collected at multiple time-points during the infusion period, at the Completion of the Last Infusion, and 24 hours Following the Completion of the Last Infusion. Urine samples will be collected at specific intervals to determine the amount of PAGN excreted/synthesized.

Patients will be assessed for safety and exploratory efficacy of OCR-002 as well as pharmacokinetic and pharmacodynamic variables for up to a 6-day period which includes up to 5 days (maximum of 120 h) of infusion, at the Completion of the Last Infusion, and at 24 hours Following the Completion of the Last Infusion. Patients also will be assessed at the Day 30 post treatment period. The total intended enrollment is approximately 18 patients with minimal renal dysfunction and approximately 18 with compromised renal function. Enrollment will be discontinued when 36 evaluable patients are enrolled.

Supportive Care

Inotropic support may be used to maintain mean arterial pressure above 65 mmHg in patients who are hypotensive either before or after enrollment. Dialysis or continuous veno-venous hemofiltration (CVVH), endotracheal intubation and mechanical ventilation will be considered as indicated. Cerebral edema will be managed according to local practice with mannitol or hypertonic saline. Antibiotic therapy may be initiated and modified as required. In patients who have intracranial pressure (ICP) monitors placed, as determined by standard of care at each institution, the ICP (if available) and cerebral perfusion pressure will be monitored continuously, in addition to the mean arterial pressure, and reported hourly during the period of active study drug infusion.

5.2 Continuous Infusion Rate Adjustments

OCR-002 will be infused intravenously (IV) for up to 5 days (0 to 120 h). The Dosing regimen for Cohorts 1 and 2 is as follows:

Dose Level 1: Patients will receive the initial infusion of study drug at 0.139 g/h for the first 12 h (approximately 3.33 g/24h) and maintained at this rate for up to 120h.

Dose Level 2: Patients will receive an initial infusion of study drug at a dose of 0.139 g/h for the first 12 hours (approximately 3.33 g/24h). The dose will be increased to 0.277 g/h for the next 108h (approximately 6.65 g/24h), and maintained at this rate for the remaining treatment period, provided the previous dose level is well- tolerated with no noteworthy side effects and no safety signals are apparent.

Dose Level 3: Patients will receive an initial infusion of study drug at a dose of 0.139 g/h for the first 12 h (approximately 3.33 g/24h). The dose will be increased to 0.277 g/h for the next 12 hours, and then increased to 0.416 g/h (approximately 10 g/24h) and maintained at this rate

for the remaining treatment period, provided previous dose levels are well-tolerated with no noteworthy side effects and no safety signals are apparent.

Dose Level 4: Patients will receive an infusion of study drug at a dose of 20g/24h from initiation of infusion for a maximum time of 120 hours, provided the dose level is well tolerated with no noteworthy side effects and no safety signals are apparent.

If a patient experiences CTCAE grade 1 or 2 adverse reactions or intolerance to the assigned dose, the investigator may choose to titrate to a lower dose in 5g increments and closely monitor the patient. The infusion rate and dose may be discontinued if the patient experiences CTCAE grade 3 or higher, or any time at the investigator's discretion. (See Section 9.7 of the protocol for details on safety review, dose escalation and trial stopping criteria.)

6 PATIENT POPULATION

6.1 Number of Sites and Patients

The study will be conducted at between 6 to 12 centers in the US that are experienced, high-volume sites in the ALF Study Group. All patients enrolled in the therapy trial will have been enrolled in the ALFSG registry. Up to 36 evaluable male and female patients aged 18 to 65 years with ALI/ALF will be enrolled into two cohorts. Each patient may participate in only one cohort. For each patient, the study duration will be approximately 32 days, including Screening, Baseline, up to 5 days of treatment, the Completion of the Last Infusion, a 24 hours Following the Completion of the Last Infusion, and a post treatment period on Day 30 (approximately 30 days after Treatment Day 1-T0 unless terminated early from the trial).

6.2 Selection Criteria

6.2.1 Inclusion Criteria

1. Men and women, ages 18-65 (have not reached their 66th birthday).
2. Acute liver failure, defined as the development of coagulopathy (International normalized ratio [INR] ≥1.5) with encephalopathy in a patient with no prior history of liver disease, with onset of symptoms within 28 days of the inciting event. Patients may have either a history of acetaminophen overdose (defined as >4 g/day within 7 days of presentation) and/or detectable acetaminophen levels in the serum, with a pattern of liver function tests typical for acetaminophen toxicity (bilirubin < 10 mg/dL and alanine aminotransferase (ALT) ≥1000 IU/L), or a diagnosis of hepatitis A, hepatitis B, drug-induced liver injury, autoimmune hepatitis or indeterminate cause based on standard criteria. Standard criteria for these diagnoses are as follows:
   - hepatitis A, defined as positive anti-HAV IgM;
   - hepatitis B, defined as positive anti-HBc IgM and positive HBsAg;
   - autoimmune hepatitis, defined as follows:
     - Globulins elevated > 1.5X ULN;
     - ANA, ASMA or LKMA positive in titer of at least 1:80;
     - Negative serology for viruses associated with acute or chronic hepatitis; and/or

- Liver biopsy showing CAH;
- drug-induced liver injury, defined as presumed injury by a likely agent, with other causes excluded; or
- indeterminate cause, defined as
  - the exclusion of all the diagnoses listed in the Selection Criteria (see Section 6.2), including:
  - Budd-Chiari;
  - Hepatitis C, E, delta, drug-induced hepatitis;
  - mushroom intoxication; and
  - other viruses, defined as follows:
    - HSV: anti-HSV IgM positive and anti-HSV IgG negative and four fold increase between acute and convalescent sera and HSV seen in liver tissue;
    - EBV: anti-EBV IgM or EBV seen in liver tissue; and
    - CMV: anti-CMV IgM positive and anti-CMV IgG negative and four fold increase between acute and convalescent sera or CMV seen in liver tissue.

3. ALI patients may also be enrolled (those meeting the above criteria plus coagulopathy (INR $\geq$ 2.0) and no evidence of encephalopathy).
4. Written informed consent from the patient (ALI) or patient's legally authorized representative or family member if he/she is considered encephalopathic (ALF).
5. Ammonia level $\geq$60 µmol/L at baseline (within 8h prior to T0/initiation of infusion).
6. Serum creatinine levels as follows:
   a. Cohort 1: Creatinine $\leq$1.5 mg/dL; and
   b. Cohort 2: Creatinine >1.5 mg/dL and <10mg/dL.
7. Mean arterial pressure of >65 mmHg.

6.2.2 Exclusion Criteria

1. History of chronic liver disease.
2. Signs of overt cerebral herniation, or uncontrolled intracranial hypertension by ICP monitoring (if applicable).
3. Evidence of Wilson's disease, alcoholic hepatitis, biliary obstruction, ischemic hepatitis, severe acute renal tubular necrosis (ATN) due to shock, or any patient with ongoing hypotension.
4. Significant gastrointestinal bleeding (coffee grounds per nasogastric tube and/or melena).
5. Hemodynamic instability, defined by a mean arterial pressure of <65 mmHg.
6. Cardiopulmonary complications such as pulmonary edema, aspiration pneumonia, heart failure.
7. QT interval of >500msec at baseline ECG.
8. Pregnancy.
9. History of malignancy that has not been cured or any cancer in remission for less than 1 year. Non-melanoma skin cancers do not preclude participation in the trial.

10. Concomitant administration of drugs known to interfere with renal excretion of phenylacetylglutamine or those medications that may induce hyperammonemia such as haloperidol, valproic acid and systemic corticosteroids (prohibited during the study). Alternative ammonia modifying agents such as lactulose and rifaximin are not considered standard of care and are prohibited during the study period.
11. Any other health condition that would preclude participation in the study in the judgment of the principal investigator.

6.3 Informed Consent and Enrollment

6.3.1 Informed Consent

The Investigator will select patients in accordance with eligibility criteria detailed in Section 6.2. Prior to the study, for patients with ALF, the patient's legally authorized representative or family member will receive a comprehensive explanation of the proposed treatment including the nature and risks of the study, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. The patient and/or the patient's legally authorized representative or family member will also receive a detailed explanation of the proposed use and disclosure of their protected health information. After having the nature and risks of the study explained to them, the patient and/or the legally authorized representative or family member will be allowed sufficient time to consider participation in the study. Patients who meet criteria for ALI are, by definition, not encephalopathic and will be able to consent for enrollment without additional consents being obtained from a legally authorized representative or family member, although both consents may be obtained.

For those with ALF, the patient's legally authorized representative or family member must provide written informed consent and provide authorization to disclose the patient's protected health information in order to enroll in the study. The informed consent process will be conducted per institutional protocol and in compliance with applicable IRB requirements. Written informed consent must be obtained from the patient's legally authorized representative or family member before any study related activities are conducted. The Investigator must retain all original signed and dated informed consent forms (ICF's) (together with any subsequent IRB-approved amended versions) in the patient's file. A copy of the original signed and dated ICF (and any amendments) must be provided to the patient and/or the patient's legally authorized representative or family member.

If any new information that significantly bears on the patient's risk after receiving the study drug becomes available, the new information will be communicated by the Investigator to the patient and the patient's legally authorized representative or family member. The ICF will be updated and patient's legally authorized representative or family member will be re-consented if necessary (e.g., if patient still in the study and/or local IRB requires re-consent).

6.3.2 Enrollment

Patients will be considered enrolled into the study once informed consent has been obtained, all eligibility criteria are met, and the study drug infusion has been initiated. A study identification number will be assigned by the computer system that houses the study database. A Screen Failure Log will be maintained to capture basic information on all patients screened for the study but who failed to be enrolled. This would include demographic information and the reasons for failure to enroll.

6.3.3 Withdrawal of Consent

The patient or the patient's legally authorized representative or family member is free to withdraw participation in the study at any time and without prejudice to further treatment. The investigator must withdraw any patient from the study if requested. If a patient withdraws consent then no further research data can be collected. Data collected up to the date of the consent withdrawal will be included in the analysis.

6.3.4 Discontinuation of Study Treatment

An Investigator may discontinue a patient's treatment at any time to protect the patient's safety. Reasons that patients may have treatment discontinued include, but are not limited to the following:

Prolongation of Qt/Qt_c interval of >60 msec over baseline or a Qt/Qt_c interval above 500 msec;

Evidence of torsades de pointe phenomenon;

Grade 3 or higher CTCAE toxicity not attributed to acute liver failure in the opinion of the investigator;

Neutropenia with absolute neutrophil count <500/cumm or platelet count <20,000/cumm, or an increase in serum Cr to a value of >10mg/dL;

Liver transplantation during the study treatment;

Withdrawal of informed consent by the patient or patient's legally authorized representative or family member;

In the case of interruption of infusion for any reason, the study drug will not be restarted if more than 2 hours has elapsed;

Evidence of shock; and

Evidence of kidney injury related to study drug will invoke consideration of discontinuation of the study drug.

6.3.5 Follow-up of Patients with Discontinuation of Study Treatment

Patients who had an early discontinuation of study treatment will continue to be followed carefully through the 30-day study period unless consent is withdrawn. The follow-up may include the following:

Additional safety laboratory tests and/or other investigations;

Continued confinement in the ICU or hospital; and

Obtaining a specialist's opinion.

7 STUDY DRUG AND ADMINISTRATION

7.1 Identity of Study Drug

The chemical name for OCR-002 is ornithine phenylacetate; (L-ornithine·benzeneacetate salt (1:1), CAS-RN 952154-79-9). The molecular formula is $C_8H_7O_2 \cdot C_5H_{13}N_2O_2$.

7.2 Packaging, Supply and Labeling of Study Drug

The OCR-002 study drug will be supplied by Ocera Therapeutics, Inc. (Ocera) as a sterile small volume parenteral in single-use, 50 mL vials (200 mg/mL, 10g/vial) with a pH of approximately 6.6. Each vial contains a 1:1 molar concentration of ornithine phenylacetate in sterile water for injection with no other excipients.

The OCR-002 drug product in the vials must be diluted prior to use and is **NOT** intended for direct injection. The product will be supplied as a 4-fold hypertonic concentrate and requires dilution under aseptic conditions prior to use. Total volume of the i.v. infusion preparation is targeted to 500 mL.

Instructions will be provided to the clinical study site by Ocera that will further detail the preparation, labeling, and storage of OCR-002 in a Manual of Operations. The Manual will also instruct the pharmacist regarding preparation time before the start of the IV infusion on each infusion day, which should be as short as possible to assure maintenance of sterility given need for compounding (infusions must be prepared each day).

7.3 Storage, Handling and Dispensing

Vials of OCR-002 will be sent to the participating clinical site Investigator using standard, monitored, cold shipping methods. A Study Drug Shipping and Accountability Log will be maintained for all study drug shipped to any participating clinical site. Study drug will be stored in a secure area at the investigative site to prevent unauthorized access. Vials of OCR-002 should be stored at controlled refrigerated conditions of 2-8°C. A pharmacist or designee will prepare the IV infusion of OCR-002. The infusion bags will be labeled by the pharmacist with the following as a minimum: study number, patient number, and dose.

7.3.1 Accountability Procedures and Return or Destruction of Clinical Supplies

All study drug supplies will be used only in this clinical study and must not be used for any other purpose. The Investigator and/or designated study pharmacist must ensure that the supplies are stored in a secured area, with access limited to authorized study personnel. The Investigator is responsible for the accountability of study drug, including reconciliation and record maintenance at the clinical study site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain study drug accountability records throughout the study, including a record of the dates and amounts of study drug received, amount dispensed, and the amount unused.

A Drug Dispensing Log will be maintained and contain, at minimum, the following

information:

Identification of the patient for whom the infusion was prepared, including the patient identification number assigned for the study.

Date and quantity of drug prepared for each patient.

Any product accidentally or deliberately destroyed.

The inventory must be available for inspection during the study by the study monitor. All study drug supplies (used and unused) will be accounted for on the Study Drug Accountability Log.

Following reconciliation, the empty or partially used vials should be destroyed according to the standard operating procedures (SOPs) established by the study site or governing institution. The Investigator will document the destruction of any study drug supplies.

At the end of the study, unused drug supplies will be destroyed by the Investigator according to local procedures, provided that such disposition does not expose humans to risks from study drug. Records shall be maintained by the Investigator of any such disposition of study drug, which must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of study drug.

7.4 Timing of Dosing and Administration of OCR-002 Infusion

Study drug dosing should be initiated as soon as possible upon admission to the registry but only after obtaining informed consent, ensuring all eligibility criteria are confirmed to be met and completing the initial baseline evaluation period. The window between obtaining informed consent and initiation of OCR-002 infusion may be up to 32 hrs in order to complete any pre-study drug initiation requirements and/or to provide a time frame for study drug administration. Each cohort will receive a continuous infusion of OCR-002 for up to 5 days (between 0 to 120 hours).

7.5 Treatment Compliance

Staff of the clinical study unit will supervise the IV infusion of study drug. The date and time of infusion start, infusion stop, and the total volume administered will be documented in the source records. In the case of interruption of infusion for any reason, the study drug will not be restarted if more than 2 hours has elapsed. If for any reason the infusion is interrupted or stopped prior to the full administration, the times and circumstances of the interruption/stoppage will be recorded. It is anticipated that patients will continue to remain in the hospital for a minimum of three days after start of study.

7.6 Prior and Concomitant Medications

Throughout the study, the Investigator may prescribe concomitant medications deemed necessary to provide adequate supportive care. Standard therapy will include, but is not limited to, the administration of NAC, third generation cephalosporins, hypertonic saline and mannitol.

All concomitant medications taken during treatment must be recorded in the source documents and transcribed onto the appropriate pages of the CRF.

Concomitant administration of drugs known to interfere with renal excretion of phenylacetylglutamine or those medications that may induce hyperammonemia, such as **haloperidol, valproic acid and systemic corticosteroids, are prohibited during the study**.

Alternative ammonia modifying agents such as lactulose and rifaximin are not considered standard of care and their use is prohibited during the study period, as is the use of therapeutic hypothermia. However, spontaneous (non-induced) hypothermia of a mild-to-moderate degree does not require correction.

7.7 Precautions, Contraindications and Warnings

Adverse events should be treated in accordance with standard clinical practice. Appropriate emergency medication and equipment must be available during the confinement periods, together with personnel trained to deal with medical emergencies. The Investigator (or other co-investigator on the study team) must be readily available at all times until patients have completed the treatment period.

Prior to hospital discharge, patients will be evaluated to determine if there are any clinically significant changes from baseline. Patients with significant findings must remain in the hospital for further observation and/or treatment until the condition is either explained, resolved, or no longer requires close observation. Any patient who develops an SAE will be followed until a probable diagnosis and the relationship to study drug have been determined, and until the AE has resolved, no longer requires further follow-up, or a new chronic baseline has been established.

8 STUDY PROCEDURES BY STUDY DAY

The procedures and evaluations at each visit are outlined below.

8.1 Screening

Patients will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Individuals who are identified during screening as not eligible for the study need not complete all screening procedures. The reason for ineligible status will be documented on the Screen Failure Log.

The following procedures will be obtained or performed to evaluate each patient's general health and qualifications for participation in the study:

- Demographic information including gender, date of birth, race and ethnicity;
- Medical and medication history over the past 30 days, including prescription and non-prescription over-the-counter medications, herbal medications, vitamins, and minerals;
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia* and in female patients, a pregnancy test**;
  *** Venous sampling is the protocol-preferred method of collection for ammonia samples. Arterial ammonia samples will be accepted if this is the available method; however, this same method should be used for all subsequent ammonia samples for the patient.**

**Urine pregnancy test or blood human chorionic gonadotropin (hCG) is acceptable.

- Urinalysis***;
  ***Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Physical examination, including height and weight (body mass index will be calculated based on these variable), and vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature);
- 12-lead ECG;
- Neurological battery, including
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- Review inclusion and exclusion criteria; and
- Signed, written informed consent.

The start of the initial infusion may begin after obtaining signed informed consent; or, up to 32 h after obtaining consent should the time be necessary to complete any pre-study drug initiation requirements and/or to provide a time frame for study drug administration. Patients will be considered enrolled once the informed consent has been obtained, all eligibility criteria have been met, and the study drug infusion initiated.

8.2 Assessments at Baseline

- Collection of blood for hematology, coagulation, clinical chemistry, ammonia* and PK*;
  ***The ammonia and plasma PK samples must be taken not more than 8 hours prior to the start of the initial study drug infusion. Venous sampling is the protocol-preferred method of collection for ammonia samples. Arterial ammonia samples will be accepted if this is the available method; however, this same method should be used for all subsequent ammonia samples for the patient.**
- Vital signs and abbreviated physical exam;
- Neurological battery**, including
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
  ****Neurological exams at the Baseline visit should be performed within 8 hours prior to the start of the initial study drug infusion.**
- 12-lead ECG;***
  *****The ECG at the Baseline visit should be completed prior to the start of the initial study drug infusion.**

8.3 Assessments during Study Treatment

Treatment Day 1 - Time "0" (T0)

Treatment Day 1-T0 is the start of the initial study drug infusion. At this time, each patient will receive an initial infusion rate of OCR-002; thereafter, up and down titration decisions will be based on the patient's tolerance of the study drug infusion, no noteworthy side effects, as well as their Cohort dosing level assignment into the study. The following additional procedures and evaluations are conducted at Treatment Day 1–T0 once the study drug infusion begins:

- OCR-002 Initial Infusion:
  Dose Levels 1 through 3: initial infusion rate of 0.139 g/hour for the first 12 hours; continuation at this infusion rate for more than the first 12 hours is dependent on the patient's tolerance of the infusion, no noteworthy side effects, and the patient's Cohort dosing level assignment.

  Dose Level 4: initiate infusion rate at the full dose level of 20g/24h (approximately .83g/h) without further dose escalation for a maximum time of 120 hours provided the dose level is well tolerated with no noteworthy side effects.
- Urinalysis*;
  *Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Begin 0-12h urine collection interval;
- Collection of concomitant medications (if applicable);
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- Begin continuous AE review and reporting**.**

Each event scheduled for this time point and subsequent time points during the treatment period has a collection window of +/- 3 hours with reference to Treatment Day 1-T0 as time of start of initial study drug infusion, with the exception of ammonia sampling, which has a collection window of +/- 1 hour.

Treatment Day 1 at 6 hrs

- Ammonia collection;
- Collection of concomitant medications (if applicable);
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable);
- Document urine volume; and
- AE review and reporting.

Treatment Day 1 at 12 hrs

- OCR-002 Infusion for Dose Level 2 (the infusion rate will increase to 0.277 g/hour for the remainder of the study; for Dose Level 3, the infusion rate will increase to 0.277 g/hour for the next 12 hours), provided previous dose levels are well tolerated with no noteworthy side effects and the patient's Cohort dosing level assignment.

  Dose Level 4 - continue on maintenance infusion of OCR-002;

- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Vital signs and abbreviated physical exam;
- Neurological battery, including
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable);
- 12-lead ECG*;
  ***The ECG should be completed prior to study drug escalation on Treatment Day 1 at 12 Hours (Dose Levels 2 and 3).**
- Document urine volume, take a sample from 0-12h urine volume, and-begin 12-24h collection interval; and
- AE review and reporting.

Treatment Day 1 at 18 hrs

- Ammonia collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

End of Treatment Day 1 at 24 hrs / Day 2 at 0 h

- OCR-002 Infusion for Level 3 dosing only (the infusion rate will be increased to 0.416 g/hour for the remainder of the study), provided previous dose levels are well tolerated with no noteworthy side effects and the patient's Cohort dosing level assignment.

  Dose Level 4 - continue on maintenance infusion of OCR-002;
- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Urinalysis*;
  *Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG**;
  ****The ECG should be completed prior to study drug escalation on Treatment Day 2 at 0 Hours (Dose Levels 2 and 3).**

- Document urine volume, take a sample from 12-24h urine volume, and start 24-36h collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

Treatment Day 2 at 6 hrs

- Ammonia collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

Treatment Day 2 at 12 hrs

- Continue on maintenance infusion of OCR-002;
- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;
- Document urine volume, take a sample from 24-36h urine volume, and start 36-48h urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

Treatment Day 2 at 18 hrs

- Ammonia collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

End of Treatment Day 2 at 24 hrs/ Day 3 at 0 h

- Continue on maintenance infusion of OCR-002;
- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;

- Urinalysis*;
  *Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;
- Document urine volume, take a sample from 36-48h urine volume, and start 48-72h urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

Treatment Day 3 at 12 hrs

- Ammonia collection;
- Collection of concomitant medications (if applicable);
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

End of Treatment Day 3 at 72 Hours / Day 4 at 0 h

- Continue on maintenance infusion of OCR-002**;**
- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Urinalysis*;
  *Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;

- Document urine volume, take a sample from 48-72h urine volume, and start 72-96h urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

End of Treatment Day 4 at 96 Hours / Day 5 at 0 h

- Continue on maintenance infusion of OCR-002;
- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Urinalysis*;
  * Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;
- Document urine volume, take a sample from 72-96h urine volume, and start ~~next 24~~ 96-120h urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

Completion of the Last Infusion (at time infusion is stopped)

The following assessments should be administered on all patients who received an infusion of the study drug, including those patients who received the full course of study drug treatment and those patients who do not complete the entire course of study drug treatment.

- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Urinalysis*;
  * Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;

- Document urine volume, take a sample from 96-120h urine volume, and start 120-144h urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

24 hours Following Completion of the Last Infusion

The following assessments should be administered on all patients who received an infusion of the study drug, including those patients who received the full course of study drug treatment and those patients who do not complete the entire course of study drug treatment.

- Collection of concomitant medications (if applicable);
- Collection of blood for hematology, coagulation, clinical chemistry, ammonia and PK;
- Urinalysis*;
  * Urinalysis: dipstick plus microscopic evaluation of sediment, if clinically indicated.
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- 12-lead ECG;
- Document urine volume and take a sample from 120-144h urine volume; end urine collection;
- Continuous monitoring and collection of mean arterial pressure;
- Continuous monitoring and collection of intracranial pressure (ICP) (if applicable); and
- AE review and reporting.

*8.*4 *Follow Up or Early Termination*

A safety follow-up visit will be performed approximately 30 days from Treatment Day 1-T0 (start of infusion) for all patients who completed the study drug infusion period or who discontinued the study drug infusions but remain in the study.

- Collection of blood for hematology, coagulation, clinical chemistry, ammonia;
- Vital signs and abbreviated physical exam;
- Neurological battery, including:
  - Glasgow Coma Scale;
  - West-Haven Scale; and
  - O-Log Scale;
- Review and reporting of Serious Adverse Events (SAEs).*
  * Non-serious adverse events (AEs) and Serious Adverse Events (SAEs) are collected from Treatment Day 1 at T0 through 24 hours Following Completion of the Last

Infusion. After the 24 hours Following the Completion of the Last Infusion time point, only SAEs are collected through the Day 30 post treatment period.

9 SAFETY ASSESSMENTS

Details for safety assessments will be recorded in both the CRF and the patient's source documents. During the study, the Investigator or study site personnel will be responsible for querying and recording AEs and SAEs. Adverse events will be recorded from the start of the initial administration of OCR-002 (Treatment Day 1-T0) until 24 hours Following the Completion of the Last Infusion. Serious adverse events will be recorded from Treatment Day 1-T0 through the remainder of the study period. AEs will be evaluated by the Investigator for severity, seriousness, and relationship to study drug as outlined below. Untoward medical events which occur *after* signature of the informed consent *but before* study drug administration will be recorded as medical history.

9.1 Adverse Events

9.1.1 Adverse Event Definition

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event:

- can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product whether or not considered related to the medicinal product;
- can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose; and/or
- can be any sign or symptom not present at baseline, or if present at baseline, worsens in frequency and/or severity, independent of causal relationship to the investigational product.

9.1.2 Expected Adverse Events (with respect to study drug)

An AE or SAR is considered "expected" if: it is listed in the investigational brochure (IB); or, it is listed at the specificity or severity that has been observed; or, if an IB is not required, it is consistent with the risk information described in the general investigational plan. These adverse events are identified in the Investigator Brochure as possibly associated with the study drug, and therefore would be considered EXPECTED adverse events:

- Tachycardia
- Hypotension
- Dizziness
- Nausea
- Vomiting

- Headache
- Chills
- Somnolence
- Restlessness

Acute liver failure is associated with significant morbidity and mortality. Specifically, acetaminophen ALF carries a 28-30% mortality, while ALI carries a 10% mortality. Given these circumstances, determining drug effect and a causal relationship is particularly difficult. The following is a list of signs and symptoms that are expected to occur in patients with ALF or ALI. **These events will be collected and recorded but will not be reported on an expedited basis (e.g., IND safety report) unless the event otherwise qualifies for expedited reporting.**

System Organ Class/Preferred Term
Blood and Lymphatic System Disorders
Anemia
Leukocytosis
Neutropenia
Thrombocytopenia
Cardiac Disorders
Arrhythmias
Bradycardia
Tachycardia
Endocrine Disorders
Hyperglycemia
Hypoglycemia
Gastrointestinal Disorders
Abdominal Distension
Abdominal Pain
Ascites
Diarrhea
Flatulence
Jaundice
Nausea
Upper gastrointestinal bleeding
Vomiting
General Disorders and Administration Site Conditions
Asthenia
Fatigue
Hypothermia
Malaise
Peripheral edema
Pyrexia
Hepatobiliary Disorders
Ascites
Hepatic encephalopathy
Hepatic failure
Hepatomegaly
Jaundice
Portal hypertension
Infections and Infestations

Bacteremia
Pneumonia
Sinusitis
Upper respiratory tract infection
Urinary tract infection
Investigations
Alanine aminotransferase increased
Aspartate aminotransferase increased
Cardiac murmur
Metabolism and Nutrition Disorders
Anorexia
Hyperglycemia
Hyperkalemia
Hypernatremia
Hyperphosphatemia
Hypervolemia
Hypoalbuminemia
Hypocalcemia
Hypomagnesemia
Nervous System Disorders
Headache
Hepatic Encephalopathy
Hyperreflexia
Memory impairment
Psychiatric Disorders
Insomnia
Renal and Urinary Disorders
Azotemia
Oliguria
Renal failure, acute
Respiratory, Thoracic, and Mediastinal Disorders
Dyspnea
Epistaxis
Pleural effusions
Pulmonary edema
Tachypnea
Skin and Subcutaneous Disorders
Pruritus
Purpura
Vascular Disorders
Gastric hemorrhage
Hematoma
Hypotension

9.1.3 Other Adverse Events

In the STOP-ALF Trial, any medical conditions not present prior to the start of the initial study drug infusion but that emerge after the start of the initial study drug infusion are considered AEs. Each AE is a unique representation of a specific event used for medical documentation and scientific analysis. Adverse Events encountered from Treatment Day 1-T0 through 24 hours Following the Completion of the Last Infusion will be recorded, and Serious Adverse Events from Treatment Day 1-T0 through the Day 30 post treatment period will be recorded. Specific clarifications for reporting other events are provided below.

Pre-existing medical conditions or unchanged, chronic medical conditions

All medical conditions present upon arrival to the hospital and prior to the start of the initial study infusion are considered pre-existing conditions and are part of the patient's medical history. Those events that manifest with the same severity, frequency, or duration subsequent to study drug administration need not be recorded as adverse events. These medical conditions should be documented adequately on the medical history and/or physical examination CRFs.

Pre-existing medical conditions or unchanged, chronic medical conditions consistent with natural disease progression are NOT considered AEs unless the pre-existing medical condition is judged by the Investigator to have worsened in severity or frequency or changed in character.

Exacerbation of Pre-existing medical conditions

A pre-existing medical condition judged by the Investigator to have worsened in severity or frequency or changed in character is considered an adverse event and reported through 24 hours Following the Completion of the Last Infusion. If the judgment is that it is a serious adverse event, it is reported through the Day 30 post treatment period.

Lab Abnormalities

If a clinically significant lab abnormality is considered an expected manifestation of the pre-existing disease, it may not require AE reporting if it does not indicate treatment-emergent worsening or new evolution of a medical condition.

Treatment-emergent laboratory abnormalities (e.g., clinical chemistry, hematology, urinalysis), or other investigational studies (e.g., ECGs, X-rays) independent of an underlying medical condition that (a) require medical or surgical intervention or (b) lead to investigational medicinal product interruption or discontinuation **must be recorded as AEs**. If a new laboratory abnormality, ECG or radiographic finding is associated with new signs and/or symptoms (clinical manifestations) an AE should be recorded, either reflective of the abnormality based on the specific investigation(s) or the overall medical condition which is the etiology of that abnormality.

9.1.4 Adverse Reaction

An adverse reaction is any adverse event caused by a drug.

9.1.5 Suspected Adverse Reaction

A Suspected Adverse Reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

For purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A SAR implies a lesser degree of certainty about the causality than an adverse reaction where the adverse event is caused by the drug.

Suspected adverse reactions are a subset of all adverse events for which there is a "reasonable possibility" that the drug caused the event. A "reasonable possibility" exists if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- *A single occurrence* of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis, Stevens-Johnson Syndrome, anaphylaxis)
- *One or more occurrences of an event* that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- *An aggregate analysis of specific events* observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.1.6 Unexpected Adverse Event or Suspected Adverse Reaction

An AE or SAR is considered "unexpected" if: it is not listed in the investigational brochure (IB); or, it is not listed at the specificity or severity that has been observed; or, if an IB is not required, it is not consistent with the risk information described in the general investigational plan. "Unexpected" also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.2 Serious Adverse Events

A serious adverse event (SAE) is any AE or SAR that results in any of the following outcomes:

1. Death;
2. A life-threatening AE (this refers to an event in which the patient was at risk of death at the time of the event and not to an event which hypothetically might have caused death if it were more severe.);
3. In-patient hospitalization;
4. Prolongation of existing hospitalization;
5. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
6. A congenital anomaly/birth defect;
7. An important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Serious adverse events should not be reported for hospitalization or prolonged hospitalization in the following scenarios: for a diagnostic or elective surgical procedure related to a pre-existing condition; to allow for an efficacy measure for the study; or, for a planned surgical procedure that was not the result of a condition worsening due to participation in the study.

When reporting AEs, SAEs, or SARs, the Investigator should avoid colloquialisms and abbreviations and use correct medical terminology. Additionally, if known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms. If a

diagnosis is unknown at the time of initial reporting but subsequently established, it should be reported as follow-up information.

Pre-existing medical conditions are reported as AEs or SAEs only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

9.3 Reporting Adverse Events from Participating Clinical Sites

Safety assessments will consist of monitoring and reporting all adverse events from the start of the initial study drug infusion through 24 hours following the final infusion of study drug (typically Day 5) or for 24 hours following the final infusion of study drug for those patients who do not complete the entire course of study drug administration. Adverse events that do not meet the definition of "serious" or "suspected adverse reactions" will be reviewed periodically throughout the trial to identify any previously unidentified trends or other safety issues.

In order to ensure prompt reporting of adverse events, we require that all non-serious adverse events must be entered into the WebDCU™ database system within 5 working days following the completion of Treatment Day 1-T0 through 24 hours Following the Completion of the Last Infusion study phases (e.g., Day 1 phase is Tuesday, 02JAN2012; any AEs occurring in that phase must be entered into the WebDCU™ database system no later than Monday, 09JAN2012).

9.4 Reporting Serious Adverse Events and Suspected Adverse Reactions from Participating Clinical Sites

With regard to serious adverse events and suspected adverse reactions, both expected and unexpected and regardless of whether the SAE/SARs are considered related to the study drug and/or the disease, they will be followed in a rigorous review process through the entire trial period. Clinical performance sites are instructed to report all fatal events, unanticipated problems and other serious adverse events and suspected adverse reactions in the WebDCU™ database system **within 24 hours of first knowledge of the event**. Additionally, all current study data for that particular patient must be entered to allow for timely review by the Internal Medical Monitor (IMM) and the independent external Medical Safety Monitor (MSM). In adjudicating cases at UT Southwestern, an alternate IMM will serve in place of the IMM.

The clinical site Investigator, on the basis of his or her clinical judgment and the following definitions, determines the relationship of the adverse event to the protocol intervention as one of the following:

- Definitely: any adverse reaction and those adverse events that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive, e.g., it is confirmed by de-challenge and re-challenge.
- Probably: An AE that might be due to the use of the study agent. The relationship in time is suggestive, e.g., confirmed by de-challenge. An alternative explanation is less likely,

e.g., concomitant drug(s), concomitant disease(s); and, other causes have been eliminated or are unlikely.

- Possibly: An AE that might be due to the use of the study drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable.
- Unlikely: An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely or that there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.
- Not related: An AE for which there is no possible relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible; or a causal relationship to study drug is implausible).

The clinical site investigator in making determinations of the severity of the adverse event should consider the following for the four classes of severity of the event as it occurred:

- Mild/Grade 1: does not interfere with daily living and no medications are needed to relieve event;
- Moderate/Grade 2: somewhat interferes with daily living or medications needed to relieve event;
- Severe/Grade 3: incapacitating, activities of daily living are prohibited because of the event;
- Life threatening or Death/Grade 4.

Serious adverse events and suspected adverse reactions are collected from the start of the time of enrollment through study completion, i.e., Day 30, death, or withdrawal of consent.

9.5 Review of Serious Adverse Events and Suspected Adverse Reactions

Upon entry of a serious adverse event or suspected adverse reaction in the WebDCU™ system, the system triggers automatic e-mail notification of the SAE/SAR to the Project Manager and the IMM. When the SAE/SAR report has been reviewed and deemed to be adequate, the SAE/SAR is forwarded by the Project Manager to the MSM.

The MSM conducts independent reviews of all SAEs and SARs entered into WebDCU™. Should the IMM or MSM need additional patient data to conduct his/her review, those data may be accessed on the WebDCU™. The MSM submits his/her opinion on whether the SAE or SAR was (a) in fact, serious, (b) unexpected, and (c) related (with reasonable possibility) to the study drug within 72 hours of notification of the SAE or SAR. The MSM may contact the site for more information or discussion. Should it be determined that the narrative included in the SAE/SAR needs to be amended or enhanced, the SAE/SAR case report form will be returned electronically to the clinical site investigator for enhancement or amendment. If the Investigator and the MSM believe the SAE or SAR is serious, study drug-related (reasonable possibility, probably or definitely), and unexpected, the SAE or SAR requires expedited reporting. When

there is disagreement between the Investigator and the MSM on one or more of these criteria, the SAE or SAR will be reviewed by the IMM as the arbiter as to expedited reporting.

9.6 Expedited Reporting of Serious Adverse Events or Suspected Adverse Reactions

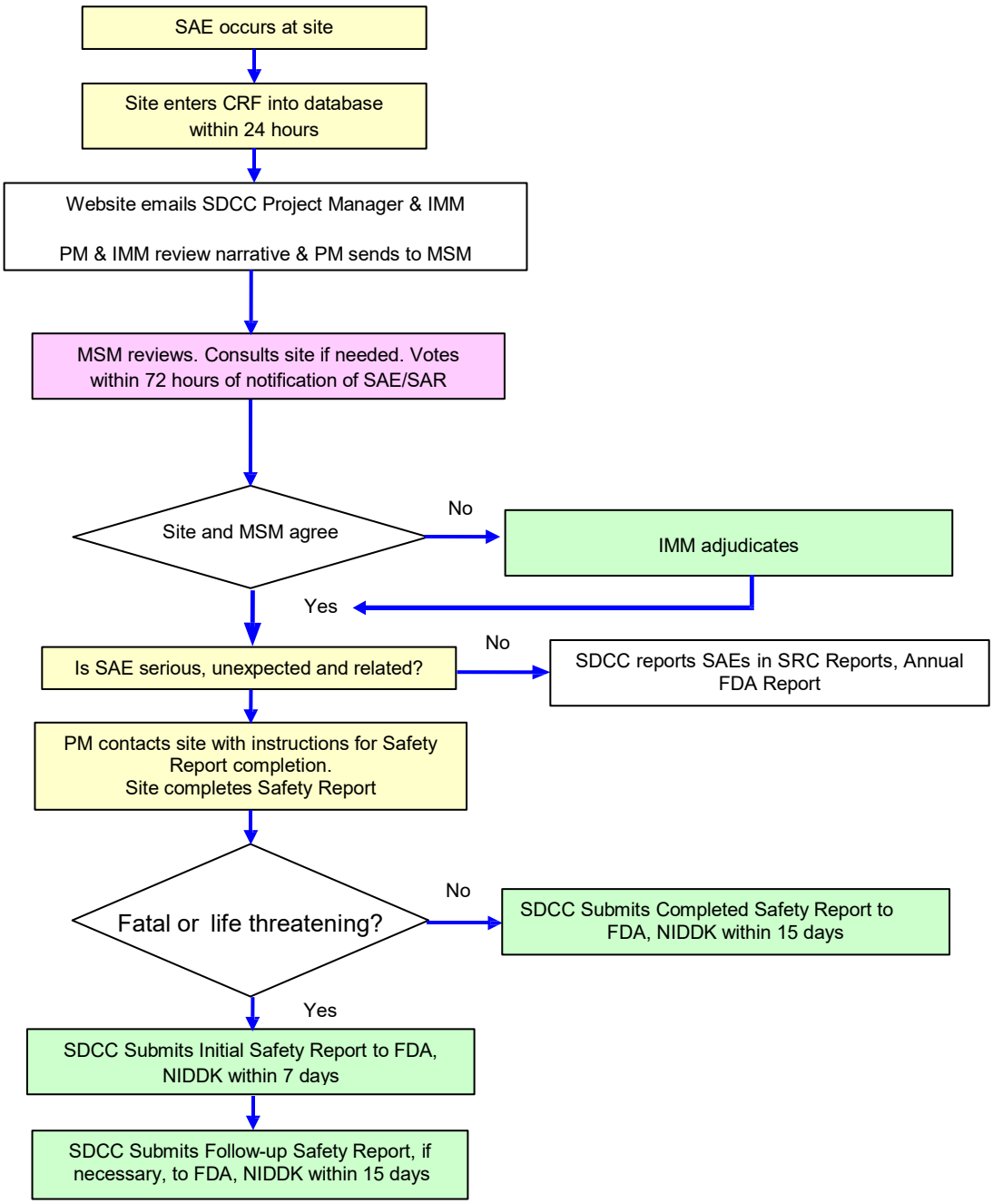
When it is confirmed that an event requires expedited reporting, the Project Manager (PM) contacts the site with instructions for completion of a safety report form. A safety report form (pre-populated with previously entered CRF data) is automatically posted in the WebDCU™ system and the site staff enters any remaining required information. Following the site's completion of the safety report form, the PM submits the report to the FDA within the regulatory timelines. The initial safety report for a SAE/SAR that was fatal or life-threatening will be submitted to the FDA within 7 days of the Executive Committee being made aware of the SAE; if the event was not life- threatening or did not result in death, the report will be submitted to the FDA within 15 days of the Executive Committee being made aware of the SAE/SAR.

The safety report filed with the FDA is posted on the WebDCU™. The PM notifies, via email, the Safety Review Committee (SRC), Ocera Therapeutics, Inc., the Trial Executive Committee members and all participating clinical site PIs and Study Coordinators (SCs) that an expedited safety report has been filed with the FDA and is available for review on the WebDCU™ (a link to the document is provided in the email communication). Each clinical site PI is then responsible for reporting to the IRB at that individual clinical site.

Follow-Up Reporting of Expedited Serious Adverse Events/ Suspected Adverse Reactions

After the submission of the initial safety report, the clinical site staff is responsible for obtaining any follow-up information about the SAE/SAR. All follow-up information should be actively sought by the clinical site staff and must be entered in the database as soon as the information becomes available. The PM distributes the follow-up safety report to all parties receiving the initial report.

Study SAE Reporting and Monitoring Flowchart



9.7 Safety Review Committee

The Safety Review Committee (SRC) will consist of three experienced ALFSG clinicians and a clinical pharmacologist with experience in clinical trials and PK measurement. All are independent of any clinical site participating in the trial and will exercise oversight of the safety of trial participants, review periodic safety reports prepared by the SDCC biostatistician, request additional data/information (if necessary), and advise the trial Sponsor and Executive Committee regarding continuation/discontinuation of the study. A primary responsibility of the SRC is to review the safety and PK data (as provided by the SDCC) and to provide recommendations on proceeding to the next dose level.

Throughout the trial the SRC will review all safety data at regular intervals and after each dose level in each cohort. In addition, the SRC will review safety and PK data for the evaluable Cohort 1 patients who complete Dose Levels 1 and 2 to determine if it is safe to enroll Cohort 1 patients into Dose Level 3 and Cohort 2 patients into Dose Level 1. Another review will be conducted prior to enrolling Cohort 2 patients into Dose Level 3. During these two specific reviews, enrollment will be paused. The SRC will also review the safety and PK data for the evaluable Cohort 2 patients who complete Dose Level 3 to determine if it is safe to enroll Cohort 2 patients into Dose Level 4. Upon completion of the study, the SRC will review safety data for all enrolled patients.

In addition to the SRC review, the IMM in consultation with the external MSM will closely monitor the incidence rates of all adverse events reported and will alert the SRC if a trend is observed for AEs collected from Baseline through the 24 hours Following the Completion of the Last Infusion period and for SAEs collected from Baseline through the Day 30 post treatment period. A summary of all AEs and SAEs, a summary of all expedited safety reports, and a listing of all patients who were terminated from the study due to study-related adverse events, will be included in reports submitted by the SDCC to the Executive Committee, the MSM, and the SRC. An annual report will be submitted to the FDA.

9.7.1 Trial Stopping Criteria

An apparent, consistent and persistent evidence of net harm that tends to overwhelm any benefit may allow for premature termination of the study.

Continuing enrollment into each dose level of each cohort will be determined on an ongoing basis and at periodic intervals as outlined in Section 9.7. The SRC will receive a report on all reported AEs and SAEs as well as the individual listings of patient with any specific event of interest. The finding of any unexpected SAEs of Grade 3 that are considered not related to acute liver failure in 2 or more patients within a given dose level or of Grade 4 or higher in one patient will lead to suspension of recruitment and review of the complete data by the MSM. Following the MSM's review, the safety report (and any comments from the MSM) will be sent to the SRC. The SRC will make the final recommendation for early termination versus continuation of the study after reviewing the available data. The decision will be guided by safety.

If the SRC does not stop the trial, the trial will proceed with enrollment as outlined in section 9.7 for Cohorts 1 and 2. In addition to the planned evaluations, the MSM and SRC will receive

quarterly safety summary reports of enrollment, baseline demographics, withdrawals from treatment and all AEs and SAEs with information on relation to study treatment.

9.8 Safety Assessments

Laboratory Test Results

Blood and urine will be collected at Screening, Baseline (blood only), Treatment Day 1 -T0 (urine only), Treatment Days 1, 2, 3, 4 and 5, at the Completion of the Last Infusion, and 24 hours Following the Completion of the Last Infusion (or Treatment Discontinuation date) for safety laboratory tests to be conducted at local laboratories. Safety assays include:

- Liver function tests (LFTs): Total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT);
- Coagulation: Prothrombin time reported as the international normalized ratio (INR); and
- Urinalysis: dipstick plus microscopic evaluation of sediment if clinically indicated.

Any laboratory test result considered by the investigator to be clinically significant should be considered an AE.

If clinically significant abnormal laboratory values occur during the trial, the patient may be retested regularly until repeat test results return to normal, stabilize, or are no longer clinically significant.

Other Safety Assessments

Vital signs (blood pressure, temperature, heart rate, and respiration) will be measured at Screening, Baseline, Treatment Days 1, 2, 3, 4 and 5, at the Completion of the Last Infusion, and 24 hours Following the Completion of the Last Infusion inclusively. Height will be measured once (at Screening).

Physical examinations will be performed at Screening, Baseline, Treatment Days 1, 2, 3, 4 and 5, at the Completion of the Last Infusion, and 24 hours Following the Completion of the Last Infusion, inclusively (or Treatment Discontinuation Visit).

Single 12-lead ECGs will be performed at Screening, Baseline, Treatment Days 1, 2, 3, 4 and 5, at the Completion of the Last Infusion, and 24 hours Following the Completion of the Last Infusion, inclusively and will be evaluated locally according to usual site procedures.

Inter-current Illness and Pre-Existing Diseases

Inter-current illnesses, including signs/symptoms of a pre-existing disease state (medical history), that are present at or before study drug administration (including those that manifest between signature of the informed consent and administration of study drug) are to be recorded as medical history/pre-existing conditions. Those events that manifest with the same severity, frequency, or duration subsequent to study drug administration need not be recorded as AEs. However, incidents for which there is an increase in severity or duration of the inter-current illness or pre-existing disease must be reported on the AE CRF.

10 DATA MANAGEMENT

10.1 Data Processing

Data management is handled by the Data Coordination Unit (referred to in this document as the SDCC), which is housed in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC). All activities are conducted in coordination with the Trial Executive Committee and the Clinical Centers. Case Report Forms (CRFs) have been developed by the SDCC with input from the Trial Executive Committee. Electronic copies of the CRFs are made available to the Clinical Centers via the WebDCU™ to be used as worksheets for capturing data for the Trial. The study database has been developed in Microsoft SQL Server based on the approved CRFs. This system allows for web-based data entry and management. The data are captured and entered (single keyed) at the Clinical Centers via the web interface. Data must be entered into the database at the Clinical Centers within 5 days of assessment/data collection. The data are managed (including data queries) by the SDCC staff using a secured Trial website.

During the design of the database, automated consistency checks and data validation rules are programmed to check for potential data errors, including missing required data, data out of pre-specified range, data conflicts and disparities within and among the CRFs. All validation rules are outlined in the Data Management Plan generated by the SDCC. In addition to the study database, the SDCC provides the Clinical Center staff access (via password) to a standard set of web-enabled tools, including patient visit calendar, accrual status, CRF completion status, and outstanding DCR status pertaining to their respective Centers.

The SDCC develops, validates, and maintains the study database and provides independent oversight and management of the flow, entry, and quality assurance of data collection activities. The SDCC also provides statistical support, including reports to the SRC and Medical Safety Monitor; and, where necessary, shields blinded investigators from access to unblinded data during the performance of the trial. The SDCC is responsible for the enrollment scheme, final statistical analysis plan and final data analysis.

10.2 Data Security and Confidentiality

During the course of the trial, user access to the files with patient identifiers, treatment assignment and files with study outcomes will be restricted to core staff with any exceptions to be approved by the Executive Committee.

In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent. No information, which identifies a specific person, hospital, or physician, will be released to, or discussed with anyone other than study staff members.

Because the SDCC uses a web-based system, source documents and CRFs will remain at the participating sites. The study database only identifies study patients by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific patient except through a password protected system. All collected information about a patient will be stored by a unique identification code.

All SDCC personnel are certified by the NIH Office of Human Subjects Research in the Protection of Human Research Subjects course.

10.3 Data Quality Assurance

Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure integrity of the study data and document processing system reliability. An appointed site monitor will perform reviews of source documents and case report form information at the sites to confirm accuracy of data capture. The STOP-ALF Site Monitoring Plan details the monitoring plan and facilitates compliance with Good Clinical Practice (GCP) guidelines, applicable FDA regulations (21 CFR 812 and 813), and the FDA's "Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring". The monitoring plan includes a combination of central, remote and on-site monitoring, and these findings will be used to identify and correct problems in data collection.

To ensure monitoring responsibilities are performed to the fullest extent possible, an experienced independent clinical research associate(s) (monitor) performs data verification for the trial either on-site or remotely, should direct access to patients' electronic medical records be permitted by the institution. For the first evaluable patient enrolled at any site, 100% of the data will be verified to source documents. For subsequent patients, a checklist of key outcome and safety data variables requiring source document verification (SDV) has been developed based on the trial's safety and efficacy endpoints. The checklist ensures that a target of no less than 40% of the clinical data submitted to the STOP-ALF database are verified against source documents at the performance sites prior to finalization of the database. Of the data on the checklist, the safety and efficacy variables represent approximately half of the data to be verified. The remaining half of source monitored data include: 100% of deaths and 100% of serious adverse events and source data reviews based on the per-patient evaluation of safety parameters defined in the protocol. All data monitored on site are verified for accuracy and thoroughness using the most appropriate source documents for all patients.

Signed informed consent documents and HIPAA documentation are monitored for all patients, along with those items outlined in the STOP-ALF Site Monitoring Plan.

Any omissions and corrections to data submitted to the WebDCU™ database are noted and queries are generated either on-site or remotely by the monitor and/or centrally by the SDCC staff.

The monitor may conduct a close-out monitoring visit either on-site or remotely, as determined by the SDCC staff based on the number of subject enrollments, amount and nature of outstanding items to be monitored, and if the monitor's direct access to the subjects' electronic medical record has been permitted by the institution. During a Site Closeout Visit, the monitor should follow the site close-out guidelines outlined in the current version of the STOP-ALF Site Monitoring Plan.

11 STATISTICAL PROCESS

11.1 Statistical Methods

Descriptive statistics will be used to evaluate safety, exploratory efficacy data, PK and PD.

11.2 Comparisons of Interest

Collected data will be evaluated overall and by cohort (patients with minimal renal dysfunction and those with compromised renal function).

11.3 Sample Size Determination

This is an exploratory pilot study and no formal sample size calculation was performed for this study.

11.4 Analysis Population

The intent-to-treat (ITT) population will include all patients who consented to the study, completed screening and were initiated intravenous infusion of study drug. The ITT population will serve as the basis for a sensitivity analysis of the PP results for all endpoints.

The per-protocol (PP) population (evaluable population) will include all patients who receive at least 72h of OCR-002 in accordance with protocol timelines. The PP population will be used for the primary analysis of all outcomes.

The safety population will include all patients who completed screening and were enrolled into the trial.

11.5 Interim Analysis

There are no interim analyses planned as this is an open-label study; however, safety data will be reviewed by the SRC continuously throughout the study period. In addition to specific dose level reports, quarterly safety reports on all enrolled patients will be provided to the SRC during the study period. These reports will include summary tables overall and by cohort and site on baseline characteristics, treatment completions and reasons for early treatment withdrawals, study completions rates and all outcomes related to safety information including all adverse events and serious adverse events.

11.6 Statistical Analyses

Tables and listings will be produced using SAS v9.2 or higher (SAS, Cary, NC). Data summaries by cohort group will be presented. For continuous variables, data will be summarized with the number of patients, mean, standard deviation, median, and minimum and maximum overall and by cohort. For categorical variables, data will be tabulated in frequency tables to display the number and proportion of patients for each category overall and by cohort. Baseline assessments for each outcome variable will be defined as the last measurement obtained before treatment initiation. Each point estimate will be presented with 2-sided 95% confidence intervals and all statistical tests will use a two-sided 5% significance level.

11.7 Safety Assessments

11.7.1 Adverse Events

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be listed by reported verbatim term and MedDRA-preferred term, start and stop date and time, study day, duration, severity, relationship to study drug, and seriousness. Additionally, data may be grouped for analysis by different levels of the MedDRA hierarchy. The incidence of AEs, the incidence of treatment-related AEs, and the severity of AEs will be tabulated by cohort.

The number and percentage of patients with SAEs and treatment-related SAEs and patients who withdraw due to an AE will be tabulated by cohort.

11.7.2 Clinical Laboratory Tests

Clinical laboratory test parameters will be listed for individual patients. Baseline for clinical laboratory parameters will be defined as the last evaluation before the start of the initial dosing with study drug. Summary statistics, including mean absolute change from baseline, will be calculated for each parameter and summarized.

11.7.3 Vital Signs

Vital signs results (systolic and diastolic blood pressure, pulse rate and body temperature) will be listed for individual patients. Each vital sign measure will be tabulated by evaluation time point. Baseline for vital signs measurements will be defined as the last evaluation before the beginning of the first OCR-002 infusion (which will generally be Baseline, pre-dose). Summary statistics, including mean absolute change from baseline, will be determined and tabulated for each measure.

11.7.4 Electrocardiograms

Means of the ECG intervals/durations will be listed for individual patients. Summary statistics, including mean absolute change from baseline, will be determined and tabulated by cohort.

11.7.5 Physical Exams

Physical examination findings at baseline will be listed. Clinically significant changes will be recorded as AEs. Symptoms of interest previously reported with OCR-002 will be recorded daily, including dizziness, headache, nausea, vomiting; daily monitoring of heart rate in relation to infusion initiation will also be recorded.

11.7.6 Plasma Ornithine, Phenylacetate, Phenylacetylglutamine and Glutamine Concentrations and Pharmacokinetic Parameters

Individual and mean plasma ornithine, phenylacetate, and PAGN concentrations at each sampling time point will be presented by listings and descriptive summary statistics. Plasma ornithine, phenylacetate, and PAGN concentration versus time profiles will be plotted.

In addition, individual and mean cumulative urinary PAGN output will be listed with descriptive statistics in tabular format.

Pharmacokinetic parameters will be calculated from plasma ornithine, phenylacetate, and PAGN. Individual plasma ornithine, phenylacetate, and PAGN parameters will be listed for each patient and summary statistics will be provided.

The following PK parameters will be calculated or derived from the data:

- Maximum observed plasma concentration (C_{max});
- Concentration at steady state (C_{ss});
- Clearance at steady state (CL_{ss}); and
- Interval estimates of exposure (e.g. $AUC_{0\text{-}24h}$) over multiple dosing days.

12 OBLIGATIONS OF THE INVESTIGATOR

All Investigators must comply with all applicable regulations. In addition, Investigators must follow local and institutional requirements pertaining, but not limited, to study drug, clinical research, informed consent (including the use and disclosure of protected health information), and IRB regulations. The Sponsor/Principal Investigator must notify the FDA, the SRC, all clinical site Principal Investigators, who are responsible for notifying their individual IRBs, and Ocera of any protocol amendments that are adopted after approval (sign-off) of the original protocol.

Except where the Investigator's signature is specifically required, it is understood that the term "Investigator" as used in this protocol and protocol-related documents refers to the Investigator at each site or appropriate study personnel that the Investigator designates to perform a certain duty. The Investigator is ultimately responsible for the conduct of all aspects of the study. Sub-Investigators or other appropriate study personnel are eligible to sign for the Investigator on designated CRF pages or laboratory reports; provided, such authority has been recorded as delegated to the Investigator and the Investigator is qualified to undertake such responsibilities.

12.1 Compliance with Good Clinical Practice

This study will be conducted in accordance with the 1997 International Conference on Harmonization (ICH) Guideline on Good Clinical Practice.

12.2 Institutional Review Board and Informed Consent Process

Prior to approval to participate in the study and receive study drug, the Institutional Review Board (IRB) for each clinical site must have approved the protocol and informed consent documents for a competent patient and/or a patient's legally authorized representative (LAR) or family member [as defined in 21CFR50.3(m)]. IRB renewal of approval of the protocol and informed consent documents must be obtained annually (or more frequently if required by an individual IRB) and for any subsequent protocol amendments.

The consent form must describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A signed consent form must be obtained from the patient, the legally authorized representative, a person with power of attorney, or a family

member and this fact must be documented in the patient's record. Copies of the consent form must be given to the patient, the LAR, or the family member and maintained in the patient's study binder. All signed informed consent documents will be reviewed and verified for accuracy and compliance by an independent Clinical Research Associate (CRA/monitor) during monitoring visits to participating clinical sites.

12.3 Source Documents

As defined in Section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6), source documents may include: original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification of accuracy and completeness; microfiches; photographic negatives; microfilm or magnetic media; x-rays; and patient files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

The PI and designees agree to maintain accurate CRFs and source documentation as part of the case histories. Source documents are the originals of any documents used by the PI or Sub-Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial.

The study CRFs will be available in printable format on the study website. The CRFs for each patient must be completed only by persons designated by the PI and who have data entry permissions for the study database. All data entered into the CRF must also be available in the source documents. The PI will allow designated STOP-ALF monitors and regulatory bodies to have direct access to the source documents to verify the data reported in the CRFs.

Once a patient completes the study, the PI must review the completed study book and sign the End of Study Form that acknowledges this review.

12.4 Retention of Documentation

In June 2005, Federal law extended the statute of limitations to six (6) years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct - - a minimum period of six (6) years.

Additionally, existing Federal regulations [56 CFR 56.115(b)] require that IRB records be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS and FDA at reasonable times and in a reasonable manner. At the end of three years, the IRB records may be boxed, labeled and sent to central storage for an additional 3-10 years. A log of stored records is maintained in the IRB office for retrieval if files are needed for audit or other purposes.

An agreement must be in place between the clinical site Principal Investigator and the Principal

Investigator/Sponsor regarding records that may be destroyed. Records will be maintained in a de-identified manner in a locked location to ensure confidentiality.

12.5 Confidentiality of Material Provided by Ocera

Any written materials provided by Ocera, as well as documentation, data, and all other information generated as part of this study will be held in strict confidence by the Investigator and participating clinical site staff. Conduct of this study will comply with all provisions of the Health Insurance Portability and Accountability Act of 1996.

12.6 Quality Assurance and Quality Control

The study will be conducted according to GCP and FDA guidelines and according to federal law.

12.7 Publication

Publication of the results of this trial will be governed by the policies and procedures developed by the ALFSG Executive Committee. All manuscripts pertaining to this study will be forwarded to the NIDDK staff for review before submission for publication. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161). The Executive Committee will follow NIH policies on data-sharing (as described at the site: http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm and any updates thereto).

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MEMORANDUM

TO: National Institutes of Health
U.S. National Library of Medicine

FROM: Valerie Durkalski-Mauldin, MPH, PhD
ALFSG Co-Principal Investigator
Statistical & Data Coordination Center (SDCC)
Department of Public Health Sciences
Medical University of South Carolina

DATE: 01May2018

RE: A Phase 2a Study to Evaluate the Safety and Tolerability of OCR-002 (ornithine phenylacetate) in the Treatment of Patients with Acute Liver Failure/Severe Acute Liver Injury (STOP-ALF)

Statistical Analysis Plan for ClinicalTrials.gov

The statistical process and analyses for the STOP-ALF Trial are outlined in Section 11 of the study protocol; a separate Statistical Analysis Plan was not compiled for the study.

_____
Valerie Durkalski-Mauldin, PhD

CC: William M. Lee, MD
ALFSG Grant Sponsor & Study Chair
STOP-ALF, Sponsor of IND
UT Southwestern Medical Center at Dallas, Principal Investigator