A Double-Blind, Placebo-Controlled Trial of Obeticholic Acid in Patients with *moderately severe* Alcoholic Hepatitis (AH)

Clinical Trial Protocol TREAT - 002

Version 1.7

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Disclosure

This study is conducted by the TREAT consortium which is funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to pursue translational investigations in alcoholic hepatitis. The TREAT Consortium is made up of investigators from Indiana University School of Medicine (Indianapolis, IN), Mayo Clinic (Rochester, MN) and Virginia Commonwealth University (Richmond, VA). Study drug and matching placebo are kindly provided by Intercept Pharmaceuticals, Inc.

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SPONSOR'S approval of the protocol

Reviewed and Approved by:

Dec 16, 2016

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Date

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SYNOPSIS

Title of Trial
A Double-Blind, Placebo-Controlled Trial of Obeticholic Acid in Patients with *moderately severe* Alcoholic Hepatitis (AH)

Name of Active Ingredient
Obeticholic Acid (OCA; 6α-ethyl chenodeoxycholic acid; 6-ECDCA) also known as INT-747

Indication
Moderately severe Alcoholic Hepatitis

Phase of Development
Phase 2

Planned Number of Investigational Sites
Four investigational trial sites at Indiana University in Indianapolis, Mayo Clinic in Rochester, Virginia Commonwealth University in Richmond, and Einstein Medical Center in Philadelphia

Planned Number of Patients
Approximately 60 patients (30 patients per arm) will be randomized in a 1:1 ratio to 1 of 2 treatment arms: **(a)** placebo, or **(b)** 10 mg OCA.

Objectives
To assess the effects of OCA in patients with moderately severe AH on:

Primary
- Change in MELD score at 6 weeks
- Incidence of serious adverse events (SAEs) during the treatment phase

Secondary
- Any SAEs during the follow-up phase
- SAEs attributable to the study medicine during the treatment and follow-up phases
- AEs and discontinuation rates during the treatment and follow-up phases
- Change in MELD score at 90 and 180 days
- Change in Child-Pugh score at 6 weeks and at 90 and 180 days
- Mortality rate at Week 6 and at 90 and 180 days
- Rates of hospitalization and lengths of stay

- Changes in intestinal inflammation and bacterial translocation
- Changes in serum oxidative stress, cytokines, and activation of innate immunity.

Design

This is a phase 2, double-blind, placebo-controlled trial of OCA in patients with moderately severe AH. Approximately 60 patients (30 patients per arm) will be randomized in a 1:1 ratio to 1 of 2 treatment arms: (a) placebo, or (b) 10 mg OCA. Study medication will be administered orally, once daily for 6 weeks.

Methodology

Screening phase: This period will consist of an ≤ 8 week duration prior to randomization during which the eligibility criteria are determined and screening laboratories and an electrocardiogram are obtained. Subjects must sign an informed consent prior to starting the screening phase.

Randomization: Subjects will be randomized to one of two treatment groups with stratification by site and block of size 4. Random assignment will be generated by the coordinating unit and provided to the site pharmacist for randomized packing for maintenance of blinding.

Treatment phase: It will consist of randomization visit (day 0) where participants are assigned to one of the treatment groups (placebo or OCA 10 mg) and then continuing the study medication for 6 weeks. Patients will have the on-treatment study visits at days 14, 28 and 42. At each visit, subjects will have brief medical history, physical examination, routine blood work, and safety evaluation. Compliance with study procedures including alcohol abstinence will be assessed. CBC, prothrombin time along with INR, and comprehensive metabolic profile (CMP, electrolytes, BUN, creatinine, and liver biochemistries) will be measured at each visit. **Special investigations** for this protocol consist of serum FGF19, bile acid C4, OCA and conjugates, fasting free fatty acids, lipid profile, insulin, adiponectin, measures of bacterial translocation (plasma LPS and sCD14), cytokine measurements (serum TNF-α, IL-1, IL-6, and IL-8), markers of oxidative stress, apoptosis, and stool for calprotectin. To promote compliance and to monitor safety, there will be telephone visits on days 7 and 21.

Follow-up phase: Subjects will return to the clinic on Days 90, 120 and 180.

Key Eligibility Criteria

Inclusion Criteria:

(a) Individuals ≥ 21 years with a diagnosis of acute AH. The diagnosis of acute alcoholic hepatitis will be based on clinical features and testing including hepatomegaly, jaundice, fever, leukocytosis, compatible liver biochemistries in the context of heavy alcohol consumption. A liver biopsy is not mandatory, but will be required to confirm the diagnosis if a firm diagnosis of AH cannot be made on clinical and laboratory criteria

(b) Moderate severity defined as MELD score > 11 and < 20

(c) Heavy alcohol consumption (defined as > 40 grams per day on average in women and > 60 grams per day on average in men for a minimum of 6 months and within the 6 weeks prior to study enrollment)

(d) Written informed consent

(e) Negative urine pregnancy test where appropriate

Exclusion Criteria:

(a) Significant active infection (e.g., sepsis, or spontaneous bacterial peritonitis; SBP). Subjects can be reconsidered after the infection is under control.

(b) Serum creatinine > 2.5 mg/dL

(c) Must not have received systemic steroids for a duration of > 1 week during the Screening period or on the day of randomization and must not be receiving any experimental medicines for AH

Treatment Regimen

1 tablet of placebo or 10 mg OCA as directed, taken orally daily with water, approximately 30 minutes prior to breakfast. The duration of treatment is 6 weeks.

Investigator's Affirmation

I have received and read the current version of the Investigator's Brochure (IB) for OCA and this Protocol TREAT-002. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects/patients according to this protocol.

I understand that all information concerning OCA supplied to me by the TREAT Consortium and from Intercept Pharmaceuticals and not previously published is confidential. This includes the IB, Clinical Trial Protocol, Case Report Forms (CRF) and any other preclinical and clinical data.

I understand that no data are to be made public or published without prior knowledge and written approval by the TREAT Steering Committee.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol TREAT – 002 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

I acknowledge that the Steering Committee of the TREAT Consortium has the right to discontinue this trial at any time.

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

ABBREVIATIONS

Abbreviation	Definition
6-ECDCA	6α-ethyl chenodeoxycholic acid
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BL	Baseline
BP	blood pressure
BAS	bile acid sequestrants
BUN	blood urea nitrogen
CDCA	chenodeoxycholic acid
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CRA	Clinical Research Associate
CRF	case report form
DCA	deoxycholic acid
DCU	data coordinating unit
dL	deciliter(s)
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GGT	gamma-glutamyltransferase
GMP	Good Manufacturing Practice
HDPE	high-density polyethylene
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ISF	investigator site file
IL-6	Interleukin-6
LTSE	long term safety extension
MELD	Model for End Stage Liver Disease
mg	milligram(s)
mL	milliliter(s)

NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PBC	primary biliary cirrhosis
PI	principal investigator
PK	pharmacokinetic(s)
SAE	serious adverse event
SUSAR	suspected, unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse event(s)
TIPS	transjugular intrahepatic portosystemic shunt
TNF-α	tumor necrosis factor-alpha
TNF-β	tumor necrosis factor-beta
UDCA	ursodeoxycholic acid
U/L	units per liter
ULN	upper limit(s) of normal
US	United States (of America)
vs	Versus
WBC	white blood cell

1. INTRODUCTION AND RATIONALE

RATIONALE, MEDICAL NEED &MECHANISM OF ACTION OF OCA IN AH

Alcoholic liver disease **(ALD)** is a complex disorder and its pathogenesis is a multi-step and multi-factorial process that progresses through a series of histopathological changes (1). More than 90% of drinkers develop alcoholic steatosis which is reversible upon abstinence. However, if alcohol abuse continues, the disease may progress to alcoholic hepatitis **(AH)**, advanced fibrosis, and cirrhosis in up to 10-15% of heavy drinkers (2, 3). It is currently not well understood why some heavy drinkers develop AH and what determines the severity of the condition. These questions can only be answered by studying sufficient numbers of patients with AH as well as heavy drinkers at risk for AH, and developing clinical studies testing basic pathophysiological mechanisms.

While alcoholic steatosis is a reversible condition, AH is associated with significant morbidity and mortality (4, 5). In mild cases, patients may recover with conservative medical management and alcohol abstinence. However, individuals with more severe AH have high mortality rates (6, 7). Using the National Inpatient Sample data, we reported that AH accounted for 0.7% of all inpatient admissions in the United States. The average length of stay (LOS) was 7 days and nearly 7% died during hospitalization. Of importance, hospitalizations for AH result in significant healthcare costs and utilization (8). The average total charges during hospitalization for AH were $37,769; which was higher than that from acute myocardial infarction (~$16,200), acute cerebrovascular disease (~$11,100), and acute pancreatitis ($9,870). Costs per hospitalization and cost adjusted for LOS were higher in those who died during the hospital stay, presumably from more severe forms of AH ($84,642 and $11,754/day, respectively) (8). These data were obtained during a period of time when current best therapy (corticosteroids or pentoxifylline) was in broad use (9); thus, they confirm the disease burden of AH in the US and attest that better understanding of pathogenesis and treatment of AH are urgently needed to improve patients' outcome.

The study of alcoholic liver injury is complicated by the multiple abnormalities that heavy alcohol use elicits in the liver and the rest of the body. We have sought more fundamental pathophysiological abnormalities that could underlie multiple changes in liver function; these have included inhibition of PPARα (10) AMPK (11), activation of SREBP1c (12) and acid sphingomyelinase (13). We have demonstrated that pharmacological intervention aimed at these abnormalities with fibrates (14) or a sphingomyelinase inhibitor (15) improves alcohol-induced fatty liver (the phenotype we have studied most). Others have shown that activation of AMPK and inhibition of SREBP1 with SIRT1 activators (16) reduces steatosis.

Farnesoid X receptor (FXR) was originally cloned as a bile salt receptor, and activation of FXR affects genes that control bile salt synthesis and transport.

Activation of FXR reduces the mRNA for 7-α hydroxylase (CYP7A1), the rate-limiting enzyme of bile salt synthesis, and the sinusoidal bile salt uptake pump, while inducing the bile salt export pump (net result is decreased intracellular bile salt load). FXR induces the small heterodimerization partner (SHP). This protein is a member of the nuclear receptor family of transcription factors, but SHP lacks a DNA binding domain, and as a result, its hetero-dimerization with other nuclear receptors (in place of the typical dimerization partner RXR) inhibits transcriptional activity of the dimer. SHP inhibition of liver receptor homologue-1 (LRH-1) is responsible for the repression of CYP7A1. Activation of FXR in the ileum leads to release of fibroblast growth factor 19 (FGF19) into the portal blood, which also represses CYP7A1 (17, 18). These FXR actions can be followed by measuring the bile salt intermediary 7α-hydroxyl-3-one-4-cholestene (C4). FXR agonists are being investigated in many liver conditions, including primary biliary cirrhosis (PBC) and NASH, and in an exploratory trial of portal hypertension in subjects with alcoholic cirrhosis. A second bile salt receptor, TGR5, is a seven transmembrane domain receptor linked to $G_{s\alpha}$ (19-22). FXR is expressed in hepatocytes, stellate cells, and endothelial cells (with ligand preference greatest for chenodeoxycholic acid), and TGR5 is also expressed on Kupffer cells (with a preference for lithocholic acid); the FXR agonist OCA used in this project activates FXR with an EC_{50} of 100 nM, whereas the EC_{50} for TGR5 is 20 μM (23).

Plasma bile salts are elevated in most patients with AH (with or without clinical cholestasis (24, 25). Intrahepatic cholestasis correlates with elevated bile salt levels, Maddrey Discriminant Function (7), histological severity, and survival (24). Many patients without histological cholestasis had elevated bile salt levels (25). There is little information about the effect of heavy alcohol use on bile salt metabolism. Vendemiale and Lieber reported that rats chronically fed a high alcohol diet had increased secretion of bile salts into the bile (26). Ackehed et al. measured fecal bile salts in 7 patients at admission for detoxification and 9 days later. They found that bile salt excretion was over twice that of normal controls, and slowly declined during abstention. Since the rate of bile salt excretion in steady state must equal bile salt synthesis, this might reflect increased rates of synthesis of bile salts in heavy drinkers, consistent with our hypothesis regarding effects of alcohol on CYP7A1 expression (27). This elevation in bile salts ought to activate the FXR signaling pathway, with a return of bile salt levels toward normal; the fact that bile salt levels are nearly always increased in AH suggests that this homeostatic system is impaired. In an unpublished study, investigators from Indiana University have shown that alcohol feeding of mice for 4 weeks reduces the levels of SHP. We do not know how alcohol feeding reduced SHP levels. We have previously shown that RXRα protein levels were reduced by alcohol feeding [18]; additional possibilities include direct effects on FXR and reduction in *cis*-retinoic acid, the ligand for RXR (28). We suggest that a primary effect of heavy alcohol use in patients with alcoholic liver disease is inhibition of the ability of FXR to induce SHP. This would result in increased levels of CYP7A1 and sinusoidal bile salt uptake

pump, and reduction in the bile salt export pump, resulting in elevated plasma and hepatocyte bile salt levels.

The ability of OCA to reverse the elevation of bile salts in patients with AH will be tested in this clinical trial (TREAT 002). Given the availability of this FXR agonist (OCA) already in phase 2 and 3 clinical trials (29, 30), this is an extremely promising therapeutic modality to explore.

1.1 NONCLINICAL EXPERIENCE WITH STUDY MEDICATION

Data from long term safety and reproductive toxicology studies conducted according to International Conference on Harmonisation (ICH) Guidelines support the use of OCA for longer term administration and in women of child bearing potential. Administration of OCA to rats (for 6 months) and dogs (for 9 months) in repeat dose toxicity studies resulted primarily in adverse effects on the liver and gastrointestinal (GI) tract at only the highest dose levels. OCA was not genotoxic in a battery of 3 genotoxicity studies. Reproductive and developmental toxicity studies in rats and rabbits demonstrated no adverse effects on fertility and embryo/fetal development at doses where OCA caused maternal toxicity. In addition, no adverse effects were noted in a pre and postnatal developmental toxicity study in rats (preliminary results).

A summary of the toxicology studies is provided in the IB.

1.2 CLINICAL EXPERIENCE WITH OBETICHOLIC ACID (OCA)

1.2.1 Phase 1

OCA was administered orally in a single ascending dose trial (Protocol 747-101) and a multiple ascending dose trial (Protocol 747-102) to evaluate the safety, tolerability and pharmacokinetics (PK) of OCA, administered orally, in healthy volunteers. In Protocol 747-101, single doses of 50 to 500 mg of OCA were administered, while doses of 25 to 250 mg of OCA were administered once daily for 12 days in the multiple dose trial (747-102).

No AEs of clinical concern were seen in the single dose trial. In the multiple dose trial, clinically significant elevations in the aminotransferases were seen at the 250 mg dose. Minor aminotransferase increases of no clinical concern were seen at the 100 mg dose level. However, in the 250 mg dose group, 6 of 8 subjects who received OCA had increases in aminotransferase(s); 4 subjects had elevations in both ALT and AST, while 2 subjects had increased ALT only. These increased values were 3 to 5 times the ULN in some subjects and were considered to be dose limiting. The increases in hepatocellular enzymes are thought to be attributable to detergent effects seen with other bile acids like CDCA. It should be noted that this dose is more than 25 times higher than the doses that will be used in this trial.

OCA is rapidly and extensively conjugated with glycine and taurine. These conjugates are present in much greater concentrations than the parent drug, and are

equipotent FXR agonists to the parent drug. OCA has demonstrated dose proportional increases in C_{max} (50 - 500 mg range) and considerable enterohepatic circulation (lasting several days after the last dose was administered) was seen. Excretion is assumed to be primarily fecal, as is typical for a bile acid, and, at a low level, was recovered in the urine.

1.2.2 Phase 2 and Phase 3

1.2.2.1 OCA in Primary Biliary Cirrhosis (Protocols 747-202 and 747-201 and 747-301)

Two (2), very similar, blinded phase 2 trials in patients with PBC have been completed. ALP (as assessed at central laboratories) was the primary endpoint in both trials. The duration of treatment in each trial during the DB phase was 3 months.

Protocol 747-202 was a dose response trial evaluating 3 doses of OCA (10 mg, 25 mg and 50 mg) versus placebo in patients with persistent elevations (> 1.5x ULN) in ALP levels on a stable dose of UDCA, followed by an open label LTSE phase (Protocol 747-202). Thirty-three (33) trial sites in 8 countries participated. The data for this trial demonstrated (31):

Highly statistically and clinically significant relative and absolute reductions in ALP were seen with all 3 doses (10, 25 and 50 mg) of OCA versus placebo ($p < 0.0001$). Mean ALP reductions were approximately 20 - 25% compared to 3% with placebo. Absolute ALP reductions ranged from approximately 65 - 75 units per liter (U/L) versus 5 U/L for placebo. Other evaluations of ALP response (e.g., response rates) showed similar statistically and clinically meaningful differences from placebo treatment.

Statistically significant improvements were also seen in GGT and ALT levels with all 3 doses, in AST at 10 mg and 25 mg, and in conjugated bilirubin (% change) at 25 mg (mean pretreatment ALT, AST and bilirubin levels were all within the normal range).

Safety: Pruritus was the only clear clinically meaningful AE that differed between OCA treatment and placebo. The incidence of pruritus was elevated at both the 25 mg and 50 mg doses in these cholestatic patients (but not at 10 mg). However, the severity of the pruritus and the incidence of discontinuations due to pruritus were dose related. Overall, 10 mg appeared to be acceptably tolerated (and efficacious).

The open label LTSE phase for protocol 747-202 is complete. This LTSE trial gave subjects the opportunity to receive at least 1 year of open label OCA treatment following completion of the double-blind, placebo-controlled trial.

Subjects continued to receive open label OCA in this phase, titrated from a starting dose of 10 mg to as high as 50 mg. Over two thirds of the subjects were titrated to 20 mg or more and one subject received a dose of 60 mg/daily. Pruritus was the

most common AE, reported in 68 of the 78 subjects (87%) and was the cause of 10 of 19 subject discontinuations in this phase.

Highly statistically ($p < 0.0001$) and clinically significant reductions in ALP from DB baseline were seen with OCA from 3 months through 1 year.

Protocol 747-201, a monotherapy trial comparing the effects of 10 mg and 50 mg OCA versus placebo, is ongoing in the LTSE phase (Protocol 747-201). The following was observed in the DB phase of this trial (32):

Highly statistically and clinically significant relative and absolute reductions in ALP were seen with both doses (10 and 50 mg) of OCA versus placebo ($p < 0.0001$) showing it has substantial efficacy in PBC when given as monotherapy.

Statistically significant improvements were also seen in GGT and in conjugated bilirubin with both doses. ALT and AST changes were not statistically significant though decreased by approximately 35% and 20%, respectively.

Statistically significant changes were seen in several domains of the PBC-40 questionnaire.

Statistically significant reductions were seen in C-reactive protein and IgM.

Safety: As in the 747-202 PBC trial, pruritus was the most common AE. The incidence of pruritus in the OCA groups, 50 mg (94%) and 10 mg (70%), was higher than in the placebo (30%) group. Similarly, the severity of pruritus increased with the dose of OCA. This translated into a higher discontinuation rate for the treated patients, notably in the 50 mg group of which 38% discontinued due to pruritus.

This trial is ongoing in the open label LTSE phase. Additional details regarding the phase 2 PBC trials and current updates about the LTSE phases are provided in the current IB.

Protocol 747-301, a phase 3, double-blind, placebo-controlled, parallel-group trial of OCA in patients with PBC is currently ongoing. This phase 3 trial has been designed to assess the efficacy, safety and tolerability of lower doses (5 mg and 10 mg) of OCA in patients with PBC. The primary endpoints are ALP and total bilirubin, assessed together as a composite endpoint, and safety.

Participating subjects are either continuing their pre-trial dose of UDCA or are not treated with UDCA, if they were unable to tolerate it previously. A five-year LTSE phase is planned to follow the initial 12 month DB phase of the trial. Enrollment has been completed and 217 patients have been randomized in a 1:1:1 ratio to (a) placebo, (b) 10 mg OCA, or (c) 5 mg titrating to 10 mg OCA. During the open label LTSE phase, patients may receive up to 25 mg of OCA for up to 5 years and continue their pre-trial dose of UDCA.

1.2.2.2 OCA in Diabetes & NAFLD

An exploratory trial was conducted in 64 patients with Type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) to evaluate safety and any potential effect of OCA on insulin resistance and glucose homeostasis (33). Patients received one of the following: placebo, 25 mg or 50 mg of OCA daily for 6 weeks. A 2-step hyperinsulinemic, euglycemic clamp was conducted before and after treatment. Improvements in glucose infusion rates at both the low and high-dose insulin clamp steps were seen with the 25 mg dose and when both doses were evaluated together, versus placebo. These effects are consistent with an improvement in metabolism and insulin sensitivity in both the liver and peripheral tissues. Weight loss was seen in a dose related manner. Improvements in GGT, ALT and AST were also seen in the patients who received OCA. There were no clear, concerning safety signals. Significant increases in FGF19 were seen at day 42. This protein is released in the small intestine under FXR control. It is closely involved in the down regulation of bile acid production (there was a significant reduction in C4 at day 42) after a meal and has recently been shown to induce significant beneficial metabolic effects, independent of insulin, post-prandially. This trial demonstrated that small doses of an oral FXR agonist can induce meaningful improvements in glucose metabolism.

1.3 RATIONALE FOR TRIAL DESIGN AND DOSE FOR STUDY MEDICATION

This proposed trial will evaluate OCA in approximately 60 moderately severe AH patients (30 patients per arm) who will be randomized to 1 of 2 treatment arms: (a) placebo, or (b) 10 mg OCA in a 1:1 ratio.

1.3.1 Rationale for Dose and Duration

Our choice to administer OCA for 42 days is based on the study by Mudaliar et al (33) which showed significant reduction in C4 levels at day 42, indicating OCA's efficacy in reducing bile salt synthesis by that time point.

We chose 10 mg dose to investigate because (a) it is among the doses that is being used in ongoing PBC and non-alcoholic steatohepatitis (NASH) clinical trials, (b) it is among the doses that is being investigated to treat portal hypertension in subjects with alcoholic cirrhosis in the United Kingdom (http://www.controlled-trials.com/ISRCTN22662520), and (c) in one study, although OCA and FGF19 levels increased in a dose-dependent fashion, OCA administered at a 10 mg dose had similar effect on serum C4 levels as OCA 50 mg (reduction in C4 concentration, reflecting inhibition of bile salt synthesis of - 6.8 ng/ml vs. -6.5 ng/ml, p=ns).

1.4 SUMMARY OF KNOWN POTENTIAL RISKS WITH STUDY MEDICATION

Pruritus has been observed in the multiple dose trials of OCA in primary biliary cirrhosis (PBC) and was the most common AE seen in the PBC 747-202 Trial, DB phase, with 67% of patients reporting a treatment emergent AE (TEAE) of pruritus. There was a relationship between the dose of OCA administered and the incidence (at 25 mg and 50 mg only), severity, and the timing of the onset of pruritus, which occurred almost invariably within the first 14 days of treatment at 50 mg. Pruritus was least tolerated at 50 mg with 24% of patients discontinuing at this dose due to pruritus.

In the 747-201 Trial, DB phase, pruritus was the most common AE that occurred in any treatment group, 50 mg (94%) and 10 mg (70%), and at a rate higher than in the placebo (30%) group. Similarly, pruritus has been the most commonly reported AE in the 747-201 LTSE to date. The severity of pruritus shows an apparent improvement with increasing dose of OCA in the LTSE. This suggests that patients who do not develop severe pruritus at lower doses are likely to tolerate higher doses if titrated up.

The mechanism of pruritus in cholestatic liver disease is unknown. Recently, autotaxins and lysophosphatidic acid have been implicated in pruritus of cholestasis [Kremer 2009, 2010, 2011]. Recent data [Kremer 2011] suggest that autotaxins may be increased in patients with the worst pruritus taking 50 mg in the 747-202 trial and that patients with high autotaxin levels were more likely to develop severe pruritus. However, plasma autotaxin levels did not explain the pruritus in the majority of patients. Assays of the plasma from the subjects receiving 250 mg dose in the multiple dose normal volunteers trial (747-102) did not show a difference in autotaxin levels between the pruritic and non-pruritic subjects. Bile acid concentrations in the PBC trial 747-202 have not shown an association with pruritus.

In the PBC 747-202 Trial, DB phase, besides pruritus, only nausea (mild or moderate) was seen more frequently in all 3 OCA groups than in the placebo group. In the 747-201 DB phase, only urinary tract infection was seen more frequently in both OCA groups than the placebo group. The current IB outlines other AEs observed in association with the use of OCA.

2. TRIAL OBJECTIVES

Primary

- Change in MELD score at 6 weeks
- Incidence of serious adverse events (SAEs) during the treatment phase

Secondary

- Any SAEs during the follow-up phase
- SAEs attributable to the study medicine during the treatment and follow-up

phases
- AEs and discontinuation rates during the treatment and follow-up phases
- Change in MELD score at 90 and 180 days
- Change in Child-Pugh score at 6 weeks and at 90 and 180 days
- Mortality rate at Week 6 and at 90 and 180 days
- Rates of hospitalization and lengths of stay
- Changes in intestinal inflammation and bacterial translocation
- Changes in serum oxidative stress, cytokines, and activation of innate immunity.

3. INVESTIGATIONAL PLAN

3.1 OVERALL TRIAL DESIGN AND PLAN

Design

This is a phase 2, double-blind, placebo-controlled trial of OCA in patients with moderately severe AH. In the DB phase, approximately 60 patients (30 patients per arm) will be randomized in a 1:1 ratio to 1 of 2 treatment arms: (a) placebo, or (b) 10 mg OCA. Study medication will be administered orally, once daily for 6 weeks.

3.2 SCHEDULE OF TRIAL PROCEDURES

The Schedule of Trial Procedures is provided in Table 1.

Table 1: Schedule of Trial Procedures

	Screening	Treatment Phase[1]				Follow-up phase		
		D0	D14	D28	D42	D90	D120	D180
Informed consent	X							
Confirmation of eligibility criteria	X	X						
Randomization		X						
History and physical	X	X	X	X	X	X	X	X
Assess Liver Scores: MELD, Child Pugh and/or Discriminant Function	X	X	X	X	X	X	X	X
AUDIT and NIAAA Questionnaires	X							
Timeline Followback Questionnaire	X	X	X	X	X	X	X	X
Concomitant medicines	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Electrocardiogram	X				X			
Evaluation of compliance			X	X	X			
Dispense study medication[2]		X	X	X	X			
CBC, CMP, INR	X	X	X	X	X	X	X	X
Pregnancy test[3]	X	X	X	X	X			
Special investigations[4]		X			X			
Specimen Banking[5]		X	X	X	X	X	X	X

[1] There is a telephone visit on D7 and D21.[2] Bottle(s) will be dispensed to the subjects for at-home dosing at the D0 and D14 visits. Subjects will be instructed to dose at the clinic at the D14, D28 and D42 visits.

[3] A serum pregnancy test (in women of childbearing potential) will be done at Screening. Urine pregnancy tests will otherwise be conducted.

[4] **Special investigations** for this protocol consist of serum FGF19, bile acid C4, OCA and conjugates, fasting free fatty acids, lipid profile, insulin, adiponectin, measures of bacterial translocation (plasma LPS and sCD14), cytokine measurements (serum TNF-α, IL-1, IL-6, and IL-8), markers of oxidative stress, apoptosis, and stool for calprotectin.

[5] Specimens to be banked include genomic DNA at D0, blood mononuclear cells at D0, D28 and D42 and blood (serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies.

3.2.1. **Duration of Trial by Phase**

Time expected for all patients to be enrolled:	~ 15 months
Duration of individual patient participation:	42 days (6 weeks) during the treatment phase 5 months during the follow up phase
Total duration of trial (excluding data collection and analysis):	21 months

The end of this trial will occur when the last patient(s) completes the D180 visit.

4. PATIENT SELECTION

4.1 PATIENT POPULATION

This trial will be conducted at 3 sites with experience in treating patients with AH. Prospective patients will be identified primarily from the hospital and/or outpatient clinics, or may be referred by physicians from other hospitals.

Throughout this protocol, the terms 'Principal Investigator (PI)', 'investigator' and 'investigator or designee' is used synonymously. Irrespective of the term used, the intention remains the same: that the overall trial responsibility remains with the PI who has agreed to personally conduct or supervise the trial and who may delegate aspects of the trial conduct, to appropriate, qualified trial site staff who have been informed about their obligations in meeting the above commitments.

Patients will be selected according to the following criteria.

4.2 INCLUSION CRITERIA

If used, the term 'baseline' (BL) within this protocol, unless otherwise specified, is intended to mean, 'prestudy' or 'pretreatment' (of study medication). It refers to values obtained during the Screening or Day 0 visits, prior to the patient's first dose of study medication.

Patients must meet all of the following criteria to enter the trial.

(a) Individuals ≥ 21 years with a diagnosis of acute AH. The diagnosis of acute alcoholic hepatitis will be based on clinical features and testing including hepatomegaly, jaundice, fever, leukocytosis, compatible liver biochemistries in the context of heavy alcohol consumption. A liver biopsy is not mandatory, but will be required to confirm the diagnosis if a firm diagnosis of AH cannot be made on clinical and laboratory criteria

(b) Moderate severity defined as MELD score > 11 and < 20

(c) Heavy alcohol consumption (defined as > 40 grams per day on average in women and > 60 grams per day on average in men for a minimum of 6 months and within the 6 weeks prior to study enrollment)

(d) Written informed consent

(e) Negative urine pregnancy test where appropriate

(f) Women of child bearing potential should be willing to practice contraception throughout the treatment period

4.3 EXCLUSION CRITERIA

(a) Significant active infection (e.g. sepsis or SBP). Subjects can be reconsidered after the infection is under control.

(b) Serum creatinine > 2.5 mg/dL

(c) Must not have received systemic steroids for a duration of > 1 week during the screening period or on the day of randomization and must not be receiving any experimental medicines for AH

(d) Presence of any other disease or condition that is interfering with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine. Patients who have undergone gastric bypass procedures will be excluded (gastric lap band is acceptable).

(e) Participation in another investigational drug, biologic, or medical device trial within 30 days prior to screening

4.3 PATIENT WITHDRAWAL FROM THE TRIAL

4.3.1 Reasons for Mandatory Trial Discontinuation

If a female patient becomes pregnant, she must stop taking study medication and must be withdrawn from the trial. The patient must be followed by the investigator through the end of her pregnancy. The mother (and infant) will be followed as considered appropriate by the investigator and the study designated physician (Dr. Chalasani or his designee). For reporting purposes, pregnancy is not considered a serious adverse event (SAE).

During the trial, if Maddrey's Discriminant Factor (DF) increases by 5 points and also exceeds 32, or MELD scores increases by 5 points and also exceeds 20, the study

medication should be stopped, however the participant will remain in the trial, completing procedures as detailed in the Schedule of Procedures (Table 1). Treating physicians may offer any other treatment that is considered as medically indicated and appropriate.

4.3.2 Other Reasons for Trial or Treatment Discontinuation

The following events are considered appropriate reasons for a patient to discontinue from the trial:

- The patient withdraws consent or requests to be withdrawn from the trial. It is fully understood that all patients volunteer for the trial and that they may withdraw their consent at any time.
- The patient experiences an adverse event that in the opinion of the site investigator or the primary investigator of the trial (i.e., study designated physician, Dr. Chalasani) is caused by or exacerbated by any of the trial procedures or study medication, of sufficient intensity to warrant discontinuation.
- The patient refuses to comply with the requirements for trial participation.

When possible, the investigator should discuss the potential discontinuation of a patient with the study designated physician (Dr. Chalasani or his designee) in advance.

4.3.3 Patient Discontinuation Notification

The investigator must notify the study designated physician (Dr. Chalasani or his designee) as soon as possible if any patient prematurely discontinues from the trial. The date when the patient is withdrawn and the primary reason for discontinuation must be recorded in the CRF; additional information may be requested to complete a discontinuation narrative. Patients will be considered “lost to follow up” only after reasonable, documented attempts to reach the patient prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a patient fails to return for required trial visits or discontinues from the trial.

If a subject stays in the study but discontinues study medication (either by participant’s choice, or by the investigator’s decision), then study measurements should be performed according to the Schedule of Trial Procedures, Table 1, (rather than expediting study visits, or measurements).

5. INVESTIGATIONAL PRODUCT (IP)

5.1 DESCRIPTION OF IP

For the purpose of this protocol, the term ‘investigational product (IP)’ is interchangeable with the term ‘study medication’.

5.1.1 Study Medication

Intercept Pharmaceuticals will provide study medication (OCA and matching placebo) which are white or light blue-green round tablets engraved with 'INT' on one side and '3547' on the other side. All study medication will be provided as a tablet for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with 30 tablets per bottle and closed with an induction seal and child proof cap. Bottles will also include two desiccant packets and cotton coil.

All study medication (OCA and matching placebo) will be manufactured according to Good Manufacturing Practice (GMP).

5.1.2 Treatment Phase

Study medication will be provided to each site (pharmacy) as open label product, overlabeled at each site and blinded based on the randomization scheduled, and then provided to subjects in a blinded manner (i.e., the investigator, site staff and patient will be unable to distinguish treatment assignment). Study medication will consist of either 10 mg OCA or matching placebo tablets.

5.2 PACKAGING, LABELING, AND STORAGE

The packaging and labeling of study medication for provision to the clinical trial sites will be performed according to GMP standards by designated qualified vendors.

The designated IP distribution vendor will be responsible for the distribution of the study medication to the clinical trial sites. Study medication should be stored at controlled room temperature (15°C to 30°C) and protected from excess humidity.

Study medication will be packaged for the trial as described below.

5.2.1 Packaging and Labeling

Study medication for the trial will be packaged and labeled as open label bottles containing 30 tablets and sent to each investigative site (pharmacy). Each site will be responsible for overlabeling (i.e., blinding) the bottles with a unique non sequential bottle number for the purpose of identifying and allocating the bottle. The bottle number will not reveal any information about the treatment dose contained in the bottle. The investigative pharmacist at each individual trial site will prepare the study medication for appropriate dispensing to the subjects according to standard operating procedures.

5.3 DOSE, ADMINISTRATION AND BLINDING

Two (2) treatment groups will be evaluated in the trial: (a) placebo or (b) 10 mg OCA. Study medication will be administered orally, once daily for 6 weeks (42 days) during the study. Each daily dose will be made up of 1 tablet.

Patients will be instructed to begin dosing on the day after the Day 0 visit (i.e., on Day 1) and to take study medication with water, approximately 30 minutes prior to breakfast. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

5.3.1 Dispensing Procedures

On Day 0, after confirmation of patient eligibility and randomization, the investigator or designee will dispense 1 bottle of study medication to the patient. Before leaving the clinic/hospital, the study staff will ensure that the patient fully understands the dosing instructions. Additional study medication (i.e., a second bottle) will be dispensed on Day 14. The clinical trial site investigator may adjust the number of bottles (1 or 2) dispensed to the subject based on clinical judgment and visit scheduling to ensure an adequate supply of study medication is available for dosing between clinic visits.

5.3.2 Blinding

All study medication will be visually identical for the OCA and placebo treatment arms, thus ensuring the double-blind nature of the trial. Study medication bottles will not be labeled with either a patient randomization number or tablet strength, to ensure that neither patient nor investigator is unblinded.

5.3.3 Missed Doses

Patients who miss a dose of study medication should be instructed to take it later the same day, as soon as they remember. 'Missed' doses should not be taken on a subsequent day (i.e., the patient should not take more than the prescribed daily dose).

5.3.4 Overdosage

The maximum dose of OCA that has been given to humans is 500 mg as a single dose and 250 mg as a multiple dose. Reversible increases in aminotransferases were seen in most of the healthy volunteers who took 250 mg OCA. There is no specific information available regarding the treatment of possible overdose with OCA. If overdose occurs in a patient enrolled in the trial, general medical supportive measures should be provided, including observation and follow up (e.g., serum chemistry) as appropriate. Due to the extensive enterohepatic recirculation of the drug it is likely that it will take several days before blood (and organ) concentrations of the drug will decrease. Treatment with cholestyramine (Questran™), colesevelam (Welcol™) and other bile acid sequestrants is both logical and recommended given that they should bind and eliminate the drug in feces. Although there is no experience with OCA, plasmapheresis might be expected to reduce circulating levels of the drug. The study designated physician (Dr. Chalasani) should be notified immediately in the event of a significant overdose.

5.4 RANDOMIZATION

5.4.1 Method of Assigning Patients to Treatment Groups

The trial will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment arms will occur on a 1:1 ratio within each sites with a block of size 4 based on a predefined randomization code generated by the TREAT data coordinating unit (DCU).

The investigator or designee will be required to register the patient on the OnCore system (TREAT's data management system) and will provide patient data to properly randomize and allocate the patient to treatment. A randomization number will be assigned and study medication dispensing information (e.g.., bottle number(s)) will be provided.

5.4.2 Site Numbers

Each trial site selected to participate in this trial will be assigned a Site Number by the TREAT consortium. The Site Number will be used to categorize patient data and to identify the site and or investigator within trial documents.

5.4.3 Screening Numbers

At the Screening Visit, after the patient has provided written informed consent, the patient will be assigned a unique 5 digit subject ID number.

5.4.4 Randomization Numbers and Schedule

Subjects will be randomized to one of two treatment groups with stratification by site and block of size 4. Random assignment will be generated by the coordinating unit and provided to the site pharmacist for randomized packing for maintenance of blinding.

5.5 UNBLINDING PROCEDURES

5.5.1 Unscheduled, Emergency Unblinding

The site pharmacist will be unblinded to randomization codes and corresponding treatment assignment as s/he will overlabel each bottle to apply the blind, prior to dispensing to any subjects at the site. Additionally, the randomization codes and corresponding treatment assignment will be maintained by the TREAT DCU. The study designated physician (Dr. Chalasani or his designee), or the individual investigators will not have access to this information. In the event that a medical emergency necessitates unblinding (i.e., in situations where knowledge of the blinded treatment is necessary for further medical management of the patient), the site investigator (or his/her designee) will contact the designated study physician to discuss the rationale for unblinding. If there is a difference of opinion between the designated study physician and the site investigator, then the site investigator retains the final right to seek unblinding. The designated study physician will

communicate with the DCU about the decision to unblind the subject and then the DCU will unblind the subject by interacting directly with the site investigator.

The Data and Safety Monitoring Committee (DSMC) will be able to unblind patients. Cases of premature unblinding (as noted above) will be reviewed by the DSMC.

Access to randomization codes and corresponding treatment assignment will also be made available to the designated study physician who is responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities and should be accessed only in the event that reporting necessitates unblinding. Aside from the site pharmacist who conducts the drug overlabeling, no other site personnel will have direct access to blinded patient treatment codes until all trial data have been entered onto the trial database and validated, and the database locked.

5.6 PRIOR AND CONCOMITANT MEDICATIONS OR PROCEDURES

Relevant information about all concomitant drugs (including prescribed, over the counter, or herbal preparations) taken prior to and during the trial must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the trial.

5.7 TREATMENT COMPLIANCE

The investigator should assess the patient's compliance with dosing of study medication on an ongoing basis, at least at each visit, and confirm by conducting drug accountability (i.e., count of returned tablets).

Patients should be instructed to retain all bottles of study medication, even if empty, and to return them to the investigator at the subsequent visit. The investigator or designee should perform drug accountability and, if applicable, follow up with the patient to retrieve any study medication that has not been returned.

If the investigator has concerns about a patient's dosing compliance s/he should discuss this with the patient, assess the reasons for noncompliance and the likelihood that the patient will remain noncompliant, and notify the designated study physician accordingly. Continued trial eligibility should be assessed based on the patient's compliance with study medication dosing and clinic visits.

5.8 STUDY MEDICATION ACCOUNTABILITY AND RETENTION

Intercept Pharmaceuticals, Inc.'s representative will send study medication to the trial sites under appropriate storage conditions. All shipments of study medication should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored at controlled room temperature until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the study medication

against the shipment documentation. The pharmacist or designee should contact the designee of Intercept Pharmaceuticals immediately to report any concerns regarding the shipment.

All study medication will be provided for use only in this trial and is not to be used for any other purpose. The investigator or designee will maintain a full record of study medication accountability, including records of individual patient dispensing and final return or disposition.

The 'Clinical Research Associate' (CRA), will review accountability records against study medication dispensed and that remaining in stock, during on-site monitoring visits and when the trial is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the study medication.

5.9 TRIAL OR SITE TERMINATION

The TREAT consortium reserves the right to terminate the trial at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the trial before all patients have completed the trial.

It is the responsibility of the individual site's PI to report to their Institutional Review Board (IRB) of discontinuation of the trial and the reason for doing so in a timely fashion according to institutional policies.

6. TRIAL PROCEDURES

6.1 SCREENING

6.1.1 Informed Consent

The investigator or designee will explain the nature, purpose and risks of the trial to the patient and will provide him/her with a copy of the written information and informed consent form (ICF). The patient will be given sufficient time to consider the trial before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the trial and that s/he can withdraw from the trial at any time. The patient must be willing and able to provide written informed consent before entering the trial. The investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient.

6.1.2 Patient Identification Assignment

After the patient has met eligibility criteria and enrolls into the study, the patient will be assigned a unique 5 digit ID number. This 5 digit number will be used to identify the participant throughout the trial and during the data analysis.

6.2 VISIT PROCEDURES

Patients should be instructed to fast overnight (at least 8 hours) immediately prior to all at-clinic visits, including the Screening Visit. While fasting, water is permitted.

6.2.1 Screening Period

The screening period will consist of ≤ 8 weeks prior to the randomization visit (Day 0. During the screening period, participants' eligibility criteria must be confirmed. Participants must sign an informed consent prior to initiating any of the screening procedures. Patients who do not fulfill all eligibility criteria cannot continue in the protocol (screening failures).

Screening period procedures are as follows:

- The participant is to review and sign the informed consent document. Informed consent must be obtained from the patient before performing any trial related procedures, including screening procedures
- Verify inclusion and exclusion criteria for eligibility
- Assess Liver Score: MELD
- Collect medical history including the alcohol consumption specifics
- The participant is to complete the AUDIT, NIAAA and Timeline Followback Questionnaires
- Perform a physical examination, including height and weight
- Record vital signs
- Record prior (within 30 days of Day 0) and current concomitant medications
- Perform a standard 12-lead electrocardiogram (ECG)
- Assess availability of liver biopsy samples (if applicable) which may have been obtained as part of standard of care
- Obtain blood samples for serum chemistry, hematology and coagulation tests
- Perform a serum pregnancy test in females of childbearing potential
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit.

6.2.2 Day 0 Procedures (Randomization) – Must present after at least 8 hours of fasting

- Collect medical history including the alcohol consumption specifics
- Perform a physical examination

- Record vital signs
- Alcohol consumption history – Timeline Followback Questionnaire
- Assess and record any pretreatment emergent AEs
- Record prior (within 30 days of Day 0) and current concomitant medications. Ascertain that participant is not receiving concomitant systemic corticosteroids on the day of randomization
- Perform a urine pregnancy test in females of childbearing potential
- Confirm inclusion and exclusion criteria for eligibility
- Assess Liver Scores: MELD, Child Pugh and Discriminant Function
- Randomize the patient only if s/he meets all inclusion criteria and no exclusion criteria
- Obtain blood samples for serum chemistry, hematology and coagulation tests
- Obtain blood samples for special investigations as outlined in section 3.2
- Obtain blood and stool samples for specimen banking as outlined in section 3.2.
- Dispense study medication and instruct the patient to begin dosing on the day after the Day 0 visit (i.e., on Day 1) and to take study medication with water, approximately 30 minutes prior to breakfast. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic (D14) visit as s/he will dose at the clinic.

6.2.3 D7 Procedures (± 1 days)

- This consists of a telephone visit where the participant will be inquired about his/her well-being, compliance with IP, concomitant medications and alcohol use.
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic visit (D14) as s/he will dose at the clinic.

Ascertain that participant is not receiving concomitant systemic corticosteroids

6.2.4 D14 Procedures (± 2 days) - Must present after at least 8 hours of fasting

- Perform a physical examination
- Record vital signs

- History and physical examination
- Assess Liver Scores: MELD, Child Pugh and Discriminant Function
- Alcohol consumption history – Timeline Followback Questionnaire
- Assess and record AEs
- Review and record concomitant medications. Confirm that participant is not receiving concomitant systemic corticosteroids.
- Evaluation of compliance
- Obtain blood samples for serum chemistry, hematology and coagulation tests
- Urine pregnancy test in females of childbearing potential
- Assess study medication compliance and perform accountability
- Instruct the patient to take the daily dose of study medication, at the clinic, with water and approximately 30 minutes prior to eating.
- Dispense study medication for at-home dosing and remind the patient to take study medication with water, approximately 30 minutes prior to breakfast. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic visit (D28) as s/he will dose at the clinic.
- Perform biosample banking for future use

6.2.5. Day 21 procedures (± 2 days)

- This consists of a telephone visit where the participant will be inquired about his/her well-being, compliance with IP, concomitant medications and alcohol use.
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic visit (D28) as s/he will dose at the clinic. Confirm that participant is not receiving concomitant systemic corticosteroids.

6.2.6. D28 Procedures (± 2 days) - Must present after at least 8 hours of fasting

- Perform a physical examination
- Record vital signs
- Alcohol consumption history – Timeline Followback Questionnaire
- Assess and record AEs

- Assess Liver Scores: MELD, Child Pugh and Discriminant Function
- Review and record concomitant medications. Confirm that participant is not receiving concomitant systemic corticosteroids.
- Assess study medication compliance and perform accountability
- Obtain blood samples for serum chemistry, hematology and coagulation tests
- Urine pregnancy test in females of childbearing potential
- Instruct the patient to take the daily dose of study medication, at the clinic, with water and approximately 30 minutes prior to eating
- The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic visit (D42) as s/he will dose at the clinic.
- Perform biosample banking for future use

6.2.7. Day 42 Procedures (+ 2 days) - Must present after at least 8 hours of fasting

- Perform a physical examination
- Record vital signs
- Assess Liver Scores: MELD, Child Pugh and Discriminant Function
- Alcohol consumption history –– Timeline Followback Questionnaire
- Assess and record AEs
- Review and record concomitant medications. Confirm that participant is not receiving concomitant systemic corticosteroids.
- Assess study medication compliance and perform accountability and obtain any remaining study medication from patient
- Obtain blood samples for serum chemistry, hematology and coagulation tests
- Perform a urine pregnancy test in females of childbearing potential
- Perform a standard 12-lead electrocardiogram (ECG)
- Obtain blood samples for special investigations as outlined in section 3.2
- Instruct the patient to take the final dose of study medication, at the clinic, with water and approximately 30 minutes prior to eating
- Perform biosample (blood and stool) banking for future use

6.2.8. Follow up phase D90, D120 and D180 (± 2 weeks) – Must present after at least 8 hours of fasting

- Perform a physical examination
- Record vital signs
- Alcohol consumption history- – Timeline Followback Questionnaire
- Assess and record AEs
- Assess Liver Scores: MELD, Child Pugh and Discriminant Function
- Review and record concomitant medications
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Perform biosample banking for future use

6.2.9. Early Termination Procedures

Subjects who withdraw consent or discontinue treatment prematurely during the Treatment Phase should complete the assessments required on Day 42. Subjects who discontinue prematurely during the Follow-up Phase should complete the assessments required on Day 180.

6.2.10. Unscheduled Safety Visits

The investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments may be conducted. As appropriate, the designated study physician should be contacted.

6.2.11. Specimen Banking

Specimens to be banked include genomic DNA at D0, blood mononuclear cells at D0, D28 and D42, and blood (serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies.

7. EFFICACY EVALUATIONS

TO ASSESS THE EFFECTS OF OCA IN PATIENTS WITH MODERATELY SEVERE AH ON:

PRIMARY OBJECTIVE

- Changes in MELD score at 6 weeks of treatment
- Incidence of SAEs during the treatment phase

Secondary Objectives

- Any SAEs during the follow-up phase
- SAEs attributable to the study medicine during the treatment and follow-up phases
- AEs and discontinuation rates during the treatment and follow-up phases
- Change in MELD score at 90 and 180 days
- Change in Child-Pugh score at 6 weeks and 90 and 180 days
- Mortality rate at 6 weeks, 90 days and 180 days
- Rates of hospitalization and lengths of stay
- Changes in intestinal inflammation and bacterial translocation
- Changes in serum oxidative stress, cytokines, and activation of innate immunity.

8. SAFETY EVALUATIONS

8.1. ADVERSE EVENTS

Adverse event (AE) data will be collected from Day 0 through the DB phase, until the patient fully completes her/his trial participation at the Follow Up visit.

8.2. PHYSICAL EXAMINATION AND VITAL SIGNS

8.2.1. Physical Examination

To assess for clinical findings, the investigator or designee will perform a physical examination at the time points specified in the Schedule of Trial Procedures (Table 1). This includes height only at Screening. The physical examination must include the following:

-General appearance

-Weight

-Eyes

-Ears, nose, and throat

-Neck

-Respiratory system

-Cardiovascular system

-Abdominal region

-Mental status

-Neurological system

8.2.2. Vital Signs

The following vital signs will be assessed at indicated visits: body temperature, sitting heart rate, and sitting blood pressure (BP). When taking heart rate and BP readings, patients should be seated quietly for a minimum of 3 minutes before the reading is taken. The heart rate should be recorded over a 60 second period.

8.3. CLINICAL LABORATORY

Blood samples for serum chemistry, hematology, and coagulation will be collected at every visit as detailed in the Schedule of Trial Procedures (section 3.2.). The number and volume of samples to be collected at each visit will be detailed in a separate document. These tests will be conducted at local laboratories at 3 participating sites.

All patients with laboratory tests containing clinically significant abnormal values should be followed regularly until the values return to normal ranges, until a valid reason for the AE (other than study medication related AE) is identified, or until further follow up is deemed medically unnecessary.

8.4. ELECTROCARDIOGRAM

Standard 12-lead ECGs will be collected at screening and Day 42 visits. The investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day 0 will also be documented as AEs and entered on the AE page of the CRF.

Investigative sites must retain a copy of all 12-lead ECGs evaluated by the investigator or designee. These ECGs must be clearly labeled with the subject's 5 digit study number, Screening or Randomization Number, date and time. There is no central review of the ECGs. The following variables will be assessed: PR, QRS, QT and QTc intervals and a clinical evaluation for each ECG will be provided.

8.5. OTHER SAFETY RELATED CLINICAL OUTCOMES

The following clinical outcomes will be assessed:

- Death (from hepatic and non-hepatic related causes)
- Complications of portal hypertension including gastroesophageal bleeding, interventions to manage variceal bleeding (e.g., variceal banding/sclerotherapy or TIPS placement) and diuretic resistant ascites
- Complications of Cirrhosis: new-onset ascites, hepatic encephalopathy, hepatorenal syndrome (type I or II), and spontaneous bacterial peritonitis).
- Hospitalization

Each of these events including hospitalizations will be adjudicated by the site

investigator as expected as part of the natural history of moderately severe AH, or unexpected (e.g., suicide, motor vehicle accident, or myocardial infarction).

9. ADVERSE EVENTS

9.1. DEFINITION OF ADVERSE EVENTS

9.1.1. Reporting Period for Adverse Events

Safety will be assessed in terms of AEs. All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from Day 0 until the patient completes trial participation (D-180).

AEs are defined as any untoward medical occurrence associated with the use of the study medication in humans, whether or not considered related to study medication. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with any use of the study medication, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose. For this trial, study medication refers to double blind OCA or placebo in the DB phase.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the trial; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the patient or asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms “sudden numbness, dizziness, and difficulty speaking.” The AE medical term of “stroke or cerebrovascular accident” should be recorded as it more accurately describes the AE.

Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study medication, must be documented in the subject’s medical records, in accordance with the investigator’s normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study medication.

9.1.1.1. Pretreatment Event(s)

Untoward events that occur during screening phase (prior to randomization) should be recorded as medical history.

9.1.2. Severity of AEs

AEs must be graded for severity (i.e., intensity). A severity category of mild, moderate, or severe, as defined in Table 2, must be entered on the AE CRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." For example, severe headache is a severe AE, but may not be a serious AE. The assessment of severity is made regardless of study medication relationship or of the seriousness of the AE.

Table 2 Severity of AEs

Grade	Clinical Description of Severity
1 = Mild	Causing no limitation of usual activities; the subject may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the subject may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

9.1.3. Relationship of AEs to Study Medication

The investigator will document her/his opinion of the relationship of the AE to treatment with study medication using the criteria outlined in Table 3. An AE for which there is a 'reasonable possibility' that the study medication caused the AE is otherwise referred to as suspected adverse reaction (SAR). 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study medication and the AE.

Table 3 Relationship of AEs to Study Medication

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the study medication level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the study medication, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the study medication; that follows a known or expected response pattern to the suspected study medication; that is confirmed by stopping or reducing the dosage of the study medication; and that could not be reasonably explained by other factors.
Possible	A reaction that follows a reasonable temporal sequence from administration of the study medication; that follows a known or expected response pattern to the suspected study medication; but that could readily be produced by a number of other factors.
Unlikely	A reaction that does not follow a reasonable temporal sequence from administration of the study medication; that does not follow a known or suspected response pattern to the suspected study medication; and that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

9.2. SERIOUS ADVERSE EVENTS

9.2.1. Definition of a Serious Adverse Event

An adverse event or suspected adverse reaction is considered 'serious' if, in the view of the investigator, it results in any of the following outcomes:

(a) Death;

(b) Is life threatening;

(c) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

(d) A congenital anomaly/birth defect;

(e) Requires in-patient hospitalization or prolongs an existing hospitalization;

(f) An important medical event that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.2.2. Reporting SAEs

In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for immediate reporting of SAEs to the study designated physician (Dr. Chalasani or his designee) as described below.

Table 4: Requirements for Reporting AEs to various stakeholders

	Local IRB	NIAAA	DSMB	Other centers	Intercept	FDA
AEs	Continuing Review	Annual Report	Every 6 months	DSMB reports (every 6 months)	DSMB reports (every 6 months)	Annual Report
TEAEs	Continuing Review	Annual Report	Every 6 months	DSMB reports (every 6 months)	DSMB reports (every 6 months)	Annual Report
SAEs	Continuing Review	2 working days	Every 6 months	DSMB reports (every 6 months)	DSMB reports (every 6 months)	Annual Report
SUSAR	5 days	2 working days	2 working days	2 working days	2 working days	7 days if death 15 days if other
Fatality	If unrelated Follow SAE timeline If related follow SUSAR timeline					

AE: Adverse Event; TEACs: Treatment Emergent Adverse Event; SAE: Serious Adverse Event; SUSAR: Serious Unsuspected Adverse Reaction; DSMB: Data and Safety Monitoring Board

The study designated physician for TREAT 002 is Naga Chalasani, MD.

Safety Officer for the DCU of the TREAT Consortium is Samer Gawrieh, MD.

All SAEs must be reported to the DCU (i.e., within 2 working days) after the investigator identifies the SAE. SAEs should be entered into the OnCore system within 2 working days of the investigator becoming aware of the event. An initial report by telephone should be followed as soon as possible by completion of the SAE CRF. Any supporting source documentation should be emailed to the assigned contact information as soon as possible. At a minimum the following information should be provided at the time of the initial report: 5-digit Study ID, a description of the event, at least one criterion classifying the event as Serious and the name and title of the reporting individual. Additionally, judgment of causality by the investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities.

Following the initial report, any additional information obtained by the investigator about the SAE must be reported promptly to the DCU.

The site investigator will assess whether the event is causally related to the study medication. The study designated physician (Dr. Chalasani) will consider the investigator's assessment, however, since he holds the IND and is primarily responsible for the overall safety of the participants, his causality assessment will take precedence over that of the site investigator. The study designated physician will determine if an SAE meets the criteria for an IND safety report (*suspected, unexpected serious adverse reaction (*SUSAR) in accordance with the FDA regulations, 312.32(c)(1)(i).

9.2.2.1. Additional Principal Investigator Responsibilities for SAEs

The safety data recorded in the CRF represent the official record of all AEs and SAEs reported in the trial. The investigator should comply with requests by the designated study physician to record the SAE on the patient's AE CRF and, if necessary, provide a copy of this CRF to the DCU. Other supporting documents such as radiology reports, hospital discharge summaries and autopsy reports should also be provided, when appropriate, in anonymized fashion. Additionally, upon request by the designated study physician, the investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow up and closure of the SAE report.

The investigator and supporting personnel responsible for patient care should discuss with the designated study physician any need for supplemental investigations of SAE(s). The results of these additional assessments must be reported to the designated study physician.

9.3. SAEs THAT ARE ANTICIPATED TO OCCUR IN THE STUDY POPULATION (EXPECTED SAEs)

Certain SAEs are anticipated to occur in this study population at some frequency independent of drug exposure. These expected SAEs have been identified as: variceal bleeding, ascites, spontaneous bacterial peritonitis, jaundice, hepatorenal syndrome, or hepatic encephalopathy. These expected SAEs as well as any related hospitalization will not be expeditiously reported as IND safety reports, but will be reported in the manner described above (9.2.2). However, if an aggregate analysis indicates that these events are occurring more frequently in the drug treatment group than in a concurrent or historical control group, the SAEs will be reported as an IND safety report (21 CRF 312.32(c)(1)(c)).

9.4. FOLLOW UP OF AEs

All AEs, including clinically significant laboratory values or physical examination findings relative to pretreatment assessments, must be followed during the trial until

the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow up.

AEs ongoing at the final visit that are deemed to be 'possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented on the CRF. The investigator must ensure that follow up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the investigator.

10.STATISTICAL METHODS

10.1. ANALYSIS SETS

Primary end point: Analysis will be based on intention-to-treat principle. We will evaluate the main outcome, change in MELD score at day 42, in the framework of the repeated measurements analysis of covariance (ANCOVA) model. Specifically, MELD score at each follow-up visit will be used as the outcome variable. The main predictor is treatment group (GROUP). We will adjust for time (visit) and baseline MELD score and include the interaction between GROUP and visit. The interaction term allows evaluation of GROUP difference at each visit. The main comparison is the differences of MELD score change at day # 28 between two groups. A random intercept will be used to adjust for the correlation among the observations from the same subject. We will also evaluate the GROUP difference at 90 and 180 days in the framework of above repeated ANCOVA model.

SAEs during treatment: The primary analysis is to compare the proportion of patients having at least one SAE during the treatment period between the two groups using Chi-square tests. *SAE during follow-up* will be analyzed similarly. Other safety outcomes include AEs, discontinuations, pre-defined laboratory abnormalities, and predefined EKG abnormalities. Other continuous outcomes will be analyzed in a similar way to MELD score, binary outcomes will be analyzed in a similar way to SAE, and censored time-to-event outcomes will be analyzed using appropriate survival analysis tools (e.g., Kaplan-Meier plots, Cox models).

10.2. DETERMINATION OF SAMPLE SIZE

We examined the power of testing the difference in change of MELD score from baseline to day 28 with sample size of 30 in each group. Assuming a 10% drop out rate at day 28, we will have 27 subjects in each group. Using a two-sample t-test, we will have 80% power to detect any difference in effect size ≥ 78% of one standard deviation (smallest detectable effect size=0.78). The analysis using repeated-measurement ANCOVA will be more powerful than a two-sample t-test.

10.3. SAFETY ANALYSIS

Descriptive statistics will be used to summarize safety data to allow a comparison between groups.

Safety data, including AEs, clinical and laboratory observations and physical examination findings, and other safety related outcomes will be summarized by treatment group.

10.3.1. AEs

AEs will be labeled according to standard medical terminology using the case report forms provided. Summary tables of treatment-emergent AEs will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study medication. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study medication discontinuation and SAEs will be provided.

10.3.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology, chemistry, and coagulogram) will be presented for all trial visits. Changes from pretreatment to each trial visit will also be summarized by treatment group/arm.

10.3.3. Additional Safety and Clinical Findings

Additional safety assessments include vital signs, physical examinations, and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and trial visit, as well as the change from BL at each visit. The percentage of patients in each treatment group with clinically significant abnormal ECG findings will be summarized.

10.3.4. Other Safety Related Clinical Outcomes

The following clinical outcomes will be assessed:

- Death (from hepatic and non-hepatic related causes)
- Complications of portal hypertension including gastroesophageal bleeding, interventions to manage variceal bleeding (e.g., variceal banding/sclerotherapy or TIPS placement) and diuretic resistant ascites
- Complications of Cirrhosis: new-onset ascites, hepatic encephalopathy, hepatorenal syndrome (type I or II), and spontaneous bacterial peritonitis).
- Hospitalization

10.4. INTERIM ANALYSES

An interim efficacy analysis during the DB phase is not planned.

10.5. HANDLING OF MISSING DATA

Missing values will not be imputed and only observed values will be used in data analyses and presentations.

10.6. DATA AND SAFETY MONITORING COMMITTEE (DSMC)

An independent DSMC will be formed to review safety data at periodic intervals from this and all other TREAT studies. Members of the DSMC will not be allowed to participate as investigators in this trial.

The DSMC will review blinded safety data and unblinded safety data (as necessary in their opinion) to ensure the safe and proper treatment of patients. The frequency of their standard meetings will be according to the agreed upon DSMC charter. In addition, Chair of the DSMC or the designated study physician may call for an ad-hoc DSMC if deemed necessary by either party. Based on review of these data, the DSMC will send a written report to the designated study physician and to the DCU. It is the responsibility of the designated study physician and the DCU to distribute these reports to all other stakeholders (NIAAA, FDA, Intercept, and individual sites)

The DSMC will operate under an appropriate charter (in compliance with relevant regulatory guidance) that will define its organization and operation. The DSMC will prepare written minutes of both its open and closed sessions. The closed minutes will be made available to the investigators only after the database is locked and the blind for the trial has been broken.

All investigators and responsible IRBs will be informed of any decisions made which alter the conduct of this trial based on recommendations from the DSMC relating to patient safety. The investigators will inform the participants of such actions and the protocol and ICF will be revised, as appropriate.

Changes to the protocol or to the ICS may be initiated by any investigator, but it is the final responsibility of the designated study physician as the IND holder to approve/finalize any such changes and to communicate to other stakeholder.

11. ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

11.1. ETHICAL CONDUCT OF THE TRIAL

This trial will be conducted in accordance with 21CFR Part 312, Good Clinical Practice (CPMP/ICH/135/95), and with the ethical principles laid down in the Declaration of Helsinki and applicable regulatory requirements.

11.2. INSTITUTIONAL REVIEW BOARD (IRB)

A properly convened IRB at each participating site will review and approve this study prior to its initiation. Currently, the IRBs of the Mayo Clinic and the Indiana University School of Medicine have reciprocal agreements in place for selected protocols and it is probable that this protocol will be eligible for reciprocity between these two IRBs. All protocol amendments will be reviewed and approved by the IRBs. Amendments can be implemented only following the IRB approval unless the amendment is necessary to reduce immediate risk to trial participants.

The IRB will be informed of any new safety information that negatively affects the risk assessment of the trial as soon as it becomes available.

Investigators will report various categories of the AEs to the IRB according the schedule described in Table 4.

10.3. PATIENT CONFIDENTIALITY AND DATA PROTECTION

All information obtained during the conduct of the trial with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Clinical monitors (e.g., CRAs), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The trial data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the TREAT consortium. All data shall be secured against unauthorized access.

Apart from the site investigators, no one will have access to participant's identify. Each site will securely maintain the code that links participants' identity to their study numbers to prevent access to unauthorized third parties. Participants will be identified according their study numbers in the data management system (OnCore) and by the investigators during any communications.

The written ICF will explain that, for data verification purposes, authorized representatives of the funding agency, IRB or Intercept which is supplying the study medicine may require direct access to parts of the hospital or practice records relevant to the trial, including patient's medical history.

10.4. ACCESS TO SOURCE DOCUMENTS AND DATA

10.4.1. Source documents

Source documents may include, but are not limited to, medical records, charts, appointment books, patient questionnaires, original laboratory records, equipment print-outs. All source documents must be made available to the CRA. The following data must be included in the source data:

(a) Consent to participate in Trial

(b) Letter to Primary Care Physician, if applicable

(c) Patient visit dates

(d) Screening and Randomization Numbers

(e) Demographic information

(f) Medical history

(g) Disease history

(h) Physical examination

(i) Vital signs

(j) Laboratory assessments (copy of laboratory reports)

(k) AEs and concomitant medications

(l) Dates of dispensing study medication

(m)ECGs

(n) Liver biopsy reports (if applicable)

(o) Patient questionnaires

(p) Drug accountability

(q) Issues with protocol compliance

(r) Completion of, or withdrawal from, trial

10.4.2. Case Report Forms

A CRF to capture trial data will be completed by trial site staff for each patient who has signed the ICF and is assigned a 5-digit participant ID. The CRF must be completed promptly after each patient visit.

10.5. INVESTIGATOR OBLIGATIONS

The investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the patients for the duration of the trial. If the investigator is not present in the clinical research facility during the assessment, he or she will leave instructions for the trial site staff and a telephone number where he or she can be reached.

10.5.1. AE Reporting

The investigator is responsible for recording AEs reported by the patient or discovered by any other means during the trial. In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for immediate reporting of SAEs to the designated study physician.

10.5.2. Protocol Deviations

The investigator is not permitted to deviate from the protocol in any significant way without proper notification to the DCU and the study designated physician (Dr. Naga Chalasani). Changes to the protocol or to the ICS may be initiated by any investigator, but it is the final responsibility of the designated study physician as the IND holder to approve/finalize any such changes and to communicate to other stakeholder Although protocol amendments can be initiated by any study personnel, it is the final responsibility of the designated study physician as the IND holder to approve/finalize any protocol amendments. Any protocol amendments can be implemented at each site only after their local IRB approval. The only exception is when the investigator considers a participant's safety to be compromised if immediate action is not taken.

10.5.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

(a) Approved ICF

(b) IRB approvals (of protocol/amendments, patient questionnaires, etc.)

(c) Form FDA 1572 equivalent

(d) Current medical license of the primary site investigator

(e) Financial disclosure forms

10.6. DATA QUALITY ASSURANCE AND QUALITY CONTROL

Logic and consistency checks will be performed on all data entered into the CRF to ensure accuracy and completeness.

Training sessions, regular monitoring of the trial at the trial sites, instruction manuals, data verification, cross-checking and data audits will be performed to ensure quality of all trial data. Investigators' meetings and/or on-site trial initiations will be performed to prepare investigators and other trial site personnel for appropriate collection of trial data.

10.7. SITE MONITORING & AUDITING

10.7.1. Trial Monitoring

Trial records at each site will be monitored at regular intervals by a clinical research associate (CRA). The role of the CRA is to aid the investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the investigator's understanding of all applicable regulations concerning the clinical evaluation of the study medication and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential

documentation is available. Responsibility for properly implementing the protocol and maintaining complete trial records remain with each investigator.

In order to perform this role, the CRA must perform source data verification (SDV) and as such must be given access to the patient's primary source documentation (e.g., paper or electronic medical records) that support data entries in the CRF. The investigator may exercise judgment in allowing the CRA access to particular sections of the patient's medical records if these are deemed irrelevant to the performance, observations or conduct of this trial.

10.7.2. Trial Auditing

The investigator should understand that it may be necessary for the IRB and / or a regulatory agency to conduct one or more site audits during or after the trial and agrees to allow access to all trial related documentation and information and be available for discussion about the trial.

10.8. ARCHIVING AND RECORD RETENTION

The investigator should retain all correspondence relating to this trial in the Investigator Site File (ISF). Any trial documents stored elsewhere should have their location referenced in the ISF.

All documents relating to the trial including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed trial patient log and confidential patient identification list will be retained by the investigator for a minimum period of 15 years, in accordance with regulations. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the investigator should obtain written authorization from the Sponsor prior to the destruction of any records. The investigator will notify the Sponsor if ownership of documents or responsibility for the trial site is transferred. The Sponsor will inform investigators should it become aware of any changes in storage requirements.

10.9. PUBLICATION POLICY

No data are to be made public or published without prior knowledge and written approval by the TREAT Consortium Steering Committee.

The TREAT consortium publication policies will be applied. Intercept will have the opportunity to review each paper prior to its submission for publication.

11. LIST OF PLANNED LABORATORY ANALYTES

Serum Chemistry
sodium
potassium
calcium
chloride
bicarbonate
albumin
BUN
creatinine
total bilirubin
unconjugated (indirect) bilirubin
conjugated (direct) bilirubin
aspartate aminotransferase (AST; SGOT)
alanine transaminase (ALT; SGPT)
alkaline phosphatase (ALP)
glucose
total protein

MELD Score Calculation

http://www.mayoclinic.org/meld/mayomodel6.html

Hematology
hemoglobin
hematocrit
WBC with differential
platelets
RBC count (incl. MCV, HBE [MCH], MCHC)
prothrombin time (PT and INR)

Urine and Serum pregnancy test

Special investigations
serum FGF19
bile acid C4
fasting free fatty acids
lipid profile
insulin
adiponectin,
bacterial translocation (plasma LPS and sCD14)
cytokine measurements (serum TNF-α, IL-1, IL-6, and IL-8)
markers of oxidative stress
apoptosis
stool for calprotectin

EXPLORATORY EVALUATIONS

The following are the analyses that might be analyzed in the serum/plasma and peripheral blood mononuclear cells (PBMC).

Table 5: Exploratory evaluations

Cytokines/chemokines	Serum TNF-α, IL-1, IL-6, IL-8, and others as described in section D.
NK cells	Flow cytometry of PBMC for $CD3^{-}CD56^{+}$ cells. Cytotoxic activity will be measured by assessing intracellular perforin and granzyme expression.
Cytotoxic T cells	Flow cytometry of PBMC for $CD3+CD56^{+}$ cells. Cytotoxic activity will be measured by assessing intracellular perforin and granzyme expression.
Dendritic Cells (DC)	Flow cytometry for the number and phenotype (HLA-DR level). DCs in PBMCs lack CD3, $CD14^{hi}$, CD19, and CD56, but strongly express HLA-DR. Spontaneous ex-vivo cytokine production will be analyzed.
Complement activation	Plasma C3a levels and plasma circulating immune complexes

Table 6: Total Blood Volumes¶

	Sample Blood Volume (ml)								
Sample Type	**Screen**	**Day 0**	**Day 14**	**Day 28**	**Day 42**	**Day 90**	**Day 120**	**Day 180**	**Total Volume (ml)**
Chemistry	5	5	5	5	5	5	5	5	40
Hematology	3	3	3	3	3	3	3	3	24
Coagulation	3	3	3	3	3	3	3	3	24
Serum Pregnancy	3								3
Biospecimen Banking[1]		38	12	32	32	12	12	12	150
Special Investigations		20			20				40
Total	14	69	23	43	63	23	23	23	281

¶These are estimated volume and may vary from center to center, depending on local laboratory requirements.

[1] This volume may be lower if a particular center does not collect PBMCs as part of biospecimen banking.

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APPENDIX 1 – PROTOCOL AMENDMENT 1 (PROTOCOL VERSION 1.1): SUMMARY OF CHANGES

1. Background

   Protocol TREAT-002 has been prepared as a phase 2 trial to evaluate the efficacy of OCA in Patients with moderately severe AH.

   Protocol Version 1.0 was submitted to the US FDA. Based on comments raised by the FDA, Amendment 1 (Protocol Version 1.1) was prepared with minor clarifications.

2. Summary of Changes

   The following revisions were made to the protocol under Amendment 1. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1, October 10, 2013	TREAT-002, **v.1.1, November 20, 2013**
Page 1	Version 1	Version 1**.1**
Page 5 and 19; Inclusion Criteria	(b) Moderate severity defined as MELD score > 11 and < 20	(b) Moderate severity defined as MELD score > 11 and < **19**
Page 5 and 19; Inclusion Criteria	(c) Must not be receiving systemic steroids > 1 week at the time of Screening or any experimental medicines for AH	(c) Must not **have received** systemic steroids **for a duration of** > 1 week **during** the Screening period **or on the day of randomization and must not be receiving** any experimental medicines for AH
6.2.2, p. 27; 6th bullet	• Record prior (within 30 days of Day 0) and current concomitant medications.	• Record prior (within 30 days of Day 0) and current concomitant medications. **Ascertain that participant is not receiving concomitant systemic corticosteroids on the day of randomization.**
6.2.3, p. 28	3rd bullet added.	• Ascertain that participant is not receiving concomitant systemic corticosteroids
6.2.4, p. 28	• Review and record concomitant medications.	• Review and record concomitant medications. **Confirm that participant is not receiving concomitant systemic corticosteroids.**

Section	Original Text	Revised Text
6.2.5, p. 29	2nd bullet edited.	• The subject should be reminded that fasting (8 hours) is required prior to his/her next visit. The subject should not take study medication on the morning of the next clinic visit (D28) as s/he will dose at the clinic. **Confirm that participant is not receiving concomitant systemic corticosteroids.**
6.2.6, 6.2.7, p. 29/30	5th bullet edited.	• Review and record concomitant medications. **Confirm that participant is not receiving concomitant systemic corticosteroids.**

APPENDIX 2 – PROTOCOL AMENDMENT 2 (PROTOCOL VERSION 1.2): SUMMARY OF CHANGES

1. Background

Protocol Version 1.1 was reviewed by the TREAT Consortium Investigators. Based on comments by the investigators, Amendment 2 (Protocol Version 1.2) was prepared with minor changes.

2. Summary of Changes

The following revisions were made to the protocol under Amendment 2. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1.1, November 20, 2013	Header: TREAT-002, **v.1.2, January 17, 2014**
Page 1	Version 1.1	Version 1**.2**
Page 1	ClinicalTrials.Gov Identifier: Pending	ClinicalTrials.Gov Identifier: **NCT02039219**
Page 1	None	**IND Number: 120229**
Page 3 Table of Contents	None	**Table 6: Total Blood Volumes (Page 48)**
Page 18 Table 1	[5] Specimens to be banked include genomic DNA at D0, and blood (mononuclear cells**,** serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies	[5] Specimens to be banked include genomic DNA at D0, **blood mononuclear cells at D0, D28 and D42** and blood (serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies
Page 31 Section 6.2.10 Specimen Banking	Specimens to be banked include genomic DNA at D0, and blood (mononuclearcells**,** serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies.	Specimens to be banked include genomic DNA at D0, **blood mononuclear cells at D0, D28 and D42,** and blood (serum and plasma) samples at D0, D14, D28, D42, D90, D120 and D180. Stool samples collected at D0 and D42 will also be banked for future ancillary studies.
Page 37 Section 9.2.2	Safety officer for the TREAT Consortium is Suthat Liangpunsakul, MD	Safety officer for the TREAT Consortium is **Samer Gawrieh, MD**

Section	Original Text	Revised Text
Page 47 Table 6	None	**Table 6 added to show total blood volumes.**

APPENDIX 3 – PROTOCOL AMENDMENT 3 (PROTOCOL VERSION 1.3): SUMMARY OF CHANGES

1. Background

Protocol Version 1.2 was reviewed by the TREAT Consortium Investigators at the annual consortium meeting. Based on the discussion by the investigators, Amendment 3 (Protocol Version 1.3) was prepared with minor changes.

2. Summary of Changes

The following revisions were made to the protocol under Amendment 3. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1.2, January 17, 2014	Header: TREAT-002, **v.1.3, April 15, 2014**
Page 1	Version 1.2	Version 1**.3**
Page 3 Table of Contents	None	**Appendix 3 – page 57**
Page 18 Table 1: Schedule of Procedures	Row 14: Gut permeability & Hepatic CYP2E1 Row 5: Alcohol Consumption History Row 6: None	Row 14: Gut permeability & Hepatic CYP2E1**(optional)** Row 5**: AUDIT and NIAAA Questionnaires** Row 6**: Timeline Followback Questionnaire**
Page 28 Section 6.2.1 Screening Period	None	**The participant is to complete the AUDIT, NIAAA and Timeline Followback Questionnaires**
Page 29 Section 6.2.2 Day 0 Procedure	None	**Perform a standard 12-lead** electrocardiogram **(ECG)**
Page 29 Section 6.2.2 Day 0 Procedures	Perform gut permeability study Perform CYP2E1 Hepatic measurement study Alcohol Consumption History	Perform gut permeability study **(Subjects may opt out)** Perform CYP2E1 Hepatic measurement study (**Subjects may opt out)** Alcohol consumption history – **Timeline Followback Questionnaire**
Page 30 Section 6.2.4 Day 14 Procedures	Alcohol Consumption History	Alcohol consumption history – **Timeline Followback Questionnaire**

Section	Original Text	Revised Text
Page 31 Section 6.2.6 Day 28 Procedures	Alcohol Consumption History	Alcohol consumption history – **Timeline Followback Questionnaire**
Page 31 Section 6.2.7 Day 42 Procedures	Perform gut permeability study Perform CYP2E1 Hepatic measurement study Alcohol Consumption History	Perform gut permeability study **(Subjects may opt out)** Perform CYP2E1 Hepatic measurement study (**Subjects may opt out)** Alcohol consumption history – **Timeline Followback Questionnaire**
Page 32 Section 6.2.8 Follow up Phase	Alcohol Consumption History	Alcohol consumption history – **Timeline Followback Questionnaire**
Page 37 Section 9.2.2 Table 4: Requirements for Reporting AEs to various stakeholderS Table Column: NIAAA	None	**NIAAA** **AEs – Annual Report** **TEAEs – Annual Report** **SAEs – 2 working days** **SUSAR- 2 working days**
Page 37 Section 9.2.2 Table 4: Requirements for Reporting AEs to various stakeholderS Table Row: SUSAR	Local IRB – 5 days. Report to NIAAA in 48 hours DSMB – 7 days if death. 15 days if other Other Centers: 5 days Intercept: 5 days FDA: – 7 days if death. 15 days if other	Local IRB – 5 days **NIAAA- 2 working days** DSMB – **2 working days** Other Centers: **2 working days** Intercept: **2 working days** FDA: – 7 days if death. 15 days if other
Page 37 Section 9.2.2 Reporting SAE	All SAEs must be reported to the DCU (i.e., within 24 hours or the next working day after the investigator identifies the SAE. SAEs should be entered into the OnCore system within 24 hours (or the next working day) of the investigator becoming aware of the event.	All SAEs must be reported to the DCU (i.e., within **2 working days**) after the investigator identifies the SAE. SAEs should be entered into the OnCore system within **2 working days** of the investigator becoming aware of the event.

Section	Original Text	Revised Text
Page 37 Section 9.2.2 Reporting SAE	Any supporting source documentation should be faxed or emailed to the assigned contact information as soon as possible. At a minimum the following information should be provided at the time of the initial report: 5-digit participant ID, a description of the event, at least one criterion classifying the event as Serious and the name and title of the reporting individual.	Any supporting source documentation should be emailed to the assigned contact information as soon as possible. At a minimum the following information should be provided at the time of the initial report: 5-digit **Study** ID, a description of the event, at least one criterion classifying the event as Serious and the name and title of the reporting individual.

APPENDIX 4 – PROTOCOL AMENDMENT 4 (PROTOCOL VERSION 1.4): SUMMARY OF CHANGES

1. Background

   Protocol Version 1.3 was reviewed and was noted that further clarification was needed in the study procedure section of the protocol

2. Summary of Changes

   The following revisions were made to the protocol under Amendment 4. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1.3, April 15, 2014	Header: TREAT-002, **v.1.4, May 15, 2014**
Page 1	Version 1.3	Version 1**.4**
Page 18 Table 1	None	**Assess Liver Scores: MELD, Child Pugh and/ or Discriminant Function**
Page 27 6.2.1 Screening Period	None	**Assess Liver Scores: MELD**
Page 28 6.2.2 Day 0 Procedures	None	**Assess Liver Scores: MELD, Child Pugh and Discriminant Function**
Page 28 6.2.2 Day 0 Procedures	Perform a Standard 12- lead electrocardiogram (ECG)	**None**
Page 29 6.2.4 Day 14 Procedures	None	**Assess Liver Scores: MELD, Child Pugh and Discriminant Function**
Page 30 6.2.6 Day 28 Procedures	None	**Assess Liver Scores: MELD, Child Pugh and Discriminant Function**
Page 30 6.2.7 Day 42 Procedures	None	**Assess Liver Scores: MELD, Child Pugh and Discriminant Function**
Page 30 6.2.7 Day 42 Procedures	None	**Perform a Standard 12- lead electrocardiogram (ECG)**
Page 31 6.2.8 Follow up	None	**Assess Liver Scores: MELD, Child Pugh and Discriminant Function**

APPENDIX 5 – PROTOCOL AMENDMENT 5 (PROTOCOL VERSION 1.5): SUMMARY OF CHANGES

1. Background

Progress of recruitment and obstacles was discussed at the annual TREAT Face to Face meeting in March 2015. A decision was made to remove the sub studies (Gut Permeability test and Hepatic CYP2E1 Measurement study).

2. Summary of Changes

The following revisions were made to the protocol under Amendment 4. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1.4, May 15, 2014	Header: TREAT-002, **v.1.5, April 15, 2015**
Page 1	Version 1.4	Version 1.**5**
Page 4-5 Objectives Secondary	• Changes in hepatic CYP2E1 activity • Changes in intestinal permeability	
Page 16-17 Trial Objectives Secondary	• Changes in hepatic CYP2E1 activity • Changes in intestinal permeability	
Page 18 Table 1 Schedule of Procedures	Gut Permeability and Hepatic CYP2E1 (optional)	
Page 28 Section 6.2.2 Day 0 Procedures	• Perform gut permeability study (Subjects may opt out) • Perform CYP2E1 activity measurement (Subjects may opt out)	
Page 30 Section 6.2.7 Day 42 Procedures	• Perform gut permeability study (Subjects may opt out) • Perform CYP2E1 activity measurement (Subjects may opt out)	
Page 32 Section 7 Efficacy Evaluations Secondary Objectives	Changes in hepatic CYP2E1 activity Changes in intestinal permeability	

Section	Original Text	Revised Text
Page 47 Table 6: Total Blood Volumes	Hepatic CYP2E1	Row Deleted and total Blood volumes adjusted

APPENDIX 6 – PROTOCOL AMENDMENT 6 (PROTOCOL VERSION 1.6): SUMMARY OF CHANGES

1. Background

   TREAT Consortium made decision to increase inclusion MELD score to <20. Language regarding the gut permeability test and hepatic CYP2E1 measurements was removed from the synopsis to correctly reflect the changes made in protocol version 1.5.

2. Summary of Changes
   The following revisions were made to the protocol under Amendment 6. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, v.1.5, April 15, 2015	Header: TREAT-002, **v.1.6, December 10, 201**
Page 1	Version 1.5	Version 1.**6**
Page 5 Treatment Phase	Gut permeability and hepatic CYP2E1 activity will be measured at days 0 and 42, with additional special investigations at days 0 and 42.	None
Page 6 Key Eligibility Criteria: Inclusion Criteria	(b) Moderate severity defined as MELD score > 11 and < 19	(b) Moderate severity defined as MELD score > 11 and < **20**
Page 20 Section 4: Patient Selection 4.2 Inclusion Criteria	**(b)** Moderate severity defined as MELD score > 11 and < 19	**(b)** Moderate severity defined as MELD score > 11 and **< 20**

APPENDIX 6 – PROTOCOL AMENDMENT 7 (PROTOCOL VERSION 1.7): SUMMARY OF CHANGES

1. Background

   TREAT Consortium added Einstein Medical Center as a study site. The protocol has been updated to reflect the addition of the new study site.

2. Summary of Changes
   The following revisions were made to the protocol under Amendment 7. (Note: Differences have been indicated in **bold font**.)

Section	Original Text	Revised Text
All pages	Header: TREAT-002, **v.1.6, December 10, 201**	Header: TREAT-002, **v.1.7, November 29, 2016**
Page 1	Version 1.6	Version 1.**7**
Page 5 Planned Number of Investigational Sites	Three investigational trial sites at Indiana University in Indianapolis, Mayo Clinic in Rochester, and Virginia Commonwealth University in Richmond	**Four** investigational trial sites at Indiana University in Indianapolis, Mayo Clinic in Rochester, Virginia Commonwealth University in Richmond, **and Einstein Medical Center in Philadelphia**