TREAT Protocol 005
Obeticholic Acid (OCA)

EFFECT OF HEAVY ALCOHOL CONSUMPTION ON FARNESOID X RECEPTOR (FXR) SIGNALING

ClinicalTrials.Gov Identifier: NCT02654236

Version 3: January 18, 2019
Revised: January 22, 2020

Investigators:

Indiana University: Suthat Liangpunsakul, Naga Chalasani, David Crabb

Disclosure

This study is conducted the TREAT consortium which is funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to pursue translational investigations in alcoholic hepatitis. TREAT Consortium contains 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.

SYNOPSIS

Title of Trial

Effect of alcohol consumption on farnesoid x receptor (FXR) signaling

Name of Active Ingredient

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

Investigational Site

Indiana University Hospital, Indianapolis, Indiana

Planned Number of Patients

Approximately 45 subjects [healthy non-drinker controls (n=15) and heavy drinkers (n=30)].

Hypotheses & Objectives

1. To test the hypothesis that heavy alcohol consumption impairs farnesoid X receptor (FXR, the bile salt nuclear receptor) signaling which results in increased hepatocyte bile salt levels which cause liver injury.

2. To test the hypothesis that impaired FXR signaling resulting from heavy alcohol consumption impairs gut integrity, promotes activation of Kupffer cells, enhances hepatic oxidative stress, and sensitizes hepatocytes to cytokine-induced necroapoptosis, and that these abnormalities can also be reversed with OCA.

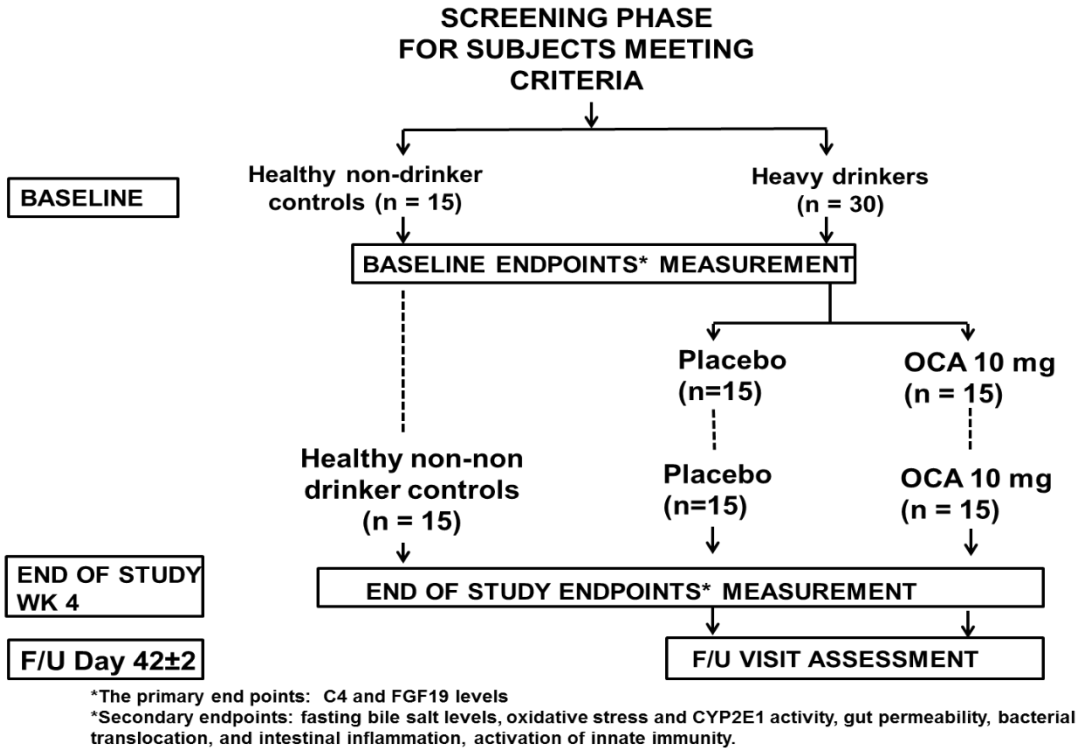
Design

This study consists of two groups of participants – heavy drinking adults (n=30) and non-drinking healthy controls (n=15). There are two components to this study – initial cross-sectional component followed by a 4 week longitudinal component. We are seeking to increase the overall number of subjects allowed to be consented to 150 to ensure that 30 heavy drinking adults can complete this study.

In the cross-sectional component, both groups of participants will undergo testing for bile acid metabolism, markers of gut integrity, oxidative stress, and inflammatory cytokines.

Both groups of participants will participate in the longitudinal component. While healthy controls will not receive any specific intervention, participants in the heavy drinking group will be randomized to receive either OCA (10 mg/day) or placebo for 28 days. At the end of 4 weeks, both groups of participants will again undergo testing for bile acid metabolism, markers of gut integrity, oxidative stress, and inflammatory cytokines.

Schematic Diagram



*The primary end points: C4 and FGF19 levels
*Secondary endpoints: fasting bile salt levels, oxidative stress and CYP2E1 activity, gut permeability, bacterial translocation, and intestinal inflammation, activation of innate immunity.

Methodology

Screening phase

Subjects will be assessed for the eligibility criteria and a written informed consent will be obtained from the eligible subjects.

Treatment phase,

This investigation will consist of the following 2 study groups:

Group A: Healthy non-drinker controls (n = 15)
Group B: Heavy drinkers with no known history of liver disease (n=30)

Heavy alcohol drinking will be defined as ongoing consumption > 40 grams per day or >98 grams in a week on average in women and > 60 grams per day or >196 grams in a week on average in men for a minimum of the past 6 months and within the 3 months prior to study enrolment. Judgment regarding daily and yearly alcohol use will be made by the site investigator. During recruiting we will inform the patient that this level of drinking is harmful and will offer referral for treatment. Absence of liver disease will be ascertained according to predefined criteria. Alcohol consumption will be quantified by interview and by a standard alcohol consumption questionnaire.

Follow-up Phase:

Heavy Drinker group will return to the clinic on Day 42

Key Inclusion Criteria:

(a) Individuals ≥ 21 – 65 years old
(b) Able to provide informed consent & negative urine pregnancy test where appropriate
(c) Healthy controls must not have consumed any alcohol within 3 months prior to the screening visit
(d) Healthy controls (non drinkers) must have normal ALT and AST values (<45 U/L)
(e) Heavy drinkers must have ALT and AST lab values <100 U/L
(f) Heavy alcohol drinking is defined as > 40 grams per day or >98 grams in a week on average in women and > 60 grams per day or >196 grams in a week on average in men for a minimum of 6 months and within the 3 months prior to study enrolment. Judgment regarding daily and yearly alcohol use will be made by the site investigator.

Exclusion Criteria:

(a) Active infection as evidenced by positive urine culture, blood culture, or pneumonia, if necessary, after review of safety labs showing abnormalities, or determination by physical exam performed by PI/sub-I.
(b) Serum creatinine > 1.5 mg/dL
(c) Known co-existing infection with hepatitis C, hepatitis B, or HIV
(d) Significant systemic or major illness including COPD, CHF and renal failure that in the opinion of the Investigator would preclude the patient from participating in and completing the study.
(e) Participation in another investigational drug, biologic, or medical device trial within 30 days prior to Screening
(f) Previous history of jaundice or signs of liver diseases such as spider angiomata, ascites, portal hypertension, or history of esophageal varices or hepatic encephalopathy
(g) Total bilirubin > 2 mg/dl and INR > 1.5
(h) Women who are pregnant or nursing
(i) 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).
(j) Subjects who are taking warfarin

Treatment Regimen

1 tablet of placebo or 10 mg OCA as directed, taken daily with water, approximately 30 minutes prior to breakfast

Route of Administration

Oral

Duration of Treatment

The duration of treatment will be 4 weeks.

Study Measurements:

The primary end points of interest are measures of FXR effect on bile salt metabolism (C4) and FGF19 levels.

Secondary endpoints are measures of:

(a) fasting serum bile salt
(b) oxidative stress and CYP2E1 activity;
(c) gut permeability, bacterial translocation, and intestinal inflammation;
(d) activation of innate immunity.

Primary Objectives	**Variable**
Measuring surrogates of FXR activity	Serum FGF19, C4 levels
Secondary Objectives	
Clinical laboratory values:	Fasting serum bile salt levels Adipocyte function (fasting NEFA, insulin, adiponectin), Oxidative stress (malondialdehyde, 8-isoprostane) CYP2E1 activity by chlorzoxazone clearance Gut permeability (lactulose/mannitol test) Bacterial translocation (plasma LPS, serum sCD14), Cytokine measurements (serum TNF-α, IL-1, IL-6, and IL-8) Intestinal inflammation (stool calprotectin). Any AE and SAEs

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF PERSONNEL

Investigation Site

Indiana University, Indianapolis, IN

Site investigators

Suthat Liangpunsakul, MD
David W. Crabb, MD
Naga P. Chalasani, MD

Division of Gastroenterology and Hepatology
Department of Medicine
Indiana University School of Medicine
702 Rotary Circle (Ste 225)
Indianapolis, IN 46202

Research Coordinators

Jennifer Lehman, RN, CCRP

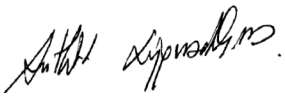
Division of Gastroenterology and Hepatology
Department of Medicine
Indiana University School of Medicine
702 Rotary Circle (Ste 225)
Indianapolis, IN 46202

SAE Reporting

Contact:	Samir Gawrieh, MD
Telephone:	1-317-278-1216
Email:	sgawrieh@iu.edu
SAE Email:	sgawrieh@iu.edu and sliangpu@iu.edu

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:



5/23/2018

Suthat Liangpunsakul, MD Date

INVESTIGATOR'S PROTOCOL APPROVAL PAGE

I have received and read the current version of the Investigator's Brochure (IB) for OCA and this Protocol TREAT-005. 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 Supporter, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this trial and not previously published is confidential information. This includes the IB, and any other preclinical and clinical data provided by the Supporter.

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

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-005 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

Suthat Liangpunsakul

Investigator's Name (Printed)

Investigator's Signature

5/23/2018

Date

ABBREVIATIONS

Abbreviation	Definition
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BA	bile acid(s)
BL	Baseline
BP	blood pressure
β-hCG	beta human chorionic gonadotrophin
BUN	blood urea nitrogen
CA	cholic acid
CDCA	chenodeoxycholic acid
CFR	Code of Federal Regulations
CIOMS	Council for International Organisations of Medical Sciences
C_{max}	maximum concentration
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DCA	deoxycholic acid
dL	deciliter(s)
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
ECG	Electrocardiogram
ELISA	enzyme linked immunosorbent assay
EOT	end of treatment
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c test
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IL-6	Interleukin-6
kg	Kilogram
LCA	lithocholic acid
LDL	low-density lipoprotein
MELD	Model for End Stage Liver Disease
mg	milligram(s)
mL	milliliter(s)
msec	Millisecond
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PBC	primary biliary cirrhosis
PI	principal investigator
PK	pharmacokinetic(s)
PO	Orally
PSC	primary sclerosing cholangitis
SAE	serious adverse event
SAP	statistical analysis plan
Sponsor	Intercept Pharmaceuticals, Inc.
SUSAR	suspected, unexpected serious adverse reaction
TE	transient elastography
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
VLDL	very low density lipoprotein
vs	Versus
WBC	white blood cell
WNL	within normal limits

1. INTRODUCTION AND RATIONALE

1.1 RATIONALE

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 completely unknown 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. Those with more severe cases of AH; however, have a high mortality rate [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, hospitalized AH patients result in significant healthcare cost 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 livery 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] and AMPK [11], and 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.

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 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. 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 have been studied particularly in primary biliary

cirrhosis and in NASH, but not in heavy drinkers or in alcoholic liver disease. 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 alcoholic hepatitis (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. As shown in Figure 1, alcohol feeding of mice for 4 weeks reduces 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.

We hypothesize that alcohol-induced impairment of signaling via farnesoid X receptor (FXR, the bile salt nuclear receptor) results in increased hepatocyte bile salt levels and that this contributes to liver injury. **To address this hypothesis**, we will conduct a study in healthy non-drinker controls (n=15) and heavy drinkers (n=30) *We expect that (a) heavy drinking is associated with impaired FXR signaling, resulting in increased bile salt synthesis (reflected by increased levels of the bile acid C4) and reduced synthesis of FGF19 (reflected by decreased plasma levels); and (b) an FXR agonist, obeticholic acid (OCA), will reverse these abnormalities.* As a secondary hypothesis, we propose that impaired FXR signaling impairs gut integrity, promotes activation of Kupffer cells, enhances hepatic oxidative stress, and sensitizes hepatocytes to cytokine-induced necroapoptosis, and that these abnormalities can also be reversed with OCA.

1.2 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.

1.3 Clinical Experience with Obeticholic Acid (OCA)

OCA has been extensively evaluated in human studies ranging from patients with primary biliary cirrhosis to non-alcoholic steatohepatitis. Please refer to the investigator brochure (IB) Section 5 pages 50-116 for full detail.

As for the 10 mg dose of OCA that we proposed in this study, in Study 747-105 (see IB Page 55, oral administration of single doses of OCA (5 mg, 10 mg, and 25 mg) resulted in rapid absorption with plasma OCA concentrations measurable as early as 15 minutes post dose. Mean Cmax values ranged from 19 ng/mL at the 5 mg dose to 79 ng/mL for the 25 mg dose. Median time to achieve peak plasma OCA concentration (Tmax) occurred between 0.5 hours and 1.8 hours post dose across all 3 dose levels. Secondary absorption peaks were observed, generally occurring following a meal, which is suggestive of enterohepatic recirculation as expected for a bile acid and thus leading to prolonged exposure.

1.4 Rationale for Trial Design and Dose for Study Medication

This proposed trial will evaluate the endpoints of interest between controls (n=15) and heavy drinkers (n=30). To determine the effect of OCA on FXR signaling, we will randomize heavy drinker subjects into placebo (n=15) and OCA (dose 10 mg orally once a day for 28 days, n= 15).

Rationale for Doses

Inherently, there is an element of arbitrariness in choosing dose of and duration of treatment in early phase clinical trials. Twenty-eight day treatment is consistent with the treatment duration for prednisolone and pentoxifylline [9], two pharmacological agents with some efficacy in patients with acute AH.

We chose 10 mg dose to investigate because (a) it is the dose that is being used in the ongoing PBC and NASH clinical trials, (b) it is the dosage 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).

Rationale for Duration

The duration of treatment has been chosen based on the similar duration of treatment of currently available therapy for AH (i.e., prednisone or pentoxyphylline).

Summary of known potential risks with study medication

Please refer to the IB section 5.3 for the reported safety across all the studies conducted with OCA. One major issue is pruritus in patients taking OCA. The dose of 10 mg in this study is similar to that was used in the longer-term, Phase 3 PBC study (747-301). In this study, lower doses of OCA and a titration strategy (titrating from 5 mg daily to 10 mg daily after

6 months of treatment) were tested. These changes appeared to result in improved safety and tolerability, and the majority of subjects (198 [92%]) completed the 1-year, double-blind phase. A total of 16 OCA-treated subjects (11%) discontinued from the study, 8 of whom were due to pruritus. An overwhelming majority of subjects who discontinued due to pruritus were randomized to initiate treatment at the 10-mg OCA dose level (7 of 8 subjects). Conversely, in subjects who initiated treatment at the 5 mg dose level (titration arm) only 1 subject discontinued due to pruritus. No placebo-treated subjects discontinued due to pruritus in any of the PBC studies. Please note that in this proposed study, the duration of treatment is much shorter (only 4 weeks), thus we expect that this potential side effect would be minimal.

2. STUDY OBJECTIVES

The objectives of our study is to test the hypothesis that heavy alcohol consumption leads to the alteration of FXR signaling and such effect of alcohol on FXR can be reversed with the treatment of OCA. The endpoints of this study are

2.1 The primary end points of interest are measures of FXR effect on bile salt metabolism (C4) and FGF19 levels

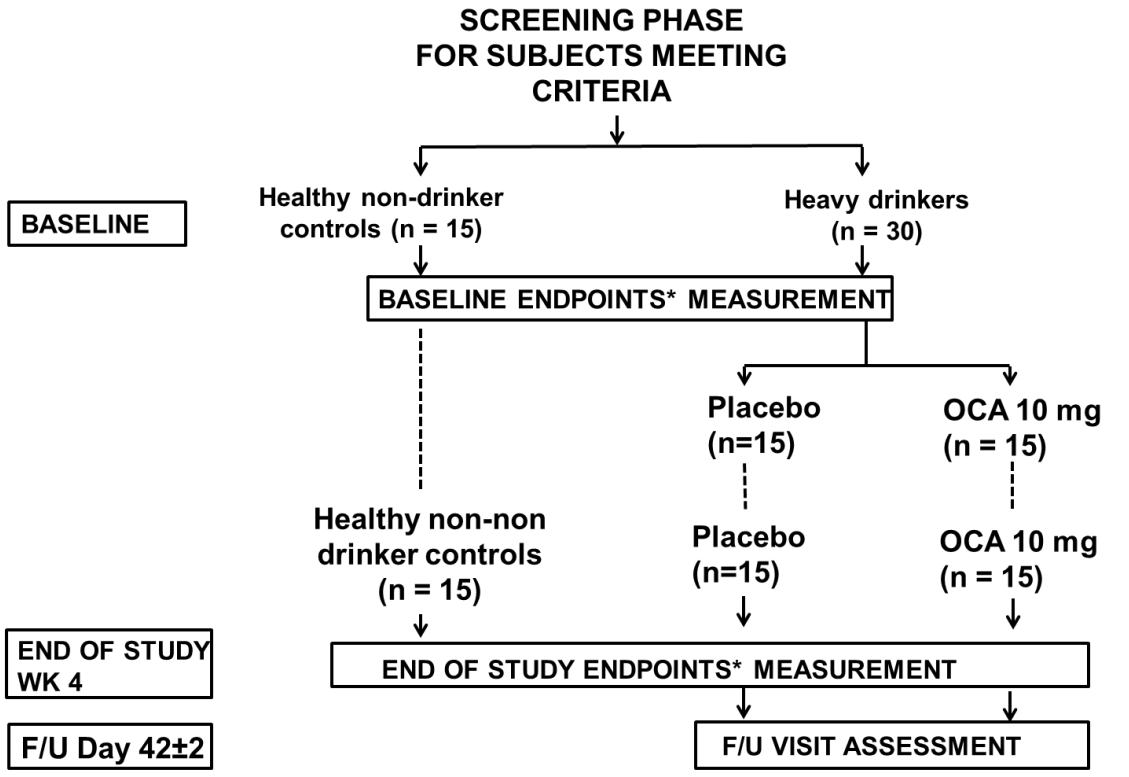
2.2 Secondary endpoints are measures of: (a) fasting serum bile salt levels, oxidative stress and CYP2E1 activity; (c) gut permeability, bacterial translocation, and intestinal inflammation; and (d) activation of innate immunity

3. INVESTIGATIONAL PLAN

3.1 OVERALL TRIAL DESIGN AND PLAN

Design

Schematic Diagram



*The primary end points: C4 and FGF19 levels
*Secondary endpoints: fasting bile salt levels, oxidative stress and CYP2E1 activity, gut permeability, bacterial translocation, and intestinal inflammation, activation of innate immunity.

3.2 SCHEDULE OF STUDY PROCEDURES

Table 1 Schedule of Study Procedures

	Screening	D0	D7	D28	D42
Informed Consent	x				
Confirmation of Eligibility Criteria	x	x			
History and physical	x	x		x	
Vitals *(Day 42- Heavy Drinker group only)*	x	x		x	x
Randomization *(Heavy Drinker group only)*		x			
Telephone Visit *(Heavy Drinker group only)*			x		
Alcohol consumption history	x	x		x	
Concomitant medications Assessment *(Day7 & 42 -Heavy Drinker group only)*	x	x	x	x	x
Adverse Event Assessment *(Day7 & 42 -Heavy Drinker group only)*		x	x	x	x
Electrocardiogram *(Heavy Drinker group only)*	x			x	
Dispense Study Medication *(Heavy Drinker group only)*		x			
Evaluation of study drug compliance *(Heavy Drinker group only)*			x	x	
CBC with Diff, CMP, PT/ INR Safety labs *(Day 28 & 42– Heavy Drinker group only)*	x	x		x	x
Urinalysis	x				
Urine Pregnancy test *(if applicable)*	x	x		x	
Hepatic CYP2E1 measurement study		x		x	
Gut Permeability Test		x		x	
Collection of Research Blood Samples for special investigations[1]		x		x	
Collection of stool specimen (optional)[1]		x		x	

[1]Special Investigation Research samples collected for this protocol consist of FGF19, C4, fasting bile acid pool, adipocyte function (fasting NEFA, insulin, adiponectin), oxidative stress (malondialdehyde, 8-isoprostane), bacterial translocation (plasma LPS, serum sCD14), cytokine measurements (serum TNF-α, IL-1, IL-6 and IL-8) and stool for calprotectin

3.3 Duration of Trial by Phase

Time expected for all patients to be enrolled:	4. 4 years
Duration of individual patient participation:	Approximately 2.5 months Up to 30 days for the screening phase 30 Days for the treatment phase *(includes 28 day intervention for Heavy Drinker group)* 14 days for the follow-up phase

5. PATIENT SELECTION

5.1 PATIENT POPULATION

Prospective patients will be identified primarily from the hospitals including Fairbanks Drug and Alcohol Rehabilitation Hospital, outpatient clinics, self-referrals or may be referred by physicians from other hospitals and clinics. Throughout this protocol, the terms 'Principal Investigator (PI)', 'investigator' and 'investigator or designee' are 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.

5.2 INCLUSION/ EXCLUSION CRITERIA

If used, the term 'baseline' (BL) within this protocol, unless otherwise specified, is intended to mean, 'pre-study' or 'pre-treatment' (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. The statistical or calculated definition(s) of 'baseline' to be used in the analyses of the data may be different and will be further defined in the statistical analysis plan (SAP) for this trial.

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

Inclusion Criteria:

(a) Individuals ≥ 21 to 65 years old
(b) Able to provide informed consent & negative urine pregnancy test where appropriate
(c) Healthy controls must have not consumed any alcohol within 3 months prior to the screening visit
(d) Healthy controls (non drinkers) must have normal ALT and AST values (<45 U/L)
(e) Heavy drinkers must have ALT and AST lab values <100 U/L
(f) Heavy alcohol drinking is defined as > 40 grams per day or 98 grams in a week on average in women and > 60 grams per day or 196 grams in a week on average in men for a minimum of 6 months and within the 3 months prior to study enrolment. Judgment regarding daily and yearly alcohol use will be made by the site investigator.
(e) Women of child bearing potential should be willing to practice contraception throughout the treatment period

Exclusion Criteria:

(a) Active infection as evidenced by positive urine culture, blood culture, or pneumonia, if necessary, after review of safety labs showing abnormalities, or determination by physical exam performed by PI/sub-I.
(b) Serum creatinine > 1.5 mg/dL
(c) Known co-existing infection with hepatitis C, hepatitis B, or HIV

(d) Significant systemic or major illness including COPD, CHF and renal failure that in the opinion of the Investigator would preclude the patient from participating in and completing the study.
(e) Participation in another investigational drug, biologic, or medical device trial within 30 days prior to Screening
(f) Previous history of jaundice or signs of liver diseases such as spider angiomata, ascites, portal hypertension, or history of esophageal varices or hepatic encephalopathy
(g) Total bilirubin > 2 mg/dl and INR > 1.5
(h) Women who are pregnant or nursing
(i) 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).
(j) Subjects who are taking warfarin

5.3 PATIENT WITHDRAWAL FROM THE TRIAL

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 pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the investigator and study physician (Dr. Liangpunsakul or designee). For reporting purposes pregnancy is not considered a serious adverse event (SAE).

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 to continue trial participation at any time.
- The patient experiences an adverse event (such as AE grade 3) that in the opinion of the investigator or Safety Monitor 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.
- Investigator's decision.

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

Patient Discontinuation Notification

The investigator must notify the study designated physician (Dr. Liangpunsakul 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(s) 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 patient is withdrawn from the trial early during the treatment phase (regardless of the cause), all of the Day 28 evaluations should be performed at the time of withdrawal, to the extent possible.

6. 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'.

5.2 Study Medication

OCA is a white, round tablet with "INT" engraved on one side and "3547" engraved on the other side. All study medication will be provided as a tablet for oral administration and provided in high density polyethylene (HDPE) bottles with an induction seal and child proof caps.

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

6.3 PACKAGING, LABELLING, AND STORAGE

The packaging and labeling of study medication supplies will be performed according to GMP standards by a designated qualified vendor and in accordance to 21 CFR 312.6. It will be Limited by Federal Law to Investigational Use Only.

The designated drug packaging/distribution vendor will also be responsible for the distribution of the study medication to the investigator and, where applicable, providing the Qualified Person (QP) release of study medication. Study medication should be stored in the containers in which they are received from the Sponsor's supplier, at controlled room temperature, and protected from excess humidity.

Study medication will be packaged for the trial as described below. Study medication for the trial will be packaged and labeled as single bottles containing 30 tablets and should be dispensed to the patient as received. The investigative pharmacist at the site will prepare the study medication for appropriate dispensing to the subjects according to standard operating procedures.

6.4 DOSE AND ADMINISTRATION

Heavy drinker subjects will be randomized to placebo or OCA (10 mg). Study medication will be administered orally, once daily for 28 days during the study. Patients will be instructed to begin dosing on the day after the Day 0 visit and after the baseline endpoint measurements are obtained (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.

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)

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 physician (Dr. Liangpunsakul or designee) should be notified immediately in the event of a significant overdose.

6.5 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.

6.6 TREATMENT COMPLIANCE

The investigator should assess the patient's compliance with dosing of study medication on an ongoing basis.

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 bottles that have 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 Sponsor accordingly. Continued trial eligibility should be assessed based on the patient's compliance with study medication dosing and clinic visits.

6.7 STUDY MEDICATION ACCOUNTABILITY AND RETENTION

Intercept Pharmaceutical, Inc's representative will send study medication to the trial site 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 under the appropriate storage conditions 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 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 (as directed by the Sponsor).

6.8 TRIAL OR SITE TERMINATION

The Sponsor 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 DSMB, it may be necessary to stop the trial before all patients have completed the trial.

The investigator must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of the trial and the reason for doing so.

7. TRIAL PROCEDURES

7.1 SCREENING

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.

Screening Numbers

At the Screening Visit, after the patient has provided written informed consent, the patient will be assigned a 5 digit subject participant (screening) number. This number will be recorded in the CRF.

Patient Identification Assignment

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

7.2 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.

Screening Procedures (≤30 days)

The Screening Visit assessments must be performed within 30 days prior to Day 0 to determine whether the patient meets all the inclusion criteria and none of the exclusion criteria. Patients who do not fulfill all eligibility criteria will not be enrolled in the trial.

Screening Visit procedures are as follows:

- The patient 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

- Collect medical and disease history
- Collect alcohol use history
- Verify inclusion and exclusion criteria for eligibility
- Perform a physical examination, including height (Screening only) and weight
- Record vital signs
- Perform a standard 12-lead electrocardiogram (ECG) *–Heavy Drinker Group Only*
- Record prior (within 30 days of screening visit) and current concomitant medications.
- Obtain blood samples for serum chemistry and hematology tests
- Obtain urine sample for dipstick urinalysis
- Perform a urine based beta human chorionic gonadotrophin (β-hCG) pregnancy test in females of childbearing potential

Day 0 Procedures (Randomization and Baseline Study Day)

- Review inclusion and exclusion criteria for eligibility
- Record vital signs
- Perform a Physical Examination
- Assess and record any pretreatment emergent events
- Record prior (within 30 days of Day 0) and current concomitant medications
- Assess Alcohol Consumption
- Perform an urine pregnancy test in females of childbearing potential
- Perform Hepatic CYP2E1 Measurement Study
- Perform Gut Permeability Test (Lactulose/ Mannitol test)
- Obtain safety labs (CMP, CBC and PT/INR)
- Obtain Research Blood samples as outlined in Table 1: Schedule of Study Procedures
- Obtain Stool Specimen (optional)
- Randomization to study drug *(Heavy drinker group only)*
- Dispense study drug *(Heavy drinker group only)* and instruct patient to begin dosing on the day after Day 0 visit and to take the study medication with water approximately 30 minutes prior to breakfast.

Day 7 Procedures (+/- 2 days)- *Heavy Drinker Group Only*

- This consists of a telephone visit where the study staff will inquire with the subject on his/her wellbeing, compliance with study medication, adverse events and concomitant medication use.

Day 28 Procedures (+/- 2 days)

Healthy non-drinkers controls will have repeated procedures at D0 performed. The same procedures will also be done in heavy drinkers when they complete the study drug for 28-day.

- Record vital signs
- Perform a Physical Examination
- Assess and record any Adverse Events
- Assess concomitant medications
- Perform a standard 12 Lead Electrocardiogram *(Heavy Drinker Group only)*
- Obtain Safety Labs (CBC, CMP and PT/ INR) *(Heavy Drinker group only)*
- Evaluation of Study Drug Compliance *(Heavy Drinker Group only)*
- Collection of all study medication and bottles *(Heavy Drinker Group only)*
- Assess Alcohol Consumption
- Perform Hepatic CYP2E1 Measurement Study
- Perform Gut Permeability Test (Lactulose/ Mannitol test)
- Obtain Research Blood samples as outlined in Table 1: Schedule of Study Procedures
- Obtain Stool Specimen (optional)
- Perform an urine pregnancy test in females of childbearing potential

Day 42 Follow-up Procedures (+/- 2 days) - *Heavy Drinker Group Only*

- Record vital signs
- Assess and record any Adverse Events
- Assess concomitant medications
- Obtain Safety Labs (CBC, CMP and PT/ INR)

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 Safety Monitor should be contacted.

7.3 PHYSICAL EXAMINATION AND VITAL SIGNS

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 (Tables 1). This includes height only at Screening.

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.

7.4 CLINICAL LABORATORY

Blood samples for serum chemistry, hematology, and coagulopathy will be collected at every visit as detailed in the Schedule of Trial Procedures (Tables 1). The number and volume of samples to be collected at each visit will be detailed in the Standard Operating Procedures.

Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a trial specific laboratory manual. 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.

7.5 ELECTROCARDIOGRAM

Standard 12-lead ECGs will be collected. 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 initials, Participant or Study ID Number, date and time.

The ECG read will be completed by the investigator or designee. At a minimum the following will be assessed: PR, QRS, QT and QTc intervals and a clinical evaluation for each ECG will be provided.

8. ADVERSE EVENTS

7.1 DEFINITION AND 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 the time the patient signs the ICF until the patient completes trial participation.

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 OCA.

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.

Pretreatment Event(s)

Untoward events that occur between the time the patient signs the ICF for the trial and the time when that patient is first administered the study medication are classified as "pre-treatment" events. Any pretreatment event should be recorded as medical history.

7.2 Severity of AEs

AEs must be graded for severity (i.e., intensity). A severity category of mild, moderate, or severe, as defined in Table 3, 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.” 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.

7.3 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 5. 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 the known characteristics of the subject's clinical state.
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.

8.4 SERIOUS ADVERSE EVENTS

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:

Death;

Is life threatening;

Results in hospitalization or prolongation of existing hospitalization;

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

A congenital anomaly/birth defect;

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.

An AE is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

7.5 Reporting SAEs

In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for immediate reporting of SAEs to the Safety Officer.

The Safety Officer for this trial is:

Samer Gawrieh, MD
Telephone: 317-278-1216
Email: sgawrieh@iu.edu
SAE Email: sgawrieh@iu.edu and sliangpu@iu.edu

All SAEs must be reported to the Safety Officer 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 as soon as possible. At a minimum the following information should be provided at the time of the initial report: patient number and initials, a description of the event, at least one criterion classifying the event as Serious, the name and title of the reporting individual, and information regarding study drug dosing. Additionally, judgment of causality by the investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the study Sponsor (e.g., CIOMS forms, FDA MedWatch Form 3500A or other equivalent form). Following the initial report, any additional information obtained by the investigator about the SAE must be reported promptly to the Safety Officer.

The investigator will assess whether the event is causally related to the study medication. The study designated physician (Dr. Liangpunsakul or designee) will consider the investigator's assessment, however, since Dr. Liangpunsakul 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 a *suspected, unexpected serious adverse reaction* (SUSAR) in accordance with FDA regulations, 312.32 (c)(1)(i) meets the criteria as being reportable as a 7-day or a 15-day safety report and will submit reports as required to FDA.

Upon becoming aware of an SAE during the conduct of the study, the study designated physician shall inform Intercept of the SAE within the time frames and using the format defined in the table below. Follow-up information shall be shared using the same time frames and

formats. Additionally, approximately every six months, the study designated physician shall provide Intercept with a list of all SAEs that were received during the previous six months.

Type of SAE:	Format	Time Frame
All SUSARs	MedWatch or CIOMS, with narrative	≤ 5 Calendar Days
SAEs (not meeting criteria for SUSAR)	Aggregate SAE listing with case narratives or MedWatch/CIOMS for each SAE,	Every 6 months

SUSAR and SAE reports are to be sent to Intercept at clinsafety@interceptpharma.com. Intercept may request, in writing, additional information about an SAE at any time, and the study designated physician (or designee) shall respond to the request as efficiently and completely as possible.

The investigator is responsible for submitting information on SUSARs/SAEs received from the Sponsor to her/his local IRB/IEC. The Sponsor will also notify the appropriate regulatory agencies as well as all participating investigators of all SUSARs/SAEs that occur during the trial within the time frames required by each regulatory agency. Documentation of the submissions to IEC/IRBs and health authorities must be retained in the appropriate trial file(s). 7-day or 15-day safety reports should be retained in the appropriate trial files, or with the IB. The Sponsor will follow country specific and local reporting requirements for all SAEs/SUSARs.

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 Safety Officer to record the SAE on the patient's AE CRF and, if necessary, provide a copy of this CRF to the sponsor. Other supporting documents such as radiology reports, hospital discharge summaries and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Safety Officer, 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 Safety Officer any need for supplemental investigations of SAE(s).

8.6 NOTIFICATION OF POST-TRIAL SAES

If the investigator becomes aware of an SAE that may be attributable to the study medication at any time after the end of the trial, the study designated physician should be notified within 2 working days.

All SAEs that occur within 30 days following the cessation of study medication, whether or not they are related to the study medication, must be reported to the

study designated physician within 2 working days by following the instructions provided in Section 7.5.

8.7 FOLLOW UP OF AEs

All AEs, including clinically significant laboratory values or physical examination findings relative to pretreatment assessments, must be followed 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.

8. DRUG INTERACTION

OCA 10 mg has shown potential weak inhibition on CYP1A2, BCRP, OATP1B1, and OATP1B3 (Rosuvastatin), and CYP2C19 (Omeprazole). The list of the medications (if any) of subjects will be reviewed by the PI before the study. Additionally, considering warfarin, metabolized by CYP2C9, is a narrow therapeutic drug, we will exclude subjects who are on warfarin from the study.

9. STATISTICAL METHODS

9.1 Cross-sectional Component:

Primary end point: The mean(SD) will be used to summarize the baseline the C4 and FGF19 level at baseline. The primary analysis is to compare the C4 and FGF19 level at baseline between the 15 health control and 30 heavy drinker using independent two-sample t-tests. The distribution assumption of C4 and FGF19 will be examined for the distribution assumption. If there is an assumption violation, appropriate transformation will be used to correct the assumption violation. We will also perform analysis of covariance (ANCOVA) analysis with C4(FGF19) at baseline as the outcome variable, group(health control vs. heavy drinker) as the main predictor adjusting for patients' characteristics.

The secondary endpoints (a) fasting serum bile salt levels, oxidative stress and CYP2E1 activity; (c) gut permeability, bacterial translocation, and intestinal inflammation; and (d) activation of innate immunity at baseline will also be compared using two-sample t-test and the ANCOVA models in a similar way to C4 and FGF19.

Power analysis: For the cross-sectional study, there are 15 health and 30 heavy drinker. We use two-sample t-test for comparison of the primary endpoint C4 and FGF19. With these sample size, we will have 83% power to detect any difference in C4(or FGF19) of effect size equal to or greater than 0.95(mean/SD) with a 5% Type I error rate.

9.2 Longitudinal component:

Primary endpoint: In the intervention phase, the main goal is to see whether OCA will alternate or reverse the C4(FGF19). So the main analysis to use two-sample t-test to compare the change of C4(FGF19) from baseline to 4 weeks between the randomized treated and placebo arm. The secondary analysis for the primary end points is to compare the C4 (FEF19) level at 4 week using two-sample t-tests to see whether the C4 level of the treated group has recover to the normal control level after 4 weeks treatment.

The secondary endpoint will be compared using two-sample t-tests in a similar way to the primary endpoints.

Power analysis: For the intervention study, there are 15 subjects in each group. We use two-sample t-test for comparison of the change of C4 and FGF19. With these sample size, we will have 82% power to detect any difference in change of C4(or FGF19) of effect size equal to or greater than 1.11(mean/SD) with a 5% Type I error rate.

9.3 Safety Analysis: Descriptive statistics will be used to summarize the AEs if occur.

Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). 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.

HANDLING OF MISSING DATA

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

DATA AND SAFETY MONITORING BOARD (DSMB)

A local DSMB (to be announced) will be formed to review safety data at periodic intervals from this trial. Members of the DSMB will not be allowed to participate as investigators in this trial and will not otherwise consult for the Sponsor.

The DSMB will review safety data to ensure the safe and proper treatment of patients. Based on review of these data, the DSMB will advise the Sponsor on the validity and scientific merit of continuing the trial.

The DSMB will operate under an appropriate charter (in compliance with relevant regulatory guidances) that will define its organization and operation. The DSMB will prepare written minutes of both its open and closed sessions.

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

10. ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

10.1 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.

10.2 Institutional Review Board (IRB)

A properly convened IRB at each participating site will review and approve this study prior to its initiation. 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 or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the trial is complete.

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. Monitors, 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, Intercept as the supporter and/or regulatory authorities) without the written consent of the Sponsor. 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 Intercept (the supporter), a regulatory authority, or an IEC / IRB 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

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) patient visit dates

(c) Screening and Randomization Numbers

(d) demographic information

(e) medical history

(f) disease history

(g) physical examination

(h) vital signs

(i) laboratory assessments (copy of laboratory reports)

(j) AEs and concomitant medications

(k) dates of dispensing study medication

(l) ECGs

(m) patient questionnaires

(n) drug accountability

(o) issues with protocol compliance

(p) completion of, or withdrawal from, trial

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 patient number. The CRF may be developed in paper format or within an electronic data capture (EDC) system. Data management vendors will be detailed within a separate trial document.

The CRF must be completed promptly after each patient visit.

11. REFERENCE LIST

1. Sozio M, Crabb DW. Alcohol and lipid metabolism. Am J Physiol Endocrinol Metab 2008;295(1):E10-E16.
2. Sozio MS, Liangpunsakul S, Crabb D. The role of lipid metabolism in the pathogenesis of alcoholic and nonalcoholic hepatic steatosis. Semin Liver Dis 2010;30(4):378-390.
3. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009;360(26):2758-2769.
4. Singal AK, Shah VH. Alcoholic hepatitis: prognostic models and treatment. Gastroenterol Clin North Am 2011;40(3):611-639.
5. Nguyen-Khac E, Thevenot T, Piquet MA et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365(19):1781-1789.
6. Boetticher NC, Peine CJ, Kwo P et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008;135(6):1953-1960.
7. Dunn W, Jamil LH, Brown LS et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology 2005;41(2):353-358.
8. Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. J Clin Gastroenterol 2011;45(8):714-719.
9. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Am J Gastroenterol 2010;105(1):14-32.
10. Galli A, Pinaire J, Fischer M, Dorris R, Crabb DW. The transcriptional and DNA binding activity of peroxisome proliferator-activated receptor alpha is inhibited by ethanol metabolism. A novel mechanism for the development of ethanol-induced fatty liver. J Biol Chem 2001;276(1):68-75.
11. You M, Matsumoto M, Pacold CM, Cho WK, Crabb DW. The role of AMP-activated protein kinase in the action of ethanol in the liver. Gastroenterology 2004;127(6):1798-1808.
12. You M, Fischer M, Deeg MA, Crabb DW. Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). J Biol Chem 2002;277(32):29342-29347.
13. Liangpunsakul S, Sozio MS, Shin E et al. Inhibitory effect of ethanol on AMPK phosphorylation is mediated in part through elevated ceramide levels. Am J Physiol Gastrointest Liver Physiol 2010;298(6):G1004-G1012.
14. Fischer M, You M, Matsumoto M, Crabb DW. Peroxisome proliferator-activated receptor alpha (PPARalpha) agonist treatment reverses PPARalpha dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice. J Biol Chem 2003;278(30):27997-28004.
15. Liangpunsakul S, Rahmini Y, Ross RA, Zhao Z, Xu Y, Crabb DW. Imipramine blocks ethanol-induced ASMase activation, ceramide generation, and PP2A activation, and ameliorates hepatic steatosis in ethanol-fed mice. Am J Physiol Gastrointest Liver Physiol 2011.
16. Ajmo JM, Liang X, Rogers CQ, Pennock B, You M. Resveratrol alleviates alcoholic fatty liver in mice. Am J Physiol Gastrointest Liver Physiol 2008;295(4):G833-G842.
17. Balesaria S, Pell RJ, Abbott LJ et al. Exploring possible mechanisms for primary bile acid malabsorption: evidence for different regulation of ileal bile

acid transporter transcripts in chronic diarrhoea. Eur J Gastroenterol Hepatol 2008;20(5):413-422.
18. Gutierrez A, Ratliff EP, Andres AM, Huang X, McKeehan WL, Davis RA. Bile acids decrease hepatic paraoxonase 1 expression and plasma high-density lipoprotein levels via FXR-mediated signaling of FGFR4. Arterioscler Thromb Vasc Biol 2006;26(2):301-306.
19. Cipriani S, Mencarelli A, Chini MG et al. The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis. PLoS One 2011;6(10):e25637.
20. Pols TW, Nomura M, Harach T et al. TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading. Cell Metab 2011;14(6):747-757.
21. Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5: a valuable metabolic target. Dig Dis 2011;29(1):37-44.
22. Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J Hepatol 2011;54(6):1263-1272.
23. Fiorucci S, Rizzo G, Donini A, Distrutti E, Santucci L. Targeting farnesoid X receptor for liver and metabolic disorders. Trends Mol Med 2007;13(7):298-309.
24. Nissenbaum M, Chedid A, Mendenhall C, Gartside P. Prognostic significance of cholestatic alcoholic hepatitis. VA Cooperative Study Group #119. Dig Dis Sci 1990;35(7):891-896.
25. Trinchet JC, Gerhardt MF, Balkau B, Munz C, Poupon RE. Serum bile acids and cholestasis in alcoholic hepatitis. Relationship with usual liver tests and histological features. J Hepatol 1994;21(2):235-240.
26. Vendemiale G, Altomare E, Lieber CS. Altered biliary excretion of acetaminophen in rats fed ethanol chronically. Drug Metab Dispos 1984;12(1):20-24.
27. Ackehed G, Hedenborg G, Wisen O, Norman A. Faecal bile acid excretion during detoxification in patients with alcohol abuse. Scand J Gastroenterol 1996;31(12):1205-1210.
28. Cai SY, He H, Nguyen T, Mennone A, Boyer JL. Retinoic acid represses CYP7A1 expression in human hepatocytes and HepG2 cells by FXR/RXR-dependent and independent mechanisms. J Lipid Res 2010;51(8):2265-2274.