Clinical Protocol

Protocol No.	UL928-01
Title:	U01 Pilot Trial of DUR-928 in Patients with Moderate and Severe Alcoholic Hepatitis
Phase	2a
IND:	143049
Version:	**Original: 26 November 2019**
Sponsor:	Craig McClain, MD 505 South Hancock St., Suite 503 Louisville, KY 40202 TEL: (502) 852-6128 FAX: (502) 852-8927
GCP Statement:	The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in the International Conference on Harmonization (ICH) Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any local requirements.

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1.0 TRIAL SYNOPSIS

Title of Trial:	U01 Pilot Trial of DUR-928 in Patients with Moderate and Severe Alcoholic Hepatitis
Sponsor:	Craig McClain, MD, University of Louisville
Phase of Development:	Phase 2a
Objectives and Primary Endpoints:	1. Assess the safety and tolerability of DUR-928 in patients with alcoholic hepatitis (AH) as determined by the absence of suspected unexpected serious adverse reaction (SUSAR). 2. Assess the pharmacodynamic signals of DUR-928 in patients with AH as determined by: a. Liver biochemical biomarkers: Improvement in Lille score at Days 4 and 7 and liver biochemistry, MELD score, and the drivers of the MELD score individually (INR/sCr and bilirubin) and CK-18 fragments (cCK18, fCK18) at Day 7 and Day 28 b. Inflammatory biomarkers: improvement of inflammatory biomarkers such as but not limited to: High-sensitivity C-reactive protein (hs-CRP), subset of cytokines (IL-1β, IL-6, IL-12, IL-18 and TNFα), ExVivo cytokine production c. Quality of Life biomarkers (eg. SF-36) at Baseline, Day 7 and Day 28 d. Plasma and urine metabolomic biomarkers at Baseline, Day 7 and Day 28
Trial Design:	The proposed study is An Open-Label, Dose Escalation Study to Assess the Safety and Pharmacodynamics signals of DUR-928 in Patients with AH. DUR-928 will be administered in 100 mL 5% dextrose or 0.9% sodium chloride by slow intravenous infusion over 2 hours (50mL/h) until entire dose is given at Day 1 and Day 4. If a patient meets the clinic or hospital discharge criteria prior to the 2nddose, the patient will receive only one dose of DUR-928 instead of 2 doses.
Trial Rationale:	The study will be conducted in 2 Parts using a parallel design. Moderate will include patients with MELD scores of 11-20, and Severe will include patients with MELD of scores 21-30. Within each Part, the study will be conducted using a starting dose level of 30 mg with sequential dose escalation following review of safety results of the prior dose level by the sponsor/investigator and the medical monitor. The planned subsequent dose of DUR-928 after the starting dose is 90 mg. At each dose level within a Part, 6 patients will be treated. If no SUSAR is observed, dose escalation to the next dose cohort within the Part will proceed. If 1 of the 6 patients demonstrates a SUSAR in a given dose level, an additional 3

patients will be treated at that dose level. If only 1 of the 9 patients demonstrates SUSAR, the next cohort of six patients will enter at the next dose level. At subsequent dose levels, the maximum tolerated dose (MTD) is defined as the dose level where no more than 1 of 9 patients experiences a SUSAR.

If no SUSAR is observed, dose escalation to the next dose cohort will proceed. All patients will be followed up to Day 28.

Trial Population: Patients with AH will be enrolled at University of Louisville affiliated hospitals or in the outpatient clinic setting. The target number of participants to complete the study is 24-36.

During the trial, patients should receive standard of care as determined by the PI. Treatment for alcoholic hepatitis involves encouragement of drinking cessation and therapies to treat complications of liver damage.

For inpatients, treatment for malnutrition includes adequate calorie and protein intake following nutritional assessment. Pentoxifylline is not an exclusion, but patients can receive no more than 3 days of corticosteroid therapy within the past 90 days. Medical therapy is that used by the NIAAA-funded AlcHepNet consortium on AH and described in part by us recently.

Inclusion Criteria:

1. Able to provide written informed consent (either from patient or patient's legally acceptable representative)
2. Male or female patients 21 years of age or older with BMI ≥ 20 to ≤ 40 kg/m^2
3. Patients with alcoholic hepatitis defined as:
   a. History of heavy alcohol abuse: > 40 g/day in females or > 60 g/day in males for a minimum period of 6 months, AND
   b. Consumed alcohol within 12 weeks of entry into the study, AND
   c. Serum bilirubin > 3 mg/dL AND AST > ALT, but less than 300 U/L AND
   d. MELD score between 11-30, inclusive
4. No evidence of active infection as determined by the investigator.

   If infection is initially suspected clinically,
   a. blood cultures, urine cultures, and peritoneal cultures should be without growth for 48 hours, AND
   b. peritoneal cell count should be less than 250 PMN/ml.

If infection is diagnosed, then the infection must be

a. treated with antibiotics, AND

b. documented negative blood cultures for 48 hours, or for SBP 25% reduction in PMN count prior to enrollment.

5. Women of child-bearing potential (defined as females who are not surgically sterile or who are not over the age of 52 and amenorrheic for at least 12 months) must utilize appropriate birth control throughout the study duration. Acceptable methods that may be used are abstinence, birth control pills ("The Pill") or patch, diaphragm, IUD (coil), vaginal ring, condom, surgical sterilization or progestin implant or injection, or sexual activity limited to a sterile (e.g., vasectomized) male partner.
6. Male patients must agree to use a medically acceptable method of contraception/birth control throughout the study duration.

Exclusion Criteria:

1. Other or concomitant cause(s) of liver disease as a result of:
    a. Autoimmune liver disease (positive anti-mitochondrial antibody and smooth muscle antibody, positive reading on anti-nuclear antibody titer > 1:160)
    b. Wilson disease (ceruloplasmin levels < 10 mcg/L)
    c. Vascular liver disease
    d. Drug induced liver disease
    e. Surface antigen positive hepatitis B (HBsAg+). Note: patients with isolated core antibody (HBcAb) are not excluded.
    f. Acute hepatitis A
    g. Acute HCV or chronic hepatitis C with a history of decompensated cirrhosis. Note: patients with stable chronic HCV or successfully treated HCV are not excluded.
2. Positive Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cocaine and opiates) except THC and legal prescription medications.
3. Any active malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas) or any other malignancy diagnosed within the last five years
4. Active tuberculosis on chest x-ray at study entry
5. Significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal failure, serious psychiatric disease, that, in the opinion of the Investigator would preclude the patient from participating in and completing the study
6. Patients requiring the use of vasopressors or inotropic support. Prior use of inotropic support will be allowed if the condition has stabilized within the first 7 days of admission to the hospital

7. Liver biopsy, if carried out, showing findings not compatible with AH
8. Any patient that has received any investigational drug or device within 30 days of dosing or who is scheduled to receive another investigational drug or device at any time during the study
9. Patients who are taking drug products that are primarily the substrates of CYP2C8, such as chloroquine, paclitaxel, rosiglitazone, repaglinide
10. Patients having >3 consecutive days of corticosteroid treatment within the past 90 days
11. If female, known pregnancy, or has a positive serum pregnancy test, or is lactating/breastfeeding
12. Serum creatinine > 2.5 mg/dL
13. Estimated Glomerular Filtration Rate (eGFR) < 60 ml/min
14. Platelet count < 30,000 platelets/uL
15. Active GI bleeding requiring transfusion of ≥2 units packed red blood cells within a 3-day interval
16. Patients who have had organ transplantation (such as liver, kidney, lung, heart, bone marrow, or stem cell etc.), other than cornea transplant
17. Stage 3 or greater encephalopathy by West Haven criteria

Pharmacodynamics & Safety Evaluation:

Assessment of Pharmacodynamic Signals:

Change in MELD score and the components of the MELD score individually (INR/sCr and bilirubin), Lille score, biochemistry (such as AST and ALT), CK-18, and biomarkers.

Method and Timing:

MELD score will be calculated at Screening, Day 1 (pre-dose), Day 7 and Day 28.

Lille score will be calculated at Days 4 and 7

Biochemistry and all safety lab parameters will be collected at Screening, Day 1 and Day 4 at pre-dose, Day 1 and Day 4 at 24 hours after dose completion/end of infusion, Day 2, Day 7, Day 28, and if hospitalized on Days 3, 4, 5, and 6.

Sample for biomarkers will be collected at Screening, Day 1 and Day 4 at pre-dose, Day 1 and Day 4, Day 2, Day 7, Day 28, and if hospitalized on Days 3, 4, 5, and 6.

Assessment of Safety Signals:

Safety will be determined based on clinical and laboratory monitoring.

Clinical: At each study visit, patients will have a physical examination with specific attention to pulmonary abnormalities, worsening in liver function as noted by increasing jaundice, ascites, or hepatic encephalopathy and presence of infection.

Laboratory: Biochemical parameters that are monitored include CRP, liver biochemistry, creatinine, and electrolytes.

The Adjudication Committee will be contacted on an as needed basis by the medical monitor to distinguish relatedness to the study drug from worsening of the underlying AH disease for any unexpected SAE and to provide advice regarding dose escalation.

The study will be halted if two or more patients in each dose cohort have either 1) AST or ALT > 500 U/L or 2) Lille score > 0.85. The study will also be halted for adjudication review if more than 2 patients have an adverse event grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the Adjudication Committee. A patient will be removed from the study but followed up if Lille scores at any time are > 0.45 (treatment failure).

Drug Induced Liver Injury (DILI)

We will discontinue an individual subject from treatment for likely DILI if:

a. Either the serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is > 8 X ULN
b. Either the ALT or AST is > 3 X the subject's admission (baseline) values, and the subject's total serum bilirubin has increased by 2X the admission (baseline value)
c. Either 1 or 2, and development of peripheral eosinophilia > 5% rash, or signs of a systemic hypersensitivity reaction.

The following parameters will be recorded for the safety evaluation:

- Adverse events
- Standard 12-lead ECG
- Safety Laboratory Tests (clinical chemistry, hematology, coagulation, and urinalysis)
- Vital Signs and Physical Examination

Statistical Data Analysis:

Pharmacodynamics:

Study results for dose-related pharmacodynamics signals will utilize descriptive statistics.

Unless otherwise specified, continuous variables will be summarized by treatment cohort (DUR-928 dose levels) using the ITT analysis set with the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentile, min, and max displayed. Categorical variables will be summarized by DUR-928 dose level using the ITT analysis set as counts and percentages. Missing data will not be estimated or carried forward in any of the analyses.

Safety:

Treatment emergent AEs will be listed and summarized by dose level. All AEs reported in this study will be coded. The overall incidences of AEs and SAEs in

	system organ class (SOC) and preferred term will be tabulated by dose level. In addition, incidence rates (frequencies and percentages) will be broken down by severity and/or relationship to study drug. Treatment emergent changes from baseline in clinical laboratory tests, ECG and vital signs will be derived by dose level.
Test drug, dosage and mode of administration:	DUR-928 at 30 and 90 mg diluted as per the protocol in 100 mL of 5% dextrose or 0.9% sodium chloride and infused over 2 hours. Refer to Section 5.1.1 for detailed instructions.
Comparator, dosage and mode of administration:	N/A
Power Calculations:	No formal sample size estimates were performed. The number of patients planned for this study is consistent with trials of this design and objectives. (See Section 9.2).
Schedule of Events:	Refer to Table 1 below.

Table 1: Schedule of Events

Trial Procedures	**Screening Day -3 to Day 0**	**Day 1**	**Day 2**	**Day 3**[1]	**Day 4**[1]	**Day 5**[1]	**Day 6**[1]	**Day 7 ± 1**[2]	**Day 28 ± 1 Trial completion or early termination**[2]
Informed consent Prior to any trial procedures	√								
Inclusion and exclusion criteria review	√	√							
Demographics	√								
Medical and surgical histories	√								
Urine Pregnancy Test[3]	√								√
12 –lead ECG[4]	√[5]							√[6]	√[6]
Vital signs (BP, HR, RR, and temperature)[7]	√	√	√	√	√	√	√	√	√
Physical Exam[8]	√	√	√	√	√	√	√	√	√
Hepatitis B, C	√[9]								
Clinical chemistry, hematology, coagulation, Urinalysis[10]	√	√[13]	√	√	√[13]	√	√	√	√
Confirmation of patient's alcohol consumption status[11]		√	√	√	√	√	√	√	√
UDS and PEth test	√							√	√
Assessment of MELD and Lille Score	√[14]	√[14]						√	√[15]
Calculation of Maddrey Score	√								
Recording of MELD and Lille score parameters	√	√[13]	√	√	√[13]	√	√	√	√
Study drug dosing[12]		√			√				
Biomarkers (blood)[14]	√	√[13]	√	√	√[13]	√	√	√	√
Biomarkers (urine)	√	√[13]	√	√	√[13]	√	√	√	√
Concomitant Medication[11]	√	√	√	√	√	√	√	√	√
Adverse Events[11]		√	√	√	√	√	√	√	√
Quality of Life (SF-36)	√							√	√

1. Patients may be discharged per hospital standards after Day 2. Collection of Day 3 (or 48 hour post-dose), Day 4, Day 5, and Day 6 biomarker samples, vital signs, physical exam, safety labs will occur only if patient is in hospital. Confirmation of status of alcohol consumption, AE and CM will be done regardless of hospitalization.
2. Day 7 and Day 28 visit will be performed via clinic visit.
3. In female patients of child-bearing potential (defined as females who are not surgically sterile or who are not over the age of 52 and amenorrheic for at least 12 months) only.
4. ECGs will be performed after patient is resting in the supine position for 10 minutes. ECGs are only performed if the patient is in hospital or during a clinic visit.
5. 12-lead ECG will be obtained from patients at screening.
6. 12-lead ECG will be obtained on Days 7 and 28.
7. Vital Signs (BP, HR, RR and T) are measured at screening, pre-dose, post-dose completion (end of infusion), daily when in hospital and at trial completion. All measurements are after the patient is resting in the sitting position for at least 3 minutes.
8. Physical Exam, including general appearance, weight, evaluation of head, ears, nose, throat and neurological exam, with specific attention to pulmonary abnormalities, worsening in liver function as noted by increasing jaundice, ascites, or hepatic encephalopathy and presence of infection.
9. HepB/C test results accepted outside the screening period if collected in the past 24 weeks of screening visit. However, if no past result is available, tests will be done at screening.
10. MELD and LILLE score parameters are included as part of safety labs.
11. If patient is not available in person, they will be contacted via phone.
12. Patients who remain hospitalized on Day 4 will receive a 2nd dose of assigned study drug.
13. To be performed pre-dose and 24 hours post-dose completion (end of infusion).
14. The time points for biomarker sample collection will be: Screening, Day 1 and Day 4 at pre-dose, Day 1 and Day 4 at 24 hours after dose completion/end of infusion, Day 2, Day 7, and if hospitalized on Days 3, 4, 5, and 6. The time window for sample collection can be within 8 hours pre-dose, ±2 hours for samples collected from 24 hours, Day 2-3 or Day 5-6 and ±1 day for samples collected at Day 7 and Day 28. Serum samples should be stored at -80^{0}C until analysis.
15. Only MELD score

LIST OF ABBREVIATIONS

AE	Adverse event
AH	Alcoholic Hepatitis
ALD	Alcoholic Liver Disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CK-18	Cytokeratin-18
CL	Clearance
C_{max}	Maximum serum concentration
Cr	Creatinine
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Cys-C	Cystatin-C
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
FFA	Free fatty acids
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GST	Glutathione S-transferase
HIV	Human immunodeficiency virus
hERG	Human ether-a-go-go related gene
HFD	High Fat Diet
HR	Heart rate
Ht	Height
HV	Healthy volunteer
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
ITT	Intention to Treat
IV	Intravenous
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide

MDF	Maddrey discriminant function
MELD	Model for End Stage Liver Disease
MTD	Maximum Tolerated Dose
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
PEth	Phosphatidylethanols
PI	Principal Investigator
PMN	Polymorphonuclear leukocyte
PO	Oral
PPARγ	Peroxisome proliferator activated receptor-gamma
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
RR	Respiratory rate
SAA	Serum Amyloid A
SAC	Safety Assessment Committee
SAD	Single ascending dose
SAE	Serious adverse event
SBP	Spontaneous bacterial peritonitis
SC	Subcutaneous
sCr	Serum creatinine
SST	Serum Separating Tube
SOFA	Sequential Organ Failure Assessment
TGF	Tubuloglomerular feedback
TIMP-2	Tissue inhibitor of metalloproteinase-2
$T_{1/2}$	Half-life
T_{max}	Time to maximum serum concentration
UDS	Urine drug screen
USAE	Unexpected serious adverse event
ULN	Upper limit of normal
V_d	Volume of distribution
Wt	Weight

2.0 DUR-928: BRIEF DEVELOPMENT HISTORY

DUR-928, 5-cholesten-3β, 25-diol 3-sulfate (25HC3S), is a recently discovered endogenous sulfated oxysterol which is under development for the treatment of Alcoholic Hepatitis (AH).

2.1 Unmet Medical Need

AH is an acute form of alcoholic liver disease (ALD) and includes a spectrum that ranges from mild injury to severe, life threatening injury. The prevalence of AH has not been accurately determined; it is believed to occur in 10% to 35% of heavy drinkers. On histology, AH is characterized by infiltration of the liver by inflammatory cells and hepatocellular injury. AH is usually associated with progressive fibrosis in the presence of continued alcohol abuse. The clinical characteristics and mortality of hospitalized AH patients in the US were published in 2011 (Liangpunsakul, 2011). There were over 56,000 hospitalizations with a primary diagnosis of AH in 2007, identified using ICD-9 code, the majority (>70%) male with a median age of 53.2 years. The average length of hospital stay was nearly 1 week (6.5 ± 7.7days) with a mortality rate during hospitalization of 6.8% and average total hospital costs of $37,769. Despite the enormous public health burden, no new drugs for AH have been successfully developed since the introduction of corticosteroids as a treatment in the early 1970s.

Corticosteroids have been utilized as a standard of care in various treatment guidelines for patients with severe AH, as manifested by hepatic encephalopathy or a Maddrey Discriminant Function > 32. However, their applicability in clinical practice is limited in "special populations" of patients who have contraindications to corticosteroids. Pentoxifylline has also been used because of its safety, but several well-conducted studies have not supported the efficacy of pentoxifylline for the treatment of severe AH. A recent study has questioned the efficacy of both prednisone and pentoxifylline in the treatment of AH. Mortality at 6 months was similar in patients on either prednisone, pentoxifylline, or both as compared with placebo (Thursz et al, 2015). Therefore, there is a need for novel therapies.

Based on the current accumulated knowledge of DUR-928 biology, the sponsor believes that DUR-928 could be used for the treatment of ALD.

2.2 Target Indication

ALD is a major cause of morbidity and mortality in the US, and is the third leading preventable cause of death in the US. In general, the risk of ALD increases with the quantity and duration of alcohol intake. ALD encompasses a clinical/histologic spectrum of disease including fatty liver, hepatitis, and cirrhosis. While fatty liver is a benign and generally reversible condition with abstinence or moderation, further progression to hepatitis is more

ominous. One in five heavy drinkers develops AH and among these patients, one in four develops cirrhosis.

AH is a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of ethanol. The pathogenesis is not completely understood.

Patients who are severely affected present with subacute onset of fever, hepatomegaly, leukocytosis, marked impairment of liver function (e.g., jaundice, coagulopathy), and manifestations of portal hypertension (e.g., ascites, hepatic encephalopathy, variceal hemorrhage). However, milder forms of AH often do not cause any symptoms.

The characteristic clinical manifestation of AH is new onset jaundice, often accompanied by malaise, tender hepatomegaly, and hepatic decompensation (ascites, encephalopathy and variceal bleeding). Patients are diagnosed to have alcoholic hepatitis in the presence of:

a. History of heavy alcohol abuse: > 40 g/day in females and > 60 g/day in males for a minimum period of 6 months

b. Consumed alcohol within 12 weeks of entry into the study

c. Serum bilirubin > 3 mg/dL and AST > ALT, but less than 300 U/L

There are several clinical scoring systems that have been used to predict the clinical outcomes of AH patients; these include the Maddrey discriminant function (MDF) score, the Lille score and the model for end stage liver disease (MELD) score. The MDF is an AH-specific prognostic score that has been used to classify a patient's severity of illness. The MDF score takes into account a patient's prothrombin time (PT) and total bilirubin. The Lille score predicts response of AH patients to treatment with glucocorticoids, such as prednisolone. This score is based on age, serum albumin, bilirubin, creatinine and PT. The MELD score is a good predictor for AH patient prognosis. Laboratory values for international normalized ratio (INR), serum creatinine (sCr) and bilirubin are used to calculate the MELD score (Menon, et al, 2001; Orman et al, 2013; O'Shea et al, 2005).

2.3 Description of Test Drug

DUR-928 is an endogenous intracellular regulatory molecule and sulfated oxysterol: 5-cholesten-3β, 25-diol 3-sulfate (25HC3S). It is highly conserved and present in all 7 species studied to date, including humans, suggesting its importance in regulation of cellular functions.

DUR-928 is under development by DURECT Corporation for multiple indications including treatment of chronic metabolic disease, such as NAFLD/NASH and PSC, and treatment of acute organ injuries, such as AKI and AH.

It has been demonstrated that DUR-928 can lower intracellular lipid accumulation, regulate inflammatory responses, and improve cell survival. Studies in both humans and animals have shown that acute lipid accumulation, even if it is not solely responsible, plays an important role in the pathogenesis of multi-organ injuries, such as heart failure, acute pancreatitis, acute lung injury, AKI, acute liver failure, and other organ injuries. Furthermore, patients with high plasma lipids, especially high LDL cholesterol and high FFA, typically have higher risk of acute organ injury or worse outcomes following acute organ injury compared to those with normal plasma lipids.

In addition to acute lipid perturbation, inflammation has been recognized as an early event in the development of acute organ injuries. Infiltration of inflammatory cells, including neutrophils, monocytes, macrophages, and lymphocytes, is an important contributor to the pathogenesis of organ injury diseases. DUR-928 has been shown, as discussed in the Investigator's Brochure, to alleviate lipid accumulation, suppress inflammatory responses, and promote cell survival or regeneration, which may render it to be effective in preventing and treating acute organ injuries and especially those acute organ injuries such as AH.

2.4 Summary of Non-Clinical Studies

Numerous nonclinical studies have been conducted, including efficacy and safety pharmacology, PK, single and repeat dose toxicity, and genotoxicity studies, all of which have demonstrated the safety and efficacy of DUR-928.

Safety pharmacology studies evaluating the effects of DUR-928 on the cardiovascular, central nervous system, and respiratory systems were conducted. An *in vitro* human ether-a-go-go related gene (hERG) assay using human kidney cells, an Irwin profile study in rats and a cardiovascular and respiratory study in dogs were conducted. No adverse effects were observed in these systems.

The potential toxicity of DUR-928 was evaluated in both acute and repeat-dose studies in rats and dogs. Toxicokinetics were evaluated as part of the toxicology studies. DUR-928 was administered as either an aqueous suspension by PO gavage or as an aqueous solution by IM or SC injection. No adverse effects attributed to DUR-928 were observed in these studies.

DUR-928 was also evaluated in *in vitro* and *in vivo* genotoxicity studies. DUR-928 was shown to be non-genotoxic/non-clastogenic in these studies.

In a hemolysis and plasma compatibility study, no hemolysis was observed in human whole blood when combined with the vehicle alone or with 3 mg/mL DUR-928 solution diluted in 5% dextrose solution. Additionally, no macroscopic changes were noted in human plasma when combined with vehicle alone or with 3 mg/mL DUR-928.

Numerous pharmacological studies have been conducted by DURECT. The results demonstrated pharmacological activities of this endogenous molecule. The utility of DUR-928 as a possible treatment for AH has been demonstrated in a murine acute liver failure model induced by either acetaminophen (APAP) alone or a combination of APAP and ethanol; a murine multi-organ failure model induced by lipopolysaccharide (LPS); a rat septic shock model induced by cecum ligation puncture (CLP); a rat acute obstructive jaundice model induced by bile duct ligation; a murine pancreatitis model induced by caerulein; a murine NAFLD/NASHmodel induced by high fat diet (HFD); a hamster NAFLD/NASH model induced by HFD; a rat NAFLD model induced by genetic obesity (Zucker obese rats); and a murine advanced NASH model induced by diabetes and HFD. The results from all of these acute and chronic disease models demonstrated that DUR-928 inhibited intracellular lipid accumulation, suppressed inflammatory responses, promoted cell survival, and reduced fibrosis. For additional details see Section 6 of the Investigator's Brochure.

2.5 Summary of Nonclinical Pharmacokinetics

PK studies with IV and PO dosing of DUR-928 have been conducted in various animal species including rats, hamsters, dogs, and monkeys. In addition, a number of PK studies have been conducted by SC and IM routes in rats and dogs. Data from these studies have been used to characterize the basic PK properties of DUR-928. For additional details see Section 5.3 of the Investigator's Brochure.

2.6 Summary of Clinical Studies to Date

A total of 264 healthy volunteer (HV) or patients have so far participated in eight completed or ongoing clinical trials with DUR-928. Among them, a total of 236 HV or patients received one or more doses of DUR-928, while 28 received placebo formulations.

DUR-928 has been evaluated in healthy subjects following intramuscular (IM) injections as single ascending doses in the range of 30-300 mg and as multiple doses of 150 mg daily for 5 days. The drug was found to be well tolerated with no significant drug related adverse events other than mild to moderate injection site tenderness. The systemic exposure increased linearly with the dose of DUR-928 administered. No accumulation of DUR-928 was observed upon repeat dosing.

DUR-928 has also been administered as a single dose IM injection (30 mg and 120 mg) to kidney function impaired patients and matched (age, gender and BMI) control healthy subjects. Preliminary data from Cohort 1 (30 mg) and Cohort 2 (120 mg) of the study shows that the pharmacokinetic properties of DUR-928 are similar between renal function impaired patients and matched control subjects. The mean C_{max} was 11-18% lower and mean AUC_{inf} was 6-10% lower in kidney impaired patients as compared to matched control subjects. The

half-life of DUR-928 was similar between two groups. The total exposure of DUR-928 was found to be dose proportional, but not the C_{max} value.

Administration of DUR-928 as an IV infusion over 2 hours was found to be safe and well tolerated at the doses ranging from 50 mg to 150 mg. PK parameters for exposure, C_{max} and AUC, following IV infusion were dose proportional.

DUR-928 has also been evaluated in healthy subjects in a single ascending dose study following oral administration with a dose range of 30 mg to 1000 mg, multiple oral doses of DUR-928 of 100 and 300 mg daily for 5 days, and a cross over food effect (fasted and fed) study of a 300 mg dose. All three studies found DUR-928 was well tolerated with no significant drug related adverse events. The systemic exposure of DUR-928 following single oral dosing did not increase beyond the 300 mg dose, indicating possible saturation in absorption. Upon repeat dosing, there was no significant accumulation observed in plasma as compared to a single dose of DUR-928. In addition, the food effect on oral bioavailability was minimal. Furthermore, a drug-drug interaction study using midazolam (CYP3A4 probe) with oral and IV administration of DUR-928 shows that pharmacokinetics of midazolam are not inhibited in presence of DUR-928 administered either orally or as IV infusion. Not only does midazolam dosing have no effect on the pharmacokinetics of DUR-928, but these results also support that DUR-928 does not inhibit or induce CYP3A4 to a clinically meaningful extent. Thus, DUR-928 is not likely to markedly affect the pharmacokinetics of CYP3A4 metabolized drugs.

An *in vitro* transporter study was performed to show that DUR-928 inhibits BCRP, OATP1B1 and OATP1B3 transporter with IC_{50} values of 148, 3.8 and 14.4 μM, respectively. However, based on the Decision Trees A2 and A4, in the FDA draft guidance for Drug Interaction Studies (February 2012), inhibition of BCRP, OATP1B1 and OATP1B3 transporters by DUR-928 did not meet the FDA criteria to require a clinical drug-drug interaction (DDI) study at the highest dose intended to be used in this trial (150 mg by IV administered). Moreover, this current AH clinical trial is a dose-escalating study, where we will only proceed to the 90 mg dose after the safety and PK data of the lower dose group is critically reviewed.

A single dose (50 mg and 200 mg) of orally administered DUR-928 was safe and well tolerated in patients with liver function impairment (NASH). PK parameters of DUR-928 in NASH patients was comparable to that observed in matched control subjects with normal liver function. A single oral dose in the range 50 mg to 200 mg resulted in a statistically significant reduction of CK-18 (both full-length and cleaved cytokeratin-18, bilirubin, IL-18 and hs-CRP in NASH patients. In NASH patients, particularly those administered the 200 mg dose of DUR-928, these statistically significant reductions from baseline were observed over an extended period encompassing multiple time points. In contrast, statistically significant

reductions from baseline for a few biomarker concentrations were noted infrequently in healthy subjects.

A total of 19 patients were enrolled into an open-label Phase 2a multi-center trial, of whom 15 had Maddrey's Discriminant Function (DF) ≥32 (SAH), 12 had MELD scores at 21-30, and 11 had baseline serum bilirubin levels >8 mg/dL. All patients received IV infused DUR-928 (at 30, 90, or 150 mg) on Day 1 and Day 4 (if still hospitalized), and were followed for 28-days.

DUR-928 at all 3 doses was safe with no drug-related serious adverse events. All patients, including SAH patients, survived the 28-day follow-up period. Treatment responders (Lille score <0.45) among all DUR-928 treated AH patients (1 patient did not return for the Day 7 visit) were 89%; among 15 SAH patients (DF ≥32), 87%; and among 12 patients with MELD 21-30, 83%. In particular, 100% of SAH patients treated with 30 or 90 mg DUR-928 (n = 11) responded to the treatment (Table). Although patients received only 1 or 2 doses of DUR-928, their MELD scores on Day 28 in SAH patients were significantly reduced from baseline (-17.5%, p=0.01).

The median reduction of MELD on Day 28 from baseline in SAH patients treated with 30 or 90 mg of DUR-928 was -19.0% (p=0.01). DUR-928 also significantly reduced serum bilirubin levels on Day 7 in AH patients, especially in patients with baseline bilirubin >8.0 mg/dL (-25.1%, p=0.02).

The combined results, including the observed biological activities in both AH and NASH patients, the efficacy demonstrated in animal disease models, the pharmacological activities reported in all *in vitro* studies, and the safety profiles demonstrated in preclinical and clinical studies, provide a biological rationale for a potential effect of DUR-928 in liver injury and support its evaluation in patients with AH in the US.

Please refer to the Investigator's Brochure for further information.

2.7 Rationale for Dose and Dose-Regimen

We proposed DUR-928 to be administered after the patient is confirmed with the clinical diagnosis of AH. A total of no more than two doses of DUR-928 will be given 72 hours apart.

We believe that a total of 2 doses 72 hours apart will be adequate as the treatment regime. Although DUR-928 has a very short half-life (1-3 hours), its pharmacological activities, as an epigenetic regulator, may last for days. For example, modulation of cell or tissue gene expression occurred between 2-6 hours after DUR-928 treatment. Modulation of serum cytokines levels by DUR-928 in animal disease models occurred between 6-20 hours after dosing. In a LPS-induced endotoxin shock model, mice survived for the entire study duration of 5 days following a single dose of DUR-928. In an APAP-induced renal and liver failure

model, mice survived for the entire study duration of 10 days following single or 2 doses of DUR-928.

2.8 Preliminary Benefit: Risk Evaluation

The utility of DUR-928 as a possible treatment for AH has been demonstrated in a murine acute liver failure model induced by either APAP alone or a combination of APAP and ethanol; a murine multi-organ failure model induced by lipopolysaccharide (LPS); a rat septic shock model induced by cecum ligation puncture (CLP); a rat acute obstructive jaundice model induced by bile duct ligation; a murine pancreatitis model induced by caerulein; NAFLD/NASH model induced by high fat diet (HFD); a hamster NAFLD/NASH model induced by HFD; a rat NAFLD model induced by genetic obesity (Zucker obese rats); and a murine advanced NASH model induced by diabetes and HFD. The results from all of these acute and chronic disease models demonstrated that DUR-928 inhibited intracellular lipid accumulation, suppressed inflammatory responses, promoted cell survival, and reduced fibrosis.

Safety pharmacology studies, *in vitro* and *in vivo* genotoxicity studies, and the potential toxicity of DUR-928 in rats and dogs were evaluated. No adverse effects attributed to DUR-928 were observed in these studies.

Numerous single and multiple dose clinical studies in healthy subjects have been conducted. The results of these studies showed that DUR-928 was well tolerated with no severe treatment-related adverse events (AEs) observed.

3.0 CURRENT TRIAL

3.1 Trial Objectives and Primary Endpoints

1. Assess the safety and tolerability of DUR-928 in patients with alcoholic hepatitis (AH) as determined by the absence of suspected unexpected serious adverse reaction (SUSAR).
2. Assess the pharmacodynamic signals of DUR-928 in patients with AH as determined by:
3. Liver biochemical biomarkers: Improvement in liver biochemistry, MELD score, and the drivers of the MELD score individually (INR/sCr and bilirubin) and CK-18 fragments (cCK18, fCK18) at Day 7 and Day 28 and Lille score at Days 4 and 7
4. Inflammatory biomarkers: improvement of inflammatory biomarkers such as but not limited to: High-sensitivity C-reactive protein (hs-CRP), subset of cytokines (IL-1β, IL-6, IL-12, IL-18 and TNFα), ExVivo cytokine production
5. Quality of Life biomarkers (eg. SF-36) at Baseline, Day 7 and Day 28
6. Plasma and urine metabolomic biomarkers at Baseline, Day 7 and Day 28

3.2 Trial Rationale and Design

The study will be conducted in 2 Parts using a parallel design. Moderate (most likely outpatient participants) will include patients with MELD scores of 11-20, and Severe (most likely inpatient participants) will include patients with MELD of scores 21-30.

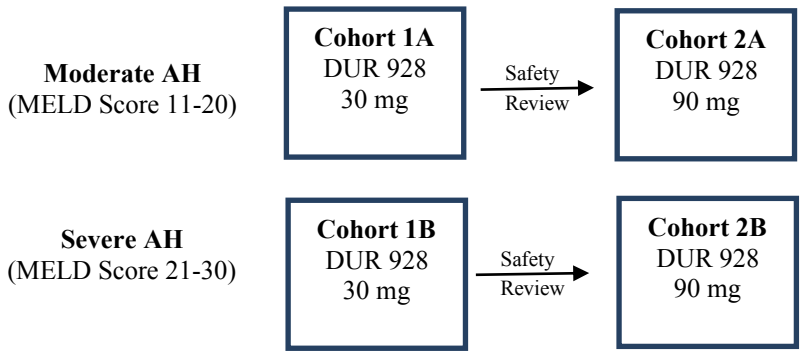
Within each Part, the study will be conducted using a starting dose level of 30 mg with sequential dose escalation following review of safety of the prior dose level by the sponsor, the principal investigators and the medical monitor. The planned subsequent dose of DUR-928 after the starting dose is 90 mg.

Patients with a MELD score of 21-30 (Severe) receiving the 30 mg dose level will occur in parallel with the 30 mg dose of DUR-928 in patients with MELD score 11-20 (Moderate). The subsequent dose escalation in each Part will not proceed until the sponsor, the principal investigators, and the medical monitor complete the review of safety of the 30 mg dose level and determine it is safe to do so.

At each dose level within a Part, 6 patients will be treated. If no SUSAR is observed, dose escalation to the next dose cohort within the Part will proceed. If 1 of the 6 patients demonstrates a SUSAR in a given dose level, an additional 3 patients will be treated at that dose level. If only 1 of the 9 patients demonstrates SUSAR, the next cohort of six patients will enter at the next dose level. If 9 patients are dosed and 2 or more demonstrate SUSAR at that dose level, the study will deescalate to the lower dose. If the dose is already at the lowest level, the Adjudication Committee will make a determination on how to proceed or if the study should be stopped. At subsequent dose levels, the maximum tolerated dose (MTD) is defined as the dose level where no more than 1 of 9 patients experiences a SUSAR.

If no SUSAR is observed, dose escalation to the next dose cohort will proceed. All patients will be followed up to Day 28.

Figure 1: Trial Schema



3.3 Population

Patients with AH will be enrolled at clinical sites in the Louisville area. The target number of participants to complete the study is 24-36. During the trial, patients should receive standard of care as determined by their PI.

3.3.1 Inclusion Criteria

To participate in this study, patients must meet all of the following criteria:

1. Able to provide written informed consent (either from patient or patient's legally acceptable representative)
2. Male or female patients 21 years of age or older with BMI ≥ 20 to ≤ 40 kg/m^2
3. Patients with alcoholic hepatitis defined as:
   a. History of heavy alcohol abuse: > 40 g/day in females or > 60 g/day in males for a minimum period of 6 months, AND
   b. Consumed alcohol within 12 weeks of entry into the study, AND
   c. Serum bilirubin > 3 mg/dL AND AST > ALT, but less than 300 U/L AND
   d. MELD score between 11-30, inclusive
4. No evidence of active infection as determined by the investigator.

   If infection is initially suspected clinically,

   a. blood cultures, urine cultures, and peritoneal cultures should be without growth for 48 hours, AND
   b. peritoneal cell count should be less than 250 PMN/ml.

   If infection is diagnosed, then the infection must be

   a. treated with antibiotics, AND
   b. documented negative blood cultures for 48 hours, or for SBP 25% reduction in PMN count prior to enrollment.
5. Women of child-bearing potential (defined as females who are not surgically sterile or who are not over the age of 52 and amenorrheic for at least 12 months) must utilize appropriate birth control throughout the study duration. Acceptable methods that may be used are abstinence, birth control pills ("The Pill") or patch, diaphragm, IUD (coil), vaginal ring, condom, surgical sterilization or progestin implant or injection, or sexual activity limited to a sterile (e.g., vasectomized) male partner.
6. Male patients must agree to use a medically acceptable method of contraception/birth control throughout the study duration.

3.3.2 Exclusion Criteria

The patient will be excluded if one of the following criteria is met:

1.0 Other or concomitant cause(s) of liver disease as a result of:

   a. Autoimmune liver disease (positive anti-mitochondrial antibody and smooth muscle antibody, positive reading on anti-nuclear antibody titer > 1:160)

   b. Wilson disease (ceruloplasmin levels < 10 mcg/L)

   c. Vascular liver disease

   d. Drug induced liver disease

   e. Surface antigen positive hepatitis B (HBsAg+). Note: patients with isolated core antibody (HBcAb) are not excluded.

   f. Acute hepatitis A

   g. Acute HCV or chronic hepatitis C with a history of decompensated cirrhosis. Note: patients with stable chronic HCV or successfully treated HCV are not excluded.

2.0 Positive Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cocaine and opiates) except THC and legal prescription medications.

3.0 Any active malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas) or any other malignancy diagnosed within the last five years

4.0 Active tuberculosis on chest x-ray at study entry

5.0 Significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal failure, serious psychiatric disease, that, in the opinion of the Investigator would preclude the patient from participating in and completing the study

6.0 Patients requiring the use of vasopressors or inotropic support. Prior use of inotropic support will be allowed if the condition has stabilized within the first 7 days of admission to the hospital

7.0 Liver biopsy, if carried out, showing findings not compatible with AH

8.0 Any patient that has received any investigational drug or device within 30 days of dosing or who is scheduled to receive another investigational drug or device at any time during the study

9.0 Patients who are taking drug products that are primarily the substrates of CYP2C8, such as chloroquine, paclitaxel, rosiglitazone, repaglinide

10.0 Patients having >3 consecutive days of corticosteroid treatment within the past 90 days

11.0 If female, known pregnancy, or has a positive serum pregnancy test, or is lactating/breastfeeding

12.0 Serum creatinine > 2.5 mg/dL

13.0 Estimated Glomerular Filtration Rate (eGFR) < 60 ml/min

14.0 Platelet count < 30,000 platelets/uL

15.0 Active GI bleeding requiring transfusion of ≥2 units packed red blood cells within a 3-day interval

16.0 Patients who have had organ transplantation (such as liver, kidney, lung, heart, bone marrow, or stem cell etc.), other than cornea transplant

17.0 Stage 3 or greater encephalopathy by West Haven criteria

3.3.3 Number of Patients

Each dose cohort will have at least 6 and no more than 9 patients. There will be 2 dose cohorts in each part of the study. The total number of participants to complete the study is at least 24 and no more than 36.

3.3.4 Dosage and Regimen

DUR-928 will be administered on Day 1 and Day 4 (if performed) in 100 mL 5% dextrose or 0.9% sodium chloride by slow intravenous infusion over approximately 2 hours (50 mL/h) until entire dose is given. If a patient meets the hospital/ clinic discharge criteria prior to the 2nd dose, the patient will receive only one dose of DUR-928 instead of 2 doses.

See Section 3.2 for details on dose escalation.

4.0 TRIAL CONDUCT

4.1 Investigative Sites

This will be a single site study with approximately 2 hospital sites in Louisville, KY.

4.2 Sponsor Obligations of Trial Conduct

No CROs will be involved with the conduct of the trial.

4.3 Duration

Patient participation is approximately 33 days.

5.0 TRIAL PROCEDURES

The study procedures are listed below and in the Schedule of Events (Table 1).

Treatment for alcoholic hepatitis involves encouragement of drinking cessation and therapies to treat complications of liver damage.

Treatment for malnutrition includes adequate calorie and protein intake following nutritional assessment. Pentoxyfilline is not an exclusion, but patients can receive no more than 3 days of corticosteroid therapy within the past 90 days. Medical therapy is that used by the NIAAA-funded AlcHepNet consortium on AH and described in part by us recently (Mitchell, Crabb).

5.1 Trial Test Drug

5.1.1 Dosing schedule and Proposed Dose

DUR-928 will be administered after the patient is confirmed with the clinical diagnosis of AH. A total of no more than two doses of DUR-928 will be given, with 72 hours between each dose.

A second dose of the assigned study treatment (test drug) will be repeated 3 days after Dose 1 to patients who are still hospitalized. If a patient meets the discharge criteria prior to Day 4, the patient will receive only one dose of DUR-928.

A Cohort Management System through RedCap or other system will be used to assign patients based on their MELD score to the appropriate Group and Cohort and associated dose.

Patients of Moderate (MELD 11-20) will follow the dose escalation procedure based on cohort; each patient will receive an intravenous infusion dose of:

- Cohort 1A: 30 mg of DUR-928in 100 mL 5% dextrose or 0.9% sodium chloride administered over approximately 2 hours via IV infusion.
- Cohort 2A: 90 mg of DUR-928 in 100 mL5% dextrose or 0.9% sodium chloride administered over approximately 2 hours via IV infusion.

Dose escalation to the next cohort will be determined after review of safety and tolerability data of the previous cohort.

Dose escalation for Severe will follow the same requirements as for Moderate. The dose levels for Severe are planned to be the same as Moderate.

Patients of Severe (MELD 21-30) will follow the dose escalation procedure based on cohort; each patient will receive an intravenous infusion dose of:

- Cohort 1B: 30 mg of DUR-928 in 100 mL 5% dextrose or 0.9% sodium chloride administered over approximately 2 hours via IV infusion.

- Cohort 2B: 90 mg of DUR-928 in 100 mL5% dextrose or 0.9% sodium chloride administered over approximately 2 hours via IV infusion.

More details on preparation and administration of study drug will be provided in the Investigation Product Manual for this study.

5.1.2 Packaging and Labeling of Test Drug

DURECT Corporation will supply the sterile ready to use DUR-928 Injection, 150 mg/5 mL (30 mg/mL) in a single-dose 5 mL glass vial, with 13 mm stopper and crimp seal. Each vial is labeled with product name, lot number, and quantity.

5.1.3 Storage of Test Drug

The DUR-928 Injection should be stored at 2 to 8°C prior to use, with excursions permitted to room temperature (15 to 30°C) for up to 24 hours.

5.1.4 Preparation of Test Drug

The DUR-928 Injection will be diluted into a 100 mL 5% dextrose or 0.9% sodium chloride intravenous solution infusion bag. The DUR-928 solution will be administered to the patient by IV infusion over approximately 2 hours. The diluted DUR-928 in the 5% dextrose or 0.9% sodium chloride infusion solution can be stored for up to 8 hours at room temperature (15 to 30°C).

More details will be provided in the Pharmacy Manual for this study.

5.1.5 Drug Accountability

All materials supplied are for use only in this clinical study and should not be used for any other purpose.

The Investigator is responsible for investigational product accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from DURECT, the amount administered to patients, and the amount of investigational product remaining.

A Drug Dispensing Log must be kept current and will contain the following information:

- Study identification of the patient to whom the drug was dispensed;
- Date(s), study treatment cohort, and quantity of the drug dispensed to each patient.

The inventory must be available for inspection by the sponsor designee during the study. Drug supplies will either be returned by the Investigator or designee to DURECT or, unused drug supplies may be destroyed by the clinical study unit according to local standard operating procedures (SOPs). Records shall be maintained by the Investigator of any such alternate disposal of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (considering the requirements of local law), and the person who disposed of the test substance.

5.2 Trial Visits and Study Procedures

Refer to Table 1 for Schedule of Events by Visit.

5.2.1 Screening (Day -3 –Day 0)

The screening visit will be performed within 4 days of the day of dosing. After obtaining informed consent, patients will be assigned a patient number and screening procedures will be performed. For the patient number, patients will be numbered consecutively within each clinical hospital site in order of their consent into the trial.

Screening procedures include completion of:

- Enter patient into RedCap database
- Review of inclusion / exclusion criteria
- Demographic information
- Medical and surgical history (including MELD score at time of AH diagnosis, if available)
- Physical examination (including weight)
- Vital signs (BP, HR, respiratory rate, temperature)
- Safety laboratory tests (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters
- Urine pregnancy test (females of childbearing potential)
- Hepatitis B, C tests
    - NOTE: HepB and C test results accepted outside the screening period if collected in the past 24 weeks of screening visit. However, if no past result is available, tests will be done at screening.
- 12-lead ECG
- Urine Drug Screen
- Drinking profile would be collected as evidence of alcohol-related liver injury including surveys and lab
    - PEth test

  - NOTE: Receipt of the Screening PEth test results is not required for enrollment. The Screening PEth test results are only intended to provide supportive information regarding the subject's alcohol consumption.

- Calculation of Maddrey Score
- Assessment of MELD
- Record prior and concomitant medications (taken within 30 days of screening)
- Biomarker sample collection (blood, stool and urine)
- ExVivo – whole blood cytokines and lipids
- Quality of Life

5.2.2 **Day 1**

The following procedures will be performed pre-dose unless otherwise noted:

- Review of inclusion / exclusion criteria to confirm eligibility
- Update patient status in RedCap
- Vital signs (BP, HR, respiratory rate, temperature) (pre-dose and post-dose completion/end of infusion)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation) at pre-dose and 24 hours (± 30 minutes) post-dose completion/end of infusion, including MELD and Lille score parameters
  - NOTE: If a patient is screened and dosed on the same day. Only the safety labs for Screening should be collected. An additional collection for Day 1 Pre-dose safety labs does **not** need to be performed.
- Physical Exam (including weight)
- Concomitant medications
- Adverse events
- Assessment of the patient's alcohol consumption status
- Assessment of MELD
- Biomarkers sample collection (blood and urine) at pre-dose
- Residual sample collection for biorepository storage
- Study Drug Dosing

5.2.3 **Day 2**

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters, at 24 hours (± 2 hours) post-dose completion (end of infusion).

- Physical Exam (including weight).
- Concomitant medications
- Adverse events
- Biomarkers sample collection (blood and urine) (24 hours post-dose completion/end of infusion)

5.2.4 Patients discharged prior to Day 7

If patients are discharged before Day 7, they will be contacted daily by telephone to assess their condition. If there is any concern, patients will be seen in-person prior to the Day 7 visit. Symptoms such as confusion or GI bleeding would merit an in-person visit.

5.2.5 Day 3

Patients will not be kept in the hospital longer than is medically required. If patients remain hospitalized on Day 3 (48 hours after initiation of dosing), the following procedures will be performed. Regardless of hospitalization, occurrence of AEs, intake of concomitant medications and confirmation of patient's alcohol consumption status will be assessed (in person or via phone contact):

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters
- Physical Exam (including weight)
- Biomarkers sample collection (blood and urine) if patient is hospitalized (48 hours post-dose completion/end of infusion)
- Concomitant medications
- Adverse events

5.2.6 Day 4, if performed (pre-dose unless otherwise noted)

Patients will not be kept in the hospital longer than is medically required. If patients remain hospitalized on Day 4, the following procedures will be performed. Regardless of hospitalization, occurrence of AEs, intake of concomitant medications and patient's alcohol consumption status will be assessed (in person or via phone contact):

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety Labs (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters, at pre-dose and 8 hours (± 30 minutes) post-dose completion (end of infusion)
- Physical Exam (including weight)

- Concomitant medications
- Adverse events
- Biomarkers sample collection (blood and urine) at pre-dose
- Study drug dosing (dose 2 of assigned study drug)
- ExVivo – whole blood cytokines/ lipids

5.2.7 Day 5 and Day 6 (if performed)

Patients will not be kept in the hospital longer than is medically required. If patients remain hospitalized on Day 5 and Day 6, the following procedures will be performed. Regardless of hospitalization, occurrence of AEs, intake of concomitant medications and patient's alcohol consumption status will be assessed (in person or via phone contact):

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters
    - NOTE: If based on the administration time of Day 4 study drug, the Day 4 8-hour post-dose safety labs fall on Day 5, then only the Day 4 8-hour post-dose safety labs should be collected. An additional collection for Day 5 safety labs does **not** need to be performed.
- Physical Exam (including weight)
- Biomarkers sample collection (blood and urine) (24 and 48 hours after the 2nd dose completion/end of infusion)
- Concomitant medications
- Adverse events

5.2.8 Day 7 (+/- 1 day)

The following procedures will be performed via clinic visit on Day 7 for all patients that have been discharged, or in the hospital if the patient is not discharged. Day 7 and Day 6 visits should not occur on the same day. If a subject is going to be discharged from the hospital on Day 6, then Day 6 visit should **not** be completed and Day 7 visit should be completed per visit window.

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation)
- 12-lead ECG
- Physical Exam (including weight)
- Concomitant medications
- Adverse events

- Assessment of the patient's alcohol consumption status
- Assessment of MELD Score
- Assessment of Lille Score
- Biomarker sample collection (blood, fecal and urine)
- ExVivo – whole blood cytokines/ lipids
- Residual sample collection for biorepository storage
- Quality of Life

5.2.9 Day 28 (+/- 1 day) Trial Completion / Early Termination

The following procedures will be performed via clinic visit on Day 28, of which the latter will be considered the trial completion date:

- Urine pregnancy test
- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation)
- 12-lead ECG if SOC
- Physical Exam (including weight)
- Concomitant medications
- Adverse events
- Assessment of the patient's alcohol consumption status
- Assessment of MELD Score
- Biomarker sample collection (blood, stool and urine)
- Residual sample collection for biorepository storage
- Quality of Life

5.3 Concomitant Medication(s)

Any required treatment deemed necessary for treatment of the patient will be under the treating physician's discretion and given as medically required. All concomitant medications will be recorded on the appropriate eCRF.

5.3.1 Prohibited Concomitant Medications

Any drug products that are primarily the substrates of CYP2C8, such as chloroquine, paclitaxel, rosiglitazone, or repaglinide.

Other investigational agents are the only other prohibited medication within this trial.

6.0 ASSESSMENT OF EFFICACY

6.1 Efficacy Assessments

Change in Lille score, MELD score and the components of the MELD score individually (INR/sCr and bilirubin), biochemistry (including AST and ALT), and biomarkers.

6.2 Method and Timing of Assessments

MELD score will be calculated on screening, Day 1 (pre-dose), Day 7 and Day 28.

Lille score will be calculated on Day 4 (optional) and 7

Biochemistry and all safety lab parameters will be collected at Screening, Day 1 and Day 4 at pre-dose, Day 1 and Day 4 at 24 hours after dose completion/end of infusion, Day 2, Day 7, Day 28, and if hospitalized on Days 3, 4, 5, and 6.

Sample for biomarkers will be collected at Screening, Day 1 and Day 4 at pre-dose, Day 1 and Day 4 at 24 hours after dose completion/end of infusion, Day 2, Day 7, Day 28 and if hospitalized on Days 3, 4, 5, and 6.

7.0 ASSESSMENT OF SAFETY

7.1 Safety Assessments

Safety will be determined based on clinical and laboratory monitoring.

Clinical: At each study follow-up visit, patients will have a physical examination with specific attention to pulmonary abnormalities, worsening in liver function as noted by increasing jaundice, ascites, or hepatic encephalopathy and presence of infection.

Laboratory: Biochemical parameters that are monitored include CRP, liver biochemistry, creatinine, and electrolytes.

Stopping Criteria: The study will be halted if two or more patients in each dose cohort have either 1) AST or ALT > 500 U/L or 2) Lille score > 0.85. The study will also be halted for adjudication review if more than 2 patients have an adverse event grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the Adjudication Committee. A patient will be removed from the study but followed up if Lille scores at any time are > 0.45 (treatment failure).

The Adjudication Committee will also be contacted *ad hoc* when there is question of symptom causality for SUSAR's.

The following parameters will be recorded for the safety evaluation:

- Adverse events
- Standard 12-lead ECG
- Safety Laboratory Tests (clinical chemistry, hematology, coagulation, and urinalysis)
- Vital Signs and Physical Examination

7.2 Method and Timing of Assessments

Safety will be evaluated using adverse events, vital signs, clinical laboratory tests and electrocardiograms. Refer to Table 1 for the frequency of assessments.

7.2.1 Adverse Event Recording

Adverse events will be recorded from the time the patient signs the informed consent form through trial completion final visit/early termination (see Section 5.2.9).

7.2.1.1 Spontaneously Reported Adverse Events

Spontaneously reported AEs; either volunteered by the patient, prompted by non-directed questioning or reported by an investigator will be documented on the eCRF.

7.2.2 12-Lead ECGs

Standard resting 12-lead ECGs will be obtained after patient is resting in the supine position for 10 minutes at Screening, at Day 7. Additional ECGs may be obtained if clinically indicated.

Overall interpretation and machine read intervals (HR, PR, QRS, QT, and QTc) will be recorded on the ECG eCRF. Clinically significant ECG findings that emerge after treatment will be recorded on the AE eCRF.

7.2.3 Laboratory Tests

All routine laboratory analyses will be conducted by a local laboratory and have been listed below. Laboratory tests will be obtained as indicated on the Schedule of Events table. When completing the safety laboratory tests there may be instances where the windows for two time points overlap due to time of study drug dosing, only one lab sample should be collected if time points overlap (see Sections 5.2.2 and 5.2.6).

Female patients of childbearing potential will have an urine pregnancy test at Screening and Day 28.

Chemistry: Alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin, alkaline phosphatase (ALP), sodium, potassium, chloride, bicarbonate, urea, glucose, calcium, uric acid, serum creatinine, albumin, total cholesterol, (LDL and HDL), triglycerides, gamma-glutamyl transpeptidase (GGT), and C-reactive Protein (CRP).

Hematology: White cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit, platelet count, mean platelet volume, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and red cell distribution width.

Urinalysis: Macroanalysis for bilirubin, blood, specific gravity, pH, protein, glucose, ketones, urobilinogen.

Coagulation: PT, INR

Phosphatidylethanols test (PEth): PEth is a highly reliable blood test (with 99% sensitivity) allowing the detection of chronic excessive alcohol abuse over the previous 3-4 weeks.

Other*:* Hepatitis B surface antigen, Hepatitis C antibody. Any viral test results will be acceptable for tests that have been performed in the past 24 weeks of screening visit. However, if no past result is available, tests will be done at screening. Patients will be counseled if Hepatitis B and C return a positive result.

7.2.4 Vital Signs

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be measured at:

a. Screening

b. Day 1 and Day 4 pre-dose and post-dose completion (end of infusion), Day 2, Day 7, and Day 28 (or Early Termination)

c. If patient is in hospital on Day 3, Day 5, Day 6

Vital signs will be measured prior any blood collection. Blood pressure and heart rate will be measured after the patient has been resting (supine or sitting) for at least 3 minutes. Measurements will be taken at the times specified in the Schedule of Events table and will be recorded on the appropriate source document and eCRF.

7.2.5 Physical Examination

A physical examination will be conducted at the Screening Visit, Day 1, Day 2, daily on Day 3-6 (if in hospital), Day 7 and Day 28 (or Early Termination). It will include general

appearance, evaluation of head, eyes, ears, nose, throat, neurological exam, weight and specific attention to pulmonary abnormalities, worsening in liver function as noted by increasing jaundice, ascites, or hepatic encephalopathy and presence of infection.

Any changes from baseline outside the normal range that emerge after treatment will be recorded on the AE eCRF.

7.2.6 Biomarkers

A 12.5 mL serum sample will be collected in two SST tubes (5 mL and 7.5 mL) at Screening (-72 hour to Day 0), Day 1 and Day 4 at pre-dose, Day 1 and Day 4 at 24 hours after dose completion/end of infusion, Day 2, Day 7, Day 28 and if hospitalized on Days 3, 4, 5, and 6, for assessment of selected exploratory biomarkers. The time window for sample collection can be within 8 hours pre-dose, ±30 minutes for samples collected at 24 hours, ±2 hours for samples collected from Day 2-3 or Day 5-6 and ±1 day for samples collected at Day 7 and Day 28. Serum samples should be stored frozen at -80^{0}C until analysis. Instructions on sample collection, processing and shipment will be provided in a separate Laboratory Manual. The following is a list of planned biomarkers but additional non-genetic biomarkers may be included if warranted.

Serum	**Urine**	**Stool**	**Questionnaire**
• ExVivo Cytokines/ lipids • Subset of cytokines, e.g. IL-1β, IL-6, and TNF-α • High-sensitivity C-reactive protein (hs-CRP), • K-18 fragments (K18-M65, K18-M30), • sCD163 and sCD206 • Lipopolysaccharide activity (LPS activity) and other gut barrier biomarkers • Metabolomics	• Metabolomics	• Metabolomics • Metagenomics	• Quality of Life (SF-36)

Biomarker urine samples will be collected in one urine cup and will be transferred into two 2 mL urine cryovials and stored for biomarker analysis as detailed in the Laboratory Manual.

The biomarker data at baseline and at each post-dose time point will be plotted and listed for each patient for evaluation of any change from baseline over time. Since the baseline level of

each marker may vary from patient to patient, percent change from baseline will be derived at each post-dose time points for each patient.

Where time-points of different sample types coincide then the following sequence applies:

1. Biomarkers (blood)
2. Safety labs
3. Biomarkers (urine, stool)

The target sample times will be provided in the CRFs. The actual sample times (times samples actually taken) will be recorded alongside the nominal times in the CRF and will be entered at the time of or as soon as possible after sampling.

Blood Volume to be taken during the study:

Approximately 340 mL of blood will be collected for protocol-related (safety labs, and biomarkers) sample collection.

7.3 Adverse Events

7.3.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign or symptom, including clinically significant laboratory values and test results, concomitant illness, accident, or worsening of an existing medical condition.

The following should not be recorded as an AE if noted at screening:

- A pre-planned procedure for an illness included in the patient's medical history, unless the condition for which the procedure was planned has worsened since prior to dosing. Please observe that complications to pre-planned procedures should be recorded as AEs
- A pre-existing condition found as a result of screening procedures

Any worsening in severity or frequency of a baseline concomitant illness or any new illness diagnosed in the trial period must be regarded as an AE.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event that, at any dose:

Results in death

Is life-threatening

Life-threatening refers to an event in which the patient is at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, might have caused death

Requires inpatient hospitalization or prolongation of existing hospitalization – Inpatient hospitalization includes an overnight admission

Results in persistent or significant disability/incapacity

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions

Results in the birth of a child with a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE (when based upon appropriate medical judgment). These events may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: Hospitalizations that occurred prior to the signing of informed consent, and where the underlying condition of AH for which the hospitalization was planned has not worsened will not be considered SAEs.

Unexpected Serious Adverse Event

An unexpected serious adverse event (USAE) is any serious adverse event that is independent of the underlying liver disease causality and is not consistent with information in the current Investigator's Brochure, the protocol, and the consent document.

Adverse Reaction

An adverse reaction (AR) is any untoward and unintended response to a test drug that has been considered to have a causal relationship with the treatment.

Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is serious and where the nature or severity of which is not consistent with information in the current Investigator's Brochure.

Abnormal Laboratory Value as an AE

An abnormal laboratory value (i.e. any clinical laboratory abnormality or change that suggests a disease and/or organ toxicity and is of a severity that requires active management [i.e. change of test drug dose, discontinuation of test drug, medical treatment, more frequent follow-up or diagnostic investigation]), will be regarded as an AE. If clinical sequelae have been associated with a laboratory abnormality the diagnosis or medical condition should be reported (e.g. renal failure, hematuria) to replace the laboratory abnormality (e.g. elevated creatinine, urine RBC increased).

7.3.1.1 **Classifications**

Severity

The Investigator will evaluate the severity of each adverse event using the following definitions:

Mild – An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities (CTCAE Grade 1).

Moderate – An event that is sufficiently discomforting to interfere with normal everyday activities (CTCAE Grade 2).

Severe – An event that prevents normal everyday activities (CTCAE Grade 3-5).

Adverse events should be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

In the event of the occurrence of a severe adverse event, the Investigator will be instructed to immediately inform the medical monitor.

An AE that has been assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event should be described as 'serious' when it meets one of the pre-defined outcomes as described in Section 7.3.1.

Causality

The Investigator is obligated to assess the relationship between test drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the test drug was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the test drug will be considered and investigated. The Investigator will also consult the Clinical Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

After careful medical consideration, the Investigator will evaluate the relationship of each adverse event to test drug applying the following definitions:

Probably Related – Good reasons and sufficient documentation to assume a causal relationship

Possibly related – A causal relationship is conceivable

Unlikely related – The event is most likely related to etiology other than the test drug

Not Related – Good reasons and sufficient documentation to exclude a causal relationship.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always assess causality for every event prior to transmission of the SAE Report Form to the Sponsor (or designee).

7.3.2 Adverse Event Reporting

All events that meet the definition of an AE that occur in the period from when the patient has signed the informed consent form (ICF) through trial completion (final visit), or early termination, must be recorded on the adverse event eCRF. All SAEs will be recorded on the appropriate eCRF and on the Serious Adverse Event Report Form from the time written informed consent has been obtained through trial completion (final visit), or early termination.

At each contact between the investigative site and the patient (visit or phone), after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information:

"How are you feeling?"

"Have you had any medical problems since your last visit/assessment?"

"Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

All AEs and SAEs will be documented in source records at each assessment time or when otherwise volunteered by the patient and recorded on the appropriate eCRF. Information to be collected includes the nature, date and time of onset, severity, duration, relationship to test drug, and outcome of the event. Even if the Investigator assesses the AE as not reasonably attributable to the test drug, its occurrence must be recorded in the source documents and reported on the eCRF along with the assessment of association.

The Investigator will treat the patient as medically required, and this may extend beyond the duration of the trial. The Investigator will record treatment and medications required to treat AEs on the appropriate eCRF(s). All SAEs, and any possibly/probably related severe AEs will be followed until resolution (no further changes in the event are expected, i.e., the point at which a patient experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

The sponsor/investigator will evaluate all AEs with respect to seriousness, causality and expectedness in accordance with Directive 2001/20/EC (3) and FDA Guidelines. The

expectedness of an AE will be determined according to the current version of the Investigators Brochure.

7.3.3 Reporting of Serious Adverse Events

Regardless of causality, the investigator must complete and submit an SAE form in the RedCap database within 24 hours of knowledge of the event for all serious adverse events.

The Investigator must indicate the SAE's relationship to test drug and sign the SAE form. When additional relevant information (final diagnosis, outcome, results of specific investigations, etc.) becomes available, the investigator must record that follow-up information in the eCRF. Follow-up information should be recorded according to the process used for reporting the initial event as described above. The investigator will follow all reportable events (i.e., SAEs) until resolution. Resolution means no further changes in the event would be expected, i.e., the point at which a patient experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering non-serious sequelae that may never resolve.

All serious adverse events will be reported on the AE CRF and concomitant medications administered in association with the serious AE will be documented on the CM CRF.

If a serious adverse event occurs and comes to the attention of the Investigator after trial completion/termination within 30 days of test drug dosing or within 30 days of the last trial visit (whichever occurs later), it must be reported immediately in the same manner as the serious adverse events occurring during the trial. Investigators are not obligated to actively seek AEs from former study participants.

The Investigator must report SAEs to the IRB/IEC (per the IRB/IEC guidelines/SOPs), including all SAEs that have occurred at the investigative site and all trial related SAEs that have resulted in an expedited safety report to a regulatory agency. If the event is fatal or life-threatening, the event needs to be reported to FDA by phone or facsimile within 7 calendar days. All expedited safety reports need a written report to the FDA within 15 calendar days. The sponsor/investigator complies with applicable regulatory requirement(s) related to the reporting of SUSARs to the FDA and the IRB (5 days). In addition, the sponsor/investigator will prepare annual safety reports covering all SUSARs that have occurred in clinical studies with the concerned test drug during the reporting period.

7.3.4 Drug Induced Liver Injury (DILI)

We will discontinue an individual subject from treatment for likely DILI if:

d. Either the serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is > 8 X ULN

e. Either the ALT or AST is > 3 X the subject's admission (baseline) values, and the subject's total serum bilirubin has increased by 2X the admission (baseline value)

f. Either 1 or 2, and development of peripheral eosinophilia > 5% rash, or signs of a systemic hypersensitivity reaction.

7.3.5 Adverse Event Follow-up

During and after participation by a patient in a clinical trial, the Investigator will ensure that adequate medical care has been provided to the patient for any AEs including clinically significant laboratory values related to the trial. The Investigator will inform the patient when medical care will be needed for intercurrent illness(es) of which Investigator becomes aware.

All SAEs and possibly/probably related severe AEs must be followed by the Investigator until resolution (no further changes in the event are expected, i.e., the point at which a patient experiencing such an AE has been appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve), until the patient is lost to follow-up, or died and until all queries related to the AEs have been resolved. If a patient dies during participation in the study or during a recognized follow-up period, the Sponsor (or designee) must be notified immediately and then provided with a copy of any post-mortem findings, including autopsy and histopathology.

7.4 Pregnancy

Urine pregnancy tests will be done at screening visit and Day 28 for females of child-bearing potential.

Female patients will be advised to notify the Investigator immediately if they become pregnant during the course of the trial.

The Investigator will complete the appropriate pregnancy reporting forms and send them to the IRB within 5 days of obtaining information of the pregnancy. The subject will be asked to sign a pregnancy consent so that all relevant data may be collected concerning the pregnancy and infant. The Investigator will follow the pregnancy through its course and complete the appropriate documentation. The infant will be followed at least until one month of age.

Abortion, stillbirth and any malformation/disease must be reported as an SAE. A pregnancy outcome other than abortion, stillbirth and any malformation/disease as well as follow-up of the infant must be reported to the FDA.

8.0 BIOREPOSITORY

Residual specimens that are available after study analysis is complete will be retained for potential future analysis of novel biomarkers to test drug efficacy. The specimens will be retained in the UofL Specimen Bank in the CTR building at 505 South Hancock Street, Room 542 for up to 10 years. No genetic testing will be performed. Appendix 2 for collection, storage, and shipment of samples.

9.0 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Trial Design Considerations

An open label dose finding study, stratified by disease severity is an appropriate design to assess the safety and tolerability of DUR-928 in this patient population.

9.2 Sample Size Determination

No formal sample size estimates were performed. The number of patients planned for this study is consistent with trials of this design and objectives.

9.3 Patient Randomization

N/A. This is an open label study.

9.4 Definition of Analysis Population

The primary analysis set for all safety analyses will be the Intent-to-Treat (ITT) set, which is defined as all enrolled patients who received at least one dose of study drug (DUR-928).

Additional details about the analysis plan, including how missing data will be handled, will be specified in the Statistical Analysis Plan.

9.5 General Statistical Analysis Considerations

The primary objective of this study is to assess dose-related safety and tolerability of DUR-928 dose-related evidence of potential efficacy of DUR-928. Study results for dose-related safety and efficacy will utilize descriptive statistics.

Unless otherwise specified, continuous variables will be summarized by treatment cohort (DUR-928 dose levels) using the ITT analysis set with the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentile, min, and max displayed. Categorical variables will be summarized by DUR-928 dose level using the ITT analysis set as counts and percentages. Missing data will not be estimated or carried forward in any of the analyses.

Except where other software maybe deemed more appropriate, all analyses will be performed using SAS statistical software (SAS Institute, Cary, NC).

9.6 Demographic and Baseline Characteristics

Continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation, and ranges. Categorical variables will be summarized using frequencies and percentages. 95% confidence intervals will also be provided when appropriate.

9.7 Changes and Deviations to the Protocol and Statistical Analysis Plan

Any deviations from the planned analyses methods and the rationale for such deviations will be carefully documented in the Statistical Analysis Plan (SAP) and as a protocol amendment, if applicable.

10.0 ACCESS TO SOURCE DATA/DOCUMENTATION

The investigative site will permit trial-related audits, IRB review and regulatory inspections by providing direct access to source data/documentation (e.g. medical records, original laboratory records and original informed consent forms). Essential documents will be maintained at the investigative site throughout the trial.

10.1 Confidentiality

By consenting to participate in this trial, each patient will agree that Sponsor personnel, their representatives or the respective Health Authorities personnel may require direct access to the patient's data/personal records including photocopying source data in an anonymous form. The patient will also agree that his/her data will be processed and stored in an anonymous form for evaluation of this trial and any later overviews. Data may also be transferred in an anonymous form to third parties (e.g., other companies or authorities that may be located in other countries with potentially different regulations for data). Data will follow the development of the test drug and will be used for documentation of the product's efficacy and safety. Data will be transferred to involved parties only within the authority given by official agencies. The informed consent form will state that any data already obtained during trial participation will be kept if consent is withdrawn.

10.2 Data Identification

All data will be recorded on a source document prior to being entered into the eCRF.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The sponsor will monitor the trial for regulatory and protocol adherence at all stages of trial conduct from inception to completion in accordance with ICH-GCP. This monitoring will be in the form of site visits and other communication and will include review of original source documents and eCRFs. The study monitor will notify the Investigator prior to conducting any site visit. These visits will include monitoring to assess facilities, required certifications, IRB records, equipment, patient recruiting ads, record-keeping, protocol adherence, data verification and transmission, adverse event reporting. Final quality assurance visits by the Sponsor should be expected, and possibly by the FDA.

The completed eCRFs will be reviewed against source documents by the monitor at each monitoring visit. If any data, signatures, or forms are missing or discrepant, the Investigator will be informed and appropriate written corrections will be made in a timely manner.

11.2 Protocol Deviations

All departures from the protocol will be referred to as protocol deviations and not protocol violations (ICH E3R1 Guidance, June 2012).

Definitions:

A protocol deviation is “any change, divergence, or departure from the study design or procedures defined in the protocol.”

An important protocol deviation is “a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being”

The Investigator should not deviate from the protocol. Except for changes intended to eliminate any immediate hazard to patients, the trial should be conducted as described in the approved protocol. In medical emergencies, the Investigator will use medical judgment and will remove the trial participant from immediate hazard followed by notification to the IRB regarding the type of emergency and the course of action taken. All protocol deviations will be documented by the investigative site.

11.3 Case Report Forms

Electronic case report forms will be used for this trial. Data entry will occur at the investigative site and will be performed by trained and qualified site personnel. The Investigator will ensure all the eCRFs are completed after each patient visit in a timely manner.

11.4 Data Safety Monitoring Committee

A Data Safety Monitoring Committee has not been planned for this trial.

11.5 Adjudication Committee

The Adjudication Committee will be the same outside experts used by DURECT Corporation in the DUR-928-01 clinical trial (Drs. Arthur McCullough and Paul Kwo) as well as Dr. Dan Hill from the University of Louisville:

Dr. Suthat Liangpunsakul, Professor of Medicine at Indiana University, is an expert in alcoholic liver disease. He is also an expert in drug toxicity. He is very knowledgeable concerning DUR-928.

Dr. Paul Kwo, Professor of Medicine at Stanford University, is a hepatologist with broad general knowledge. He has been on the Data Safety Monitoring Board for the clinical trial for DUR-928.

Dr. Dan Hill is a clinical hepatologist. He currently practices at the Robley Rex Veterans Administration Medical Center in Louisville, where this trial will be conducted. He has a broad background in hepatology and is familiar with the patient population. He will not be participating in the trial and has no conflict.

The Adjudication Committee will be contacted on an as needed basis by the medical monitor to distinguish relatedness to the study drug from worsening of the underlying AH disease for any unexpected SAE and to provide advice regarding dose escalation.

The study will be halted if two or more patients in each dose cohort have either 1) AST or ALT > 500 U/L or 2) Lille score > 0.85. The study will also be halted for adjudication review if more than 2 patients have an adverse event grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the Adjudication Committee. A patient will be removed from the study but followed up if Lille scores at any time are > 0.45 (treatment failure).

The Adjudication Committee will also be contacted *ad hoc* when there is question of symptom causality for SUSAR's.

12.0 ETHICAL CONSIDERATIONS

This trial will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and ICH guidance E6) for all studies.

All patients for this trial will be provided a consent form describing this trial and providing sufficient information for patients to make an informed decision about their participation in this trial. This consent form will be submitted with the protocol for review and approval by

the IRB. The formal consent of a patient, using the IRB-approved consent form, will be obtained before that patient is submitted to any trial procedure. This consent form must be signed by the patient or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. Each patient will be given a copy of the consent form.

12.1 Institutional Review Board / Ethics Committee

The protocol, consent form, advertisements and any other information for patients will be reviewed and approved by the Institutional Review Board (IRB) prior to the start of the trial in accordance with the International Conference on Harmonization (ICH) and institutional IRB policies. All protocol amendments and changes to the consent form occurring during the trial must also be IRB approved.

12.2 Regulatory Compliance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in the International Conference on Harmonization (ICH) Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any local requirements.

12.3 Regulatory Status

DUR-928 is an investigational product.

12.4 Patient Information and Informed Consent

Prior to participation in the trial, the Investigator or designee will obtain written consent from each patient, or legally acceptable representative, using the IRB/IEC-approved informed consent form that explains the nature, purpose, possible risks and benefits of the trial, and the duration of an individual's participation. The basic elements of the informed consent as specified by the FDA (21 CFR §50.25), and HIPAA will be followed.

Before consenting, the patient must be left with ample time to consider and to pose questions. The Investigator and/or the designated investigative site personnel who conduct the informed consent discussion must also sign and date the consent form. Each patient will be given a copy of the signed consent form. The original, signed consent forms will be maintained at the investigative site.

12.4.1 Patient Withdrawal

Patients will be informed during the informed consent process (in writing and verbally) that they are free to withdraw from the trial at any time. The Investigator may exercise his medical judgment to terminate a patient's participation in the trial due to clinically relevant changes in any clinical or laboratory parameter. A patient will be removed from the study

but followed up if Lille scores at any time are > 0.45 (treatment failure). All trial procedures normally performed at completion of the trial must be done at the time of the patient's early termination, before the scheduled final clinic visit, or on the scheduled final clinic visit as described in Section 5.2.8 unless the patient withdraws consent. If a patient withdraws consent they will be encouraged to complete an early termination visit and AE follow-up. Patients with ongoing SAEs and any possibly/probably related severe AEs will be followed until resolution. Resolution means no further changes in the event are expected, i.e., the point at which a patient experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve. Patients with ongoing adverse events (other than SAEs, and any possibly/probably related severe AEs) will be followed until resolved or until 30 days after the patient's last trial visit, whichever comes first.

Patients who withdraw prior to assignment of test drug will be considered as screen failures.

13.0 DATA HANDLING AND RECORD RETENTION

13.1 Data Ownership

The eCRFs, associated documents and reports from the trial are the property of the sponsor. The sponsor has the right to use the results for internal presentation and publication.

13.2 Retention of Trial Records

The Investigator will retain all trial documents (e.g., approved protocol, copies of completed eCRFs and electronic diaries, original informed consent forms, relevant source documents) in a secure place protected from fire and theft until:

At least 2 years after the last approval of an NDA by the US FDA;

At least 2 years after the last approval of a marketing application in an ICH region;

There are no pending or contemplated marketing applications in an ICH region; or

At least 2 years have elapsed since the formal discontinuation of the clinical development of the test drug

These documents should be retained for a longer period if required by the local/regional regulations.

The medical files of trial patients must be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Trial records must be made available by the Investigator for inspection upon reasonable request by authorized representatives of the Food and Drug Administration (FDA), or the corresponding regulatory Health Authorities of the relevant countries.

14.0 **PUBLICATION PLAN**

Confidentiality, use of data, results and other information, and publication are addressed in the Clinical Trial Agreement with DURECT Corporation that is supplying study drug.

15.0 REFERENCES

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16.0 **Appendices**

16.1 **Appendix 1: Collection, Storage of Biorepository Samples**

Plasma Collection and Storage

Draw whole blood into a 6 mL potassium EDTA (K_2EDTA) vacuum tube. Keep vials on ice or refrigerated at approximately 4^{o} C during all processing steps.

Label with patient identifier, date, and nominal sample time.

Process whole blood to plasma within 30 minutes of collection.

Centrifuge whole blood at 1300 g for 10 minutes to process the plasma.

Transfer 2 equal aliquots of approximately 1mL of plasma to each of two 1.5-2 mL polypropylene cyro vials, creating two aliquots (primary/aliquot 1 and secondary/aliquot 2). Use externally threaded vials such as VWR part # 55710-284.

Ensure vials are labeled with protocol number, patient identifier, date, and nominal sample time.

Include on label a reference to aliquot number: aliquot 1 or aliquot 2

Store both vials frozen at –80° C or colder until shipment to the central laboratory for storage and analysis. The residual samples will be kept frozen by the for up to 10 years.

16.2 **Appendix 2: Adaptation of the West Haven criteria**

	State of consciousness	Intellectual function	Personality behavior	Neuromuscular abnormalities
Grade IV				
Terms used in original description	Coma (unresponsive to verbal/noxious stimuli)	Unable to test	Unable to test	Unable to test
Adapted criteria	No eyes opening No verbal response No reaction to simple commands	Unable to test	Unable to test	Unable to test
Grade III				
Terms used in original description	Somnolence to stupor	Confusion Gross disorientation	Bizarre behavior	Clonus/rigidity/nystagmus/ Babinski sign
Adapted criteria	Somnolence	Confusion Disoriented to place Mental control=0	Bizarre behavior/anger/rage	Clonus/rigidity/nystagmus /Babinski sign
Grade II				

	State of consciousness	Intellectual function	Personality behavior	Neuromuscular abnormalities
Terms used in original description	Lethargy	Minimal disorientation to time and place Impaired subtraction	Bizarre behavior	Asterixis
Adapted criteria	Lethargy	Disorientation to time Mental control=1-4 Amnesia of recent events Impaired simple computations	Inappropriate behavior Anxiety	Slurred speech Hyperactive reflexes
Grade I				
Terms used in original description	Trivial lack of awareness	Shortened attention span Impaired addition	Euphoria or depression	Asterixis
Adapted criteria	Sleep disorder	Shortened attention span Impaired complex computations	Euphoria or depression	Tremor Impaired construction ability

16.3 Appendix 1: Sponsor/Investigator Responsibilities

Supervise the conduct of the trial and ensure that all trial personnel under his/her supervision are qualified and adequately trained to perform the tasks delegated to them.

Obtain appropriate IRB/IEC approval to conduct the trial in a timely manner.

Maintain written documentation that the trial protocol, any protocol amendments, and the informed consent form have received IRB/IEC approval.

Maintain a file with a list of IRB/IEC members, including their affiliations and qualifications. As an alternative in the United States, a General Assurance number (as assigned by the Department of Health and Human Services) fulfils this requirement.

Report to the IRB/IEC as required. The IRB/IEC must assume continued responsibility for the trial and review the research on at least an annual basis; however, some require more frequent periodic reviews.

Maintain a file of all communications with the IRB/IEC on issues related to the trial.

Complete and sign an original copy of the Statement of Investigator Form (Form FDA 1572).

Maintain a file of current curricula vitae of the Investigator and Sub-Investigator(s).

A copy of the protocol will be maintained in the regulatory file. The Investigator's signature on the 1572 and protocol signature page are evidence of agreement with the conduct of the trial.

All amendments to the protocol must be reviewed by the Investigator and submitted to the IRB/IEC in accordance with their requirements. A copy of protocol amendments will be retained by the Investigator in the regulatory file.

Submit the Investigator's Brochure to the IRB/IEC for review. Maintain written documentation that the Investigator's Brochure was received and reviewed by the IRB/IEC.

Conduct the trial in strict adherence to the protocol and ICH Good Clinical Practice.

Supervise the use of the test drug as outlined in the protocol. Only staff working under the supervision of the Investigator for the purposes of this trial will be allowed to handle the test drug.

Store the test drug in a secure and locked area. The storage, custody, and security of the test drug are the responsibility of the Investigator.

The test drug should be administered to patients under the Investigator's direct supervision or that of his/her Sub-Investigators.

Maintain adequate record of the receipt and disposition of all test drugs, including dates and quantities dispensed to individual patients.

Ensure that each patient is informed of the risks and benefits of participating in the trial, and a properly signed and witnessed informed consent form for each patient has been obtained at the time of screening.

Provide appropriate health care or referral for the patient throughout the trial.

Document all adverse events on the Adverse Event CRF. Document all serious, life-threatening, or unexpected events on the appropriate CRF; and notify FDA via email or facsimile report within 3 days as required.

Report all serious, related, and unexpected adverse events to the IRB/IEC.

Document and maintain adequate and accurate CRFs for all patients receiving test drug as required at the designated times. Review all CRFs affirming the completeness and accuracy of the data recorded. Storage, custody, and security of all trial records are the responsibility of the Investigator.

Provide the Trial Monitor with the original completed CRFs and all source documents for review at the investigative site during monitoring visits. Retain the CRFs, source documents, and informed consent forms at the investigative site.

Adhere to standard record retention policy as stated in the protocol.

Cooperate with health authority inspector(s). Facilitate activities related to audits/inspections.

- Responsible for ensuring that the trial is conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in ICH Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the HIPAA law, and any additional local requirements.

- Ensuring the proper conduct of the trial in regard to protocol adherence. The sponsor will assign Monitors for this trial. Their duties will be to aid the Sponsor/Investigator in maintaining complete, legible, well-organized, and easily readable data. In addition, Trial Monitors will assure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of a test drug, and assure an understanding of the protocol, reporting responsibilities, and the validity of the data.

- The patients will be covered by University of Louisville's insurance according to applicable regulatory requirements.