# Clinical Protocol

**Protocol No.** C928-010

**Title:** An Open- Label, Dose Escalation Study to Assess the Safety, Pharmacokinetics and Pharmacodynamic Signals of DUR-928 in Patients with Alcoholic Hepatitis.

**Phase** 2a

**IND:** 134468

**Version:** **Original: 06 December 2017**
**Amendment 1: 19 September 2018**

**Sponsor:** DURECT Corporation
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**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.

# Investigator Agreement Page

DURECT Corporation

I have read and understood the information in this protocol and agree to conduct the trial according to the protocol (subject to any amendments), in accordance with the principles of Good Clinical Practice, the Investigator responsibilities stated in this protocol, and in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate IRB/IEC and any other institutional requirements. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of patients.

I agree to conduct in person or to supervise the trial. I will provide copies of the protocol, any subsequent protocol amendments, and access to all information provided by the Sponsor to the trial personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the test drug, the trial protocol, are aware of their obligations, are qualified to perform the tasks required, and are trained in any trial specific procedures

Principal Investigator:

Printed Name: Date

Institution:

Sponsor Approval:

PPD/CCI

19Sep18

Date

## SPONSOR CONTACTS

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PPD/ CCI [redacted]

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## 2.0 TRIAL SYNOPSIS

| | |
|---|---|
| **Title of Trial:** | An Open-Label, Dose Escalation Study to Assess the Safety, Pharmacokinetics and Pharmacodynamic Signals of DUR-928 in Patients with Alcoholic Hepatitis. |
| **Sponsor:** | DURECT Corporation |
| **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).<br>2. Determine the pharmacokinetics (PK) of DUR-928 in patients with AH<br>3. Assess the pharmacodynamic signals of DUR-928 in patients with AH as determined by:<br>a. Biochemical: Improvement in liver biochemistry, MELD score, and the drivers of the MELD score individually (INR/sCr and bilirubin) at Day 7 and Day 28 and Lille score at Day 7<br>b. Biomarkers: improvement of biomarkers PPD/CCI [redacted] |
| **Trial Design:** | The proposed study is An Open-Label, Dose Escalation Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics signals of DUR-928 in Patients with AH. DUR-928 will be administered in PPD/CCI [redacted] by slow intravenous infusion over 2 hrs PPD/CCI until entire dose is given at Day 1 and Day 4. If a patient meets the hospital discharge criteria prior to the 2nd dose, 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 staggered parallel design. Part A will include patients with MELD scores of 11-20, and Part B will include patients with MELD of scores 21-30.<br>Within each Part, the study will be conducted using a starting dose level of 30 mg with sequential dose escalation following review of safety and PK results of the prior dose level by the sponsor, the principal investigators and the medical monitor. The planned subsequent doses of DUR-928 after the starting dose are 90 mg and 150 mg.<br>Patients with a MELD score of 21-30 (Part B) receiving the 30 mg dose level will only be enrolled once safety review of the 30 mg dose of DUR-928 in |

patients with MELD score 11-20 (Part A) has been completed. The subsequent dose escalation in Part B will not proceed until the sponsor, the principal investigators, and the medical monitor complete the review of safety and evaluate PK results of the 30 mg dose level and determine it is safe to do so.

PPD/CCI

If no SUSAR is observed and PK results are satisfactory, 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 approximately 10 clinical sites in the US. 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 (e.g. pentoxifylline or corticosteroids).

**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 $\geq$ 20 to $\leq$ 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.

PPD/CCI

PPD/CCI [redacted]

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. PPD/CCI [redacted]
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 PPD/CCI [redacted]
   b. Wilson disease PPD/CCI [redacted]
   c. Vascular liver disease
   d. Drug induced liver disease

   PPD/CCI [redacted] PPD/CCI [redacted]
2. Co-infection with human immunodeficiency virus (HIV)
3. Positive Urine Drug Screen PPD/CCI [redacted]
4. Any active malignancies other than curatively treated skin cancer PPD/CCI [redacted] or any other malignancy diagnosed within the last five years
5. Active tuberculosis on chest x-ray at study entry
6. Significant systemic or major illness other than liver disease, PPD/CCI [redacted]
7. Patients requiring the use of vasopressors or inotropic support. PPD/CCI [redacted]

8. Liver biopsy, if carried out, showing findings not compatible with AH
9. 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
10. PPD/CCI [redacted]
11. If female, known pregnancy, or has a positive serum pregnancy test, or is lactating/breastfeeding
12. Serum creatinine > 2.5 mg/dL
13. Patients who have had organ transplantation PPD/CCI [redacted]
14. 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 PPD/CCI [redacted], 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 Day 7

Biochemistry and all safety lab parameters will be collected PPD/CCI [redacted]

PPD/CCI [redacted]

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 PPD/CCI [redacted]

Laboratory: Biochemical parameters that are monitored PPD/CCI [redacted]

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.

PPD/CCI

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.

Due to the small number of patients expected to be enrolled at each center, all summaries and analyses will be performed using data pooled across sites. 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 using the current Medical Dictionary for Regulatory Activities (MedDRA). 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.

**Pharmacokinetics:** Plasma concentration data of DUR-928 from each patient will be used to calculate relevant PK parameters determined using a standard linear/log-trapezoidal rule non-compartmental method with an appropriate PK data analysis program.

PK parameters for DUR-928 will be summarized by dose group and Part A or B

using descriptive statistics.

Method and Timing:

PPD/CCI

**Test drug, dosage and mode of administration:**

DUR-928 at 30, 90 and 150 mg diluted as per the protocol in PPD/CCI and infused over 2 hrs.

Refer to Section 7.1.1 for detailed instructions.

**Comparator, dosage and mode of administration:**

N/A

**Power Calculations:**

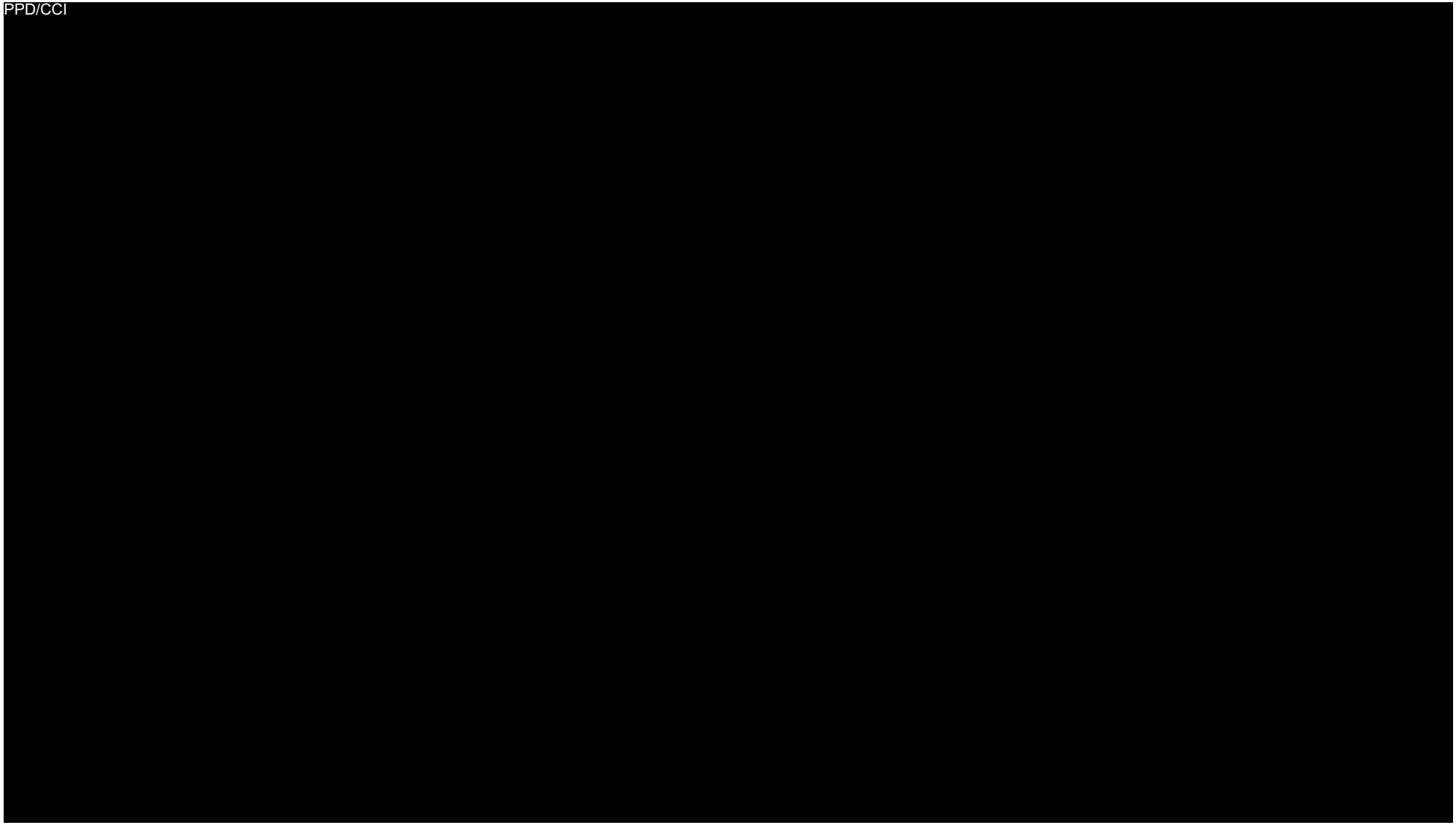
No formal sample size estimates were performed. The number of patients planned for this study is consistent with trials of this design and objectives. (See Section 11.2).

**Schedule of Events:**

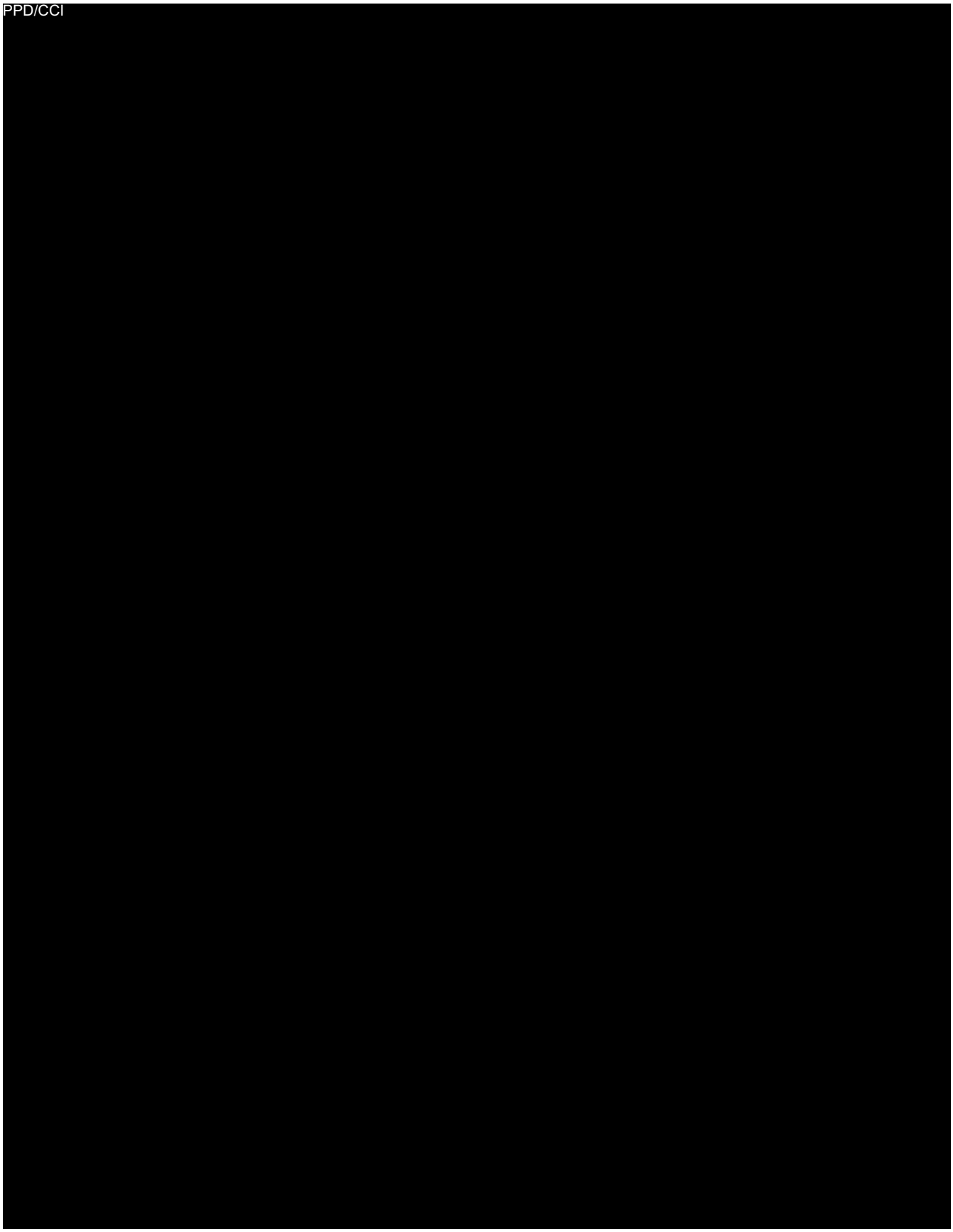
Refer to Table 1 below.

**Table 1: Schedule of Events**

PPD/CCI



PPD/CCI



## 3.0 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 |
| 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 |
| PK | Pharmacokinetic |
| 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 |

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI [redacted]

# 5.0 CURRENT TRIAL

## 5.1 Trial Objectives and Primary Endpoints

1. Assess the safety and tolerability of DUR-928 in patients with AH as determined by the absence of SUSARs.
2. Determine the PK of DUR-928 in patients with AH.
3. Assess the pharmacodynamic signals of DUR-928 in patients with AH as determined by:
    a. Biochemical: Improvement in liver biochemistry, MELD score, and the components of the MELD score individually (INR/sCr and bilirubin) at Day 7 and Day 28 and Lille score at Day 7
    b. Biomarkers: improvement of biomarkers PPD/CCI [redacted]

## 5.2 Trial Rationale and Design

The study will be conducted in 2 Parts using a staggered parallel design. Part A will include patients with MELD scores of 11-20, and Part B 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 and PK results of the prior dose level by the sponsor, the principal investigators and the medical monitor. The planned subsequent doses of DUR-928 after the starting dose are 90 mg and 150 mg.

Patients with a MELD score of 21-30 (Part B) receiving the 30 mg dose level will only be enrolled once safety review of the 30 mg dose of DUR-928 in patients with MELD score 11-20 (Part A) has been completed. 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 and evaluate PK results of the 30 mg dose level and determine it is safe to do so.

PPD/CCI [redacted]

PPD/CCI

[redacted]

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

**Figure 1: Trial Schema**

PPD/CCI

[redacted]

## 5.3 Population

Patients with AH will be enrolled at clinical sites in the US. 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.

### 5.3.1 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 $\geq$ 20 to $\leq$ 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.

PPD/CCI [redacted]

5. Women of child-bearing potential (defined as females who are <u>not</u> surgically sterile or who are <u>not</u> over the age of 52 and amenorrheic for at least 12 months) must utilize appropriate birth control throughout the study duration. PPD/CCI [redacted]

6. Male patients must agree to use a medically acceptable method of contraception/birth control throughout the study duration.

### 5.3.2 Exclusion Criteria

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

1. Other or concomitant cause(s) of liver disease as a result of:
   a. Autoimmune liver disease PPD/CCI [redacted]
   b. Wilson disease PPD/CCI [redacted]
   c. Vascular liver disease
   d. Drug induced liver disease

PPD/CCI [redacted]

2. Co-infection with human immunodeficiency virus (HIV)
3. Positive Urine Drug Screen PPD/CCI [redacted]

4. Any active malignancies other than curatively treated skin cancer PPD/CCI or any other malignancy diagnosed within the last five years
5. Active tuberculosis on chest x-ray at study entry
6. Significant systemic or major illness other than liver disease, PPD/CCI
7. Patients requiring the use of vasopressors or inotropic support. PPD/CCI
8. Liver biopsy, if carried out, showing findings not compatible with AH
9. 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
10. PPD/CCI
11. If female, known pregnancy, or has a positive serum pregnancy test, or is lactating/breastfeeding
12. Serum creatinine > 2.5 mg/dL
13. Patients who have had organ transplantation PPD/CCI
14. Stage 3 or greater encephalopathy by West Haven criteria

### 5.3.3 **Number of Patients**

Each dose cohort will have at least 4 and no more than 6 patients. There will be 3 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.

### 5.3.4 **Dosage and Regimen**

DUR-928 will be administered on Day 1 and Day 4 (if performed) in PPD/CCI by slow intravenous infusion over approximately 2 hrs PPD/CCI until entire dose is given. If a patient meets the hospital discharge criteria prior to the 2nd dose, the patient will receive only one dose of DUR-928 instead of 2 doses.

See Section 5.2 for details on dose escalation.

# 6.0 TRIAL CONDUCT

## 6.1 **Investigative Sites**

This will be a multicenter study with approximately 10 clinical sites in the US.

## 6.2 **Sponsor Obligations of Trial Conduct**

Sponsor responsibilities such as data management (including electronic data capture), site management, site monitoring, medical monitoring, and central laboratory services for PK and biomarkers will be transferred to one or more contract research organizations (CROs).

## 6.3 **Duration**

Patient participation is approximately 33 days.

## 6.4 **Discontinuation of Trial**

DURECT Corporation reserves the right to terminate the trial at any time.

# 7.0 TRIAL PROCEDURES

The study procedures are listed below PPD/CCI .

## 7.1 **Trial Test Drug**

### 7.1.1 **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 hrs 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 will be used to assign patients based on their MELD score to the appropriate Part and Cohort and associated dose.

Patients of Part A (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 PPD/CCI administered over approximately 2 hrs via IV infusion.

- Cohort 2A: 90 mg of DUR-928 in PPD/CCI administered over approximately 2 hrs via IV infusion.
- Cohort 3A: 150 mg of DUR-928 in PPD/CCI administered over approximately 2 hrs via IV infusion

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

Dose escalation for Part B will follow the same requirements as for Part A. The dose levels for Part B are planned to be the same as Part A.

Patients of Part B (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 PPD/CCI administered over approximately 2 hrs via IV infusion.
- Cohort 2B: 90 mg of DUR-928 in PPD/CCI administered over approximately 2 hrs via IV infusion.
- Cohort 3B: 150 mg of DUR-928 in PPD/CCI administered over approximately 2 hrs via IV infusion

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

### 7.1.2 **Packaging and Labeling of Test Drug**

The sponsor will supply the sterile ready to use DUR-928 Injection, PPD/CCI. Each vial is labeled with product name, lot number, and quantity.

### 7.1.3 **Storage of Test Drug**

PPD/CCI

### 7.1.4 **Preparation of Test Drug**

The DUR-928 Injection will be diluted into a PPD/CCI intravenous solution infusion bag. The DUR-928 solution will be administered to the patient by IV infusion over approximately 2 hrs. The diluted DUR-928 in PPD/CCI

PPD/CCI [redacted]

[redacted]

### 7.1.5 **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 study monitor during the study. Drug supplies will either be returned by the Investigator or designee to DURECT or, if requested in writing by the Sponsor, 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 (taking into account the requirements of local law), and the person who disposed of the test substance. Documentation of the disposition of all IP will be provided to DURECT. If the clinical study unit is unable to dispose of the investigational product, unused drug will be returned to DURECT.

## 7.2 **Trial Visits and Study Procedures**

PPD/CCI [redacted].

### 7.2.1 **Screening** PPD/CCI [redacted]

The screening visit will be performed PPD/CCI [redacted] 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 site in order of their consent into the trial. Only their assigned patient number and date of birth will identify patients to the Sponsor in order to maintain anonymity.

Screening procedures include completion of:

- Enter patient into Cohort Management System
- 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
- Serum pregnancy test (females of childbearing potential)
- Hepatitis B , C and HIV 1/HIV 2 tests
  - PPD/CCI [redacted]
- 12-lead ECG
- Urine Drug Screen
- PEth test
  - PPD/CCI [redacted]
- Calculation of Maddrey Score
- Assessment of MELD
- Record prior and concomitant medications PPD/CCI [redacted]
- Biomarker sample collection PPD/CCI [redacted]

### 7.2.2 **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 Cohort Management System
- Vital signs (BP, HR, respiratory rate, temperature) (pre-dose and post-dose completion/end of infusion)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation) PPD/CCI [redacted]

- PPD/CCI [redacted]

- 12-lead ECG (post-dose completion/end of infusion)
- Physical Exam (including weight)
- Concomitant medications
- Adverse events
- Assessment of the patient's alcohol consumption status
- Assessment of MELD
- Pharmacokinetic sample collection PPD/CCI [redacted]
- Biomarkers sample collection PPD/CCI [redacted]
- Study Drug Dosing

### 7.2.3 **Day 2**

- Vital signs (BP, HR, respiratory rate, temperature)
- Safety labs (clinical chemistry, hematology, urinalysis, coagulation), including MELD and Lille score parameters, PPD/CCI [redacted]
- 12-lead ECG
- Physical Exam (including weight).
- Concomitant medications
- Adverse events
- Assessment of the patient's alcohol consumption status
- Pharmacokinetic sample collection PPD/CCI [redacted]
- Biomarkers sample collection PPD/CCI [redacted]

### 7.2.4 **Day 3**

Patients will not be kept in the hospital longer than is medically required. If patients remain hospitalized on Day 3 (48 hrs 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), PPD/CCI [redacted]
- 12-lead ECG
- Physical Exam (including weight)
- Assessment of the patient's alcohol consumption status
- Biomarkers sample collection PPD/CCI [redacted]
- Pharmacokinetic sample collection PPD/CCI [redacted]
- Concomitant medications
- Adverse events

### 7.2.5 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), PPD/CCI [redacted]
- 12-lead ECG (post-dose completion/end of infusion)
- Physical Exam (including weight)
- Concomitant medications
- Adverse events
- Assessment of the patient's alcohol consumption status
- Biomarkers sample collection PPD/CCI [redacted]
- Study drug dosing (dose 2 of assigned study drug)

### 7.2.6 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), PPD/CCI [redacted]
- 12-lead ECG
- Physical Exam (including weight)
- Assessment of the patient's alcohol consumption status
- Biomarkers sample collection [redacted]
- Concomitant medications
- Adverse events

### 7.2.7 **Day 7 (+/- 1 day)**

The following procedures will be performed via clinic visit on Day 7, 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 PPD/CCI [redacted]
- UDS and PEth test

### 7.2.8 **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:

- Serum pregnancy test
- 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
- Biomarker sample collection PPD/CCI
- UDS and PEth test

### 7.3 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.

#### 7.3.1 Prohibited Concomitant Medications

PPD/CCI

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

## 8.0 ASSESSMENT OF EFFICACY

### 8.1 Efficacy Assessments

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

### 8.2 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 7

Biochemistry and all safety lab parameters will be collected at PPD/CCI

PPD/CCI [redacted]

# 9.0 ASSESSMENT OF SAFETY

## 9.1 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:** PPD/CCI [redacted] 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. PPD/CCI [redacted]

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

## 9.2 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.

### 9.2.1 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 7.2.8).

#### 9.2.1.1 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.

### 9.2.2 **12-Lead ECGs**

Standard resting 12-lead ECGs will be obtained after patient is resting in the supine position for 10 minutes at Screening, post-dose completion (end of infusion) on Day 1 and Day 4 daily at Day 2-6 while patient hospitalized, at Day 7 and Day 28. 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.

### 9.2.3 **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 7.2.2 and 7.2.6).

Female patients of childbearing potential will have a serum pregnancy test at Screening and Day 28.

***Chemistry***: PPD/CCI [redacted]

***Hematology:*** PPD/CCI [redacted]

***Urinalysis:*** PPD/CCI [redacted]

***Coagulation***: PPD/CCI [redacted]

***Urine Drug Screen:*** PPD/CCI [redacted]

***Phosphatidylethanols test (PEth)***: PPD/CCI [redacted]

***Other***: PPD/CCI [redacted]

Note: If HIV antibody screening returns a positive result, test will be confirmed by Western Blot.

### 9.2.4 **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.

### 9.2.5 **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.

### 9.2.6 **Biomarkers**

PPD/CCI [redacted]

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[redacted]

[redacted]

[redacted]

## 9.3 Adverse Events

### 9.3.1 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).

#### 9.3.1.1 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 9.3.1.

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 make an assessment of causality for every event prior to transmission of the SAE Report Form to the Sponsor (or designee).

### 9.3.2 **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.

DURECT's designee 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.

### 9.3.3 **Reporting of Serious Adverse Events**

Regardless of causality, the investigator must complete and submit an SAE form to PPD/CCI within 24 hrs 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.

PPD/CCI will follow all SAEs 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). PPD/CCI will report all SAEs to DURECT within 1 business day of receipt.

All serious adverse events will also 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 to PPD/CCI 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. Concurrently, the Investigator must send DURECT documentation of such IRB/IEC notification or if reporting is not required immediately per IRB/IEC guidelines, then a copy of the local SOP stating the reporting guidelines should be supplied by the site to DURECT and the CRO.

DURECT complies with applicable regulatory requirement(s) related to the reporting of SUSARs to the competent authorities and the IRBs/IECs. In addition, DURECT will prepare annual safety reports covering all SUSARs that have occurred in clinical studies with the concerned test drug during the reporting period.

### 9.3.4 **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.

### 9.4 **Pregnancy**

Serum 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 must complete the appropriate pregnancy reporting forms and send them to DURECT (or DURECT's designee) within 14 calendar days of obtaining information of the pregnancy. The Investigator will follow the pregnancy through its course and complete the appropriate documentation and forward immediately to DURECT (or DURECT's designee). The infant must be followed at least until one month of age. Consent of a parent must be obtained before registration of infant data.

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 by the Investigator within 14 calendar days of obtaining the information using the appropriate pregnancy reporting forms.

## 10.0 PHARMACOKINETICS

Plasma concentration data of DUR-928 from each patient will be used to calculate relevant pharmacokinetic parameters determined using standard non-compartmental method with linear/log-trapezoidal rule utilizing an appropriate pharmacokinetic data analysis program.

Pharmacokinetic parameters, such as $C_{max}$, $T_{max}$, $T_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{inf}$, CL, and $V_d$, for DUR-928 will be calculated and summarized by dose group and Part A or B using descriptive statistics.

PPD/CCI

[redacted]

# 11.0 STATISTICAL METHODS AND DATA ANALYSIS

## 11.1 **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.

## 11.2 **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.

## 11.3 **Patient Randomization**

N/A. This is an open label study.

## 11.4 **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).

The PK evaluable data set is defined as including those patients who have met criteria for analysis defined in the SAP.

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

### 11.5 General Statistical Analysis Considerations

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

Due to the small number of patients expected to be enrolled at each center, all summaries and analyses will be performed using data pooled across centers. 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.

A thorough description of the statistical methods as well as presentation of study results will be developed and finalized prior to locking the database. Deviations from the statistical analysis plan (SAP) will be documented in the clinical trial report.

Except where other software maybe deemed more appropriate, all analyses will be performed using SAS Version 9.4 statistical software (SAS Institute, Cary, NC).

### 11.6 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.

### 11.7 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.

## 12.0 ACCESS TO SOURCE DATA/DOCUMENTATION

The investigative site will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documentation (e.g. medical records, original laboratory records and original informed consent forms). The Investigator should immediately notify DURECT of any Health Authority inspection. Essential documents must be maintained at the investigative site throughout the trial.

## 12.1 **Confidentiality**

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## 12.2 **Data Identification**

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

# 13.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 **Monitoring**

DURECT or DURECT's designee 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. DURECT's monitor or designee will notify the Investigator prior to conducting any site visit. These visits will include monitoring to assess facilities, required certifications, IRB/IEC 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.

## 13.2 **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 DURECT and the IRB/IEC regarding the type of emergency and the course of action taken. All protocol deviations will be documented by the investigative site or monitor on the designated log.

### 13.3 **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. Specific instructions are provided in the eCRF completion guidelines.

### 13.4 **Coding**

MedDRA will be used to code adverse events. WHO-Drug will be used to code concomitant medications.

### 13.5 **Data Safety Monitoring Committee**

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

### 13.6 **Adjudication Committee**

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.

PPD/CCI [redacted]

PPD/CCI [redacted]

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

## 14.0 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 signed consent form.

### 14.1 **Institutional Review Board / Ethics Committee**

The protocol, consent form, advertisements and any other information for patients will be reviewed and approved by DURECT Corporation (or DURECT's designee) and by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of the participating investigative site prior to the start of the trial at that site in accordance with the International Conference on Harmonization (ICH) and institutional IRB/IEC policies. All protocol amendments and changes to the consent form occurring during the trial must also be IRB/IEC approved.

### 14.2 **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.

### 14.3 **Regulatory Status**

DUR-928 is an investigational product.

## 14.4 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.

### 14.4.1 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. PPD/CCI [redacted] DURECT Corporation also reserves the right to terminate the trial at any time. 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 7.2.7 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. If a patient discontinues prior to completion of the 24 hour PK sample they will be replaced, since PK is one of the criteria for dose escalation assessment.

# 15.0 DATA HANDLING AND RECORD RETENTION

## 15.1 **Data Ownership**

The eCRFs, associated documents and reports from the trial are the property of DURECT. DURECT has the right to use the results for registration purposes, internal presentation and promotion.

## 15.2 **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 or by an agreement with DURECT. It is the responsibility of the Sponsor to inform the Investigator/Institution when these documents no longer need to be archived.

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.

DURECT will maintain the documentation pertaining to the trial as long as the test drug is on the market.

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

DURECT will provide the Investigator with information concerning the current status of the test drug as it relates to the Investigator's responsibility for the retention of trial records. The Investigator should contact DURECT prior to disposing of any such records. DURECT will arrange for continued storage of all records, if necessary.

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CCI [redacted]

[redacted]

[redacted]

[redacted]

## 18.0 REFERENCES

PPD/CCI [redacted]

# 19.0 Appendices

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PPD/CCI

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