OFFICIAL TITLE: A RANDOMIZED, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE SAFETY AND EFFICACY OF DUR-928 IN SUBJECTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC)

NCT Number: NCT03394781

Document Date: September 13, 2018

Clinical Protocol

Protocol No. C928-008

Title: A Randomized, Open-label, Phase 2 Study to Evaluate Safety and Efficacy of DUR-928 in Subjects with Primary Sclerosing Cholangitis (PSC)

Phase 2

IND: 133885

Version: **Original: 23 AUG 2017**
Amendment 01: 27 SEP 2017
Amendment 02: 30 MAY 2018
Amendment 03: 13 SEP 2018

Sponsor: DURECT Corporation
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Cupertino, CA 95014, USA
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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

C928-008
13 SEP 2018

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 subjects.

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:
Address:

Sponsor Approval:

PPD/CCI

9/13/18
Date

PPD/CCI

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2.0 TRIAL SYNOPSIS

Title of Trial: A Randomized, Open-label, Phase 2 Study to Evaluate Safety and Efficacy of DUR-928 in Subjects with Primary Sclerosing Cholangitis (PSC)

Sponsor: DURECT Corporation

Phase of Development: Phase 2

Objective:

Primary:

- To evaluate safety of DUR-928 in subjects with PSC
- To evaluate percent change (%) of serum alkaline phosphatase (ALP) from baseline

Secondary:
To evaluate % change of liver enzymes and selected biomarkers from baseline

Efficacy Endpoints:

Primary Efficacy Endpoint
% change of serum ALP from baseline through the end of the study treatment and throughout the follow-up period.

Secondary Efficacy Endpoint:

- % of subjects with ≥ 20% reduction of serum ALP from baseline
- % of subjects with ≥ 30% reduction of serum ALP from baseline
- % of subjects with ≥ 40% reduction of serum ALP from baseline
- % change of liver enzymes, including ALT, AST, GGT, bilirubin from baseline, through the end of study treatment and throughout the follow-up period.
- % change of selected biomarkers from baseline through the end of study treatment and throughout the follow-up period.
- % change of serum bile acids (sBA) from baseline through the end of study treatment and throughout the follow-up period.

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Safety Assessments:

- Adverse Events (AEs) will be recorded from signing the informed consent form through the end of study or early termination visit
- Vital Signs, Physical Examinations and 12-lead ECG findings
- Safety Laboratory Tests (chemistry, hematology, and urinalysis)

Trial Design:

The proposed study is a randomized, open-label, 2 dose (10 mg and 50 mg, both once daily) study to evaluate the safety and efficacy of DUR-928 administered orally for 28 days, both at the end of dosing and throughout the follow-up period (28 days post-dose).

Trial Rationale:

PSC is an unmet medical need and an idiopathic condition characterized by the presence of beading and stricture formation of the intra and/or extrahepatic bile ducts that cannot be ascribed to another cause, thus differentiating PSC from secondary sclerosing cholangitis. Therefore, PSC is a diagnosis that can be established in the absence of toxic, infectious, or inflammatory processes, which may lead to the characteristic bile duct injury pattern (Lindor et al, 2015). 70-80% of patients with PSC have associated chronic inflammatory bowel disease (IBD).

Currently there is no medical treatment for PSC patient. Liver transplantation is the only management intervention which exists currently for selected patients with end-stage disease.

PSC patients invariably have persistently elevated serum ALP levels, this parameter is routinely measured and monitored in the clinic. Normalization of ALP has been found to be a reliable biomarker associated with better prognosis, and thus been suggested as a valuable and readily available treatment endpoint (Stanich et al, 2011).

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[redacted]

PPD/CCI [redacted]

Trial Population: Forty adult male and female subjects, diagnosed with PSC, with or without IBD aged between 18 and 80 years (inclusive), will be enrolled into the study, to result in at least thirty-six evaluable subjects.

Inclusion Criteria:

1. Subjects must be able and willing to provide written informed consent to participate in the study
2. Males and females subjects aged between 18 and 80 years, inclusive, at the time of signing informed consent
3. Verified diagnosis of PSC PPD/CCI [redacted] prior to Day 1, with or without IBD, based on either a magnetic resonance cholangiogram (MRC) or endoscopic retrograde cholangiogram (ERC) demonstrating bile duct abnormalities consistent with sclerosing cholangitis. In addition, these subjects will be required to enter the study with a Mayo risk score (Kim et al, 2000) of 0-3, inclusive. For subjects with IBD, documented evidence of IBD either by prior endoscopy or in previous medical records should be ≥ 6 months prior to Day 1
4. Serum ALP ≥1.5 times ULN PPD/CCI [redacted]
5. In subjects receiving treatment with ursodeoxycholic acid (UDCA), therapy must be stable for at least 3 months prior to Day 1 (no dose adjustment), and at a dose not greater than 20 mg/kg/day so that in subjects who are taking UDCA, the investigational drug can be given as a co-medication
6. Subjects of childbearing potential must agree to use a medically acceptable method of contraceptive to prevent pregnancy in the subject and/or the partner for the duration

of their participation in the trial, and up to 2 months after the last study drug dosing. PPD/CCI [redacted]

Exclusion Criteria:

1. Presence of documented secondary sclerosing cholangitis PPD/CCI [redacted] on prior clinical investigations
2. Small duct PSC
3. Bacterial cholangitis PPD/CCI [redacted]
4. Presence of percutaneous drain or endoscopic bile duct stent PPD/CCI [redacted]
5. History of, or suspicion of cholangiocarcinoma by MRC/ERC and other cross-sectional imaging or clinical judgment, at screening
6. Prior liver transplantation, or currently listed for liver transplantation on the basis of recurrent cholangitis and with a match-run MELD-Na^+ score $\geq$ 10
7. Presence of other concomitant liver diseases PPD/CCI [redacted]
8. Cirrhosis and/or hepatic impairment and/or hepatic decompensation PPD/CCI [redacted]

9. Subjects with evidence of cirrhosis, as determined by local transient elastography (TE, e.g., FibroScan®) values of ≥ 14.4 kPa (Corpechot et al, 2014), PPD/CCI
10. Moderate–to-Severe active IBD or flare in colitis activity PPD/CCI
11. Active Crohn's disease not currently in remission, as assessed by the investigator and the CRO's medical monitor
12. Use of oral prednisolone PPD/CCI and/or hospitalization for IBD PPD/CCI
13. AST, ALT, and Total Bilirubin concentrations above the allowed cut-offs, PPD/CCI
14. International normalized ratio (INR) ≥ 1.2
15. PPD/CCI
16. PPD/CCI
17. PPD/CCI
18. PPD/CCI
19. Any active malignant disease (within 3 years), other than non-melanomatous skin cancer
20. Human immunodeficiency virus (HIV) infection
21. Existing or intended pregnancy, and/or breast feeding
22. Has received any study medication in the context of another

clinical trial within the 30 days prior to screening

23. PPD/CCI [redacted]

24. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

PPD/CCI [redacted]

Pharmacokinetics: At selected center(s), blood samples will be collected for drug concentration measurements in approximately 5 subjects from each dose group. These samples will be collected on Day 1 and Day 28 of dosing. PPD/CCI [redacted]

Plasma concentration data of DUR-928 from each available 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 for DUR-928 will be summarized using descriptive statistics.

PPD/CCI [redacted]

Test drug, dosage and mode of administration:	DUR-928 10 mg PO daily for 28 days DUR-928 50 mg PO daily for 28 days
Comparator, dosage and mode of administration:	N/A
Power Calculations:	Forty subjects will be randomized in total. Considering an early withdrawal rate of 10%, a sample size of 36 subjects (18 subjects per dose group), PPD/CCI [redacted] compared to baseline in serum ALP after 4 weeks of treatment using a one-group t-test. PPD/CCI [redacted] (see Section 11.1).
Schedule of Events:	Refer to Table 1 below.

Table 1: Schedule of Events

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Footnotes for Schedule of Events Table:

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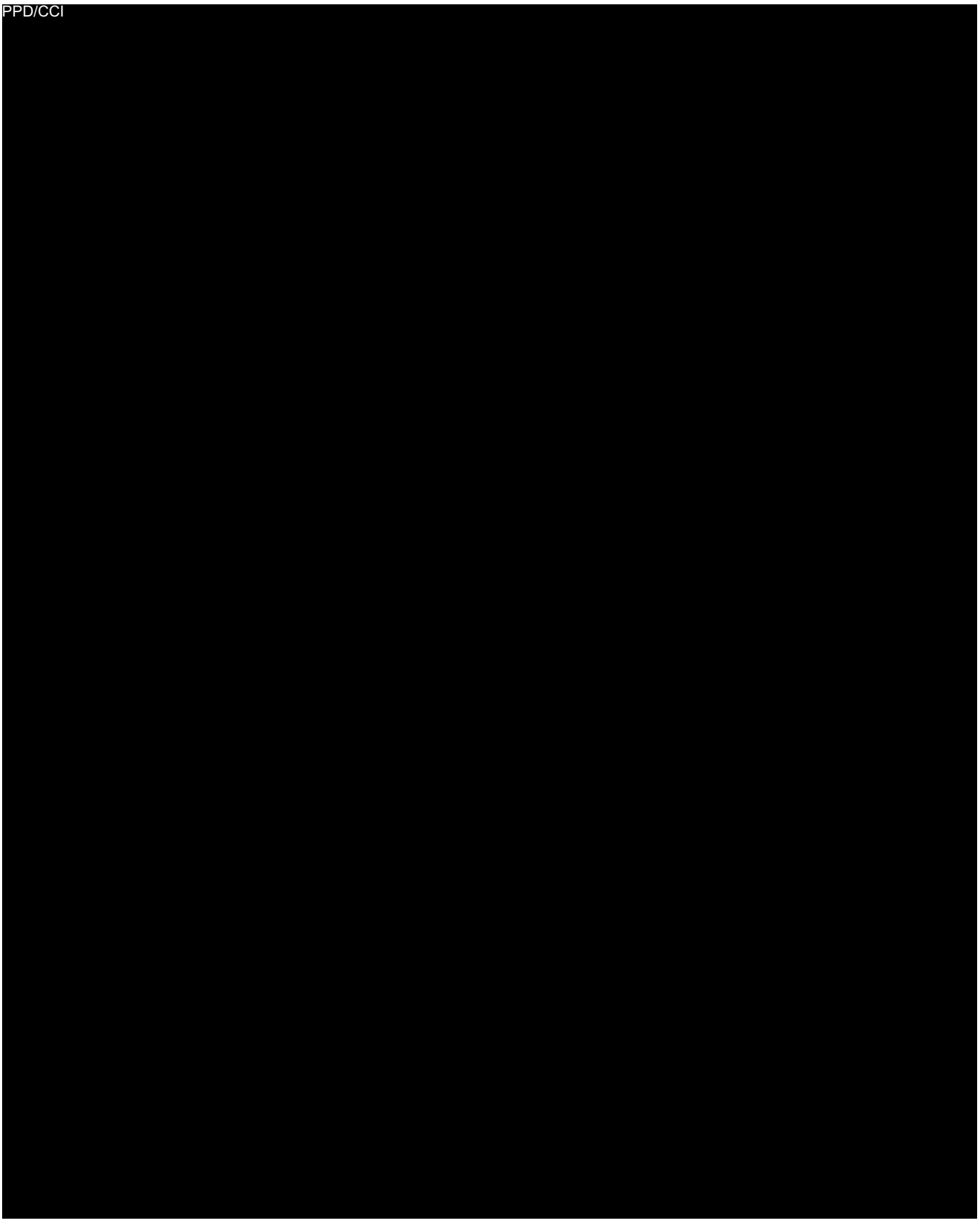

3.0 LIST OF ABBREVIATIONS

AE	Adverse event
AH	Alcoholic Hepatitis
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AR	Adverse Reaction
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of federal regulations
CK	Cytokeratin
CM	Concomitant Medication
C_{max}	Maximum serum concentration
CPK	Creatine Kinase or Creatine Phosphokinase
Cr	Creatinine
CRP	C-reactive protein
ECG	Electrocardiogram
ERC	Endoscopic Retrograde Cholangiogram
DILI	Drug-Induced Liver Injury
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HDPE	High-Density Polyethylene
HFD	High Fat Diet
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
Ht	Height
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International conference on harmonization
ICU	Intensive care unit
IEC	Independent Ethics Committee
I/R	Ischemia/reperfusion
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug

INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
LDL	Low-density lipoprotein
LPS	Lipopolysaccharides
MRC	Magnetic Resonance Cholangiogram
NDA	New Drug Application
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PI	Principal Investigator
PK	Pharmacokinetic
PO	Oral
PSC	Primary Sclerosing Cholangitis
RR	Respiratory rate
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sBA	Serum Bile Acids
SC	Subcutaneous
sCr	Serum creatinine
SD	Standard deviation
SUSAR	Suspected unexpected Serious Adverse Reaction
TE	Transient Elastography
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum serum concentration
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
USAE	Unexpected Serious Adverse Event
WHO	World Health Organization
Wt	Weight

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PPD/CCI

5.0 CURRENT TRIAL

5.1 Trial Objective

Primary:

- To evaluate safety of DUR-928 in subjects with PSC
- To evaluate percent change (%) of serum alkaline phosphatase (ALP) from baseline

Secondary:

- To evaluate % change of liver enzymes and selected biomarkers from baseline

5.2 Trial Rationale

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PPD/CCI

5.3 Population

Forty (36 evaluable) adult male and female subjects, diagnosed with PSC, aged between 18 and 80 years, inclusive, will be enrolled into the study.

5.3.1 Inclusion Criteria

1. Subjects must be able and willing to provide written informed consent to participate in the study

2. Males and females subjects aged between 18 and 80 years, inclusive, at the time of signing informed consent

3. Verified diagnosis of PSC [redacted] prior to Day 1, with or without IBD, based on either a consistent magnetic resonance cholangiogram (MRC) or endoscopic retrograde cholangiogram (ERC) demonstrating bile ducts abnormalities consistent with sclerosing cholangitis. In addition, these subjects will be required to enter the study with a Mayo risk score (Kim et al, 2000) of 0-3, inclusive. For subjects with IBD, documented evidence of IBD either by prior endoscopy or in previous medical records should be ≥ 6 months prior to Day1.

4. Serum (ALP) ≥ 1.5 times ULN [redacted]

5. In subjects receiving treatment with ursodeoxycholic acid (UDCA), therapy must be stable for at least 3 months prior to Day 1 (no dose adjustment) and at a dose not greater than 20 mg/kg/day so that for subjects who are taking UDCA, the investigational drug can be given as a co-medication

6. Subjects of childbearing potential must agree to use a medically acceptable method of contraceptive to prevent pregnancy in the subject and/or the partner for the duration of their participation in the trial up to 2 months after the last study drug dosing. [redacted]

5.3.2 Exclusion Criteria

1. Presence of documented secondary sclerosing cholangitis PPD/CCI [redacted] on prior clinical investigations
2. Small duct PSC
3. Bacterial cholangitis PPD/CCI [redacted]
4. Presence of percutaneous drain or endoscopic bile duct stent PPD/CCI [redacted]
5. History of, or suspicion of cholangiocarcinoma by MRC/ERC and other cross sectional imaging , or clinical judgment at screening
6. Prior liver transplantation, or currently listed for liver transplantation on the basis of recurrent cholangitis and with a match-run MELD-Na^+ score $\geq$ 10
7. Presence of other concomitant liver diseases PPD/CCI [redacted]
8. Cirrhosis and/or hepatic impairment and/or hepatic decompensation PPD/CCI [redacted]
9. Subjects with fibrosis evidence of cirrhosis, as determined by local transient elastography (TE, e.g., FibroScan®) values of ≥14.4 kPa (Corpechot et al, 2014) PPD/CCI [redacted]
10. Moderate to Severe active IBD or flare in colitis activity PPD/CCI [redacted]
11. Active Crohn's disease not currently in remission, as assessed by the investigator and the CRO's medical monitor

12. Use of oral prednisolone PPD/CCI and/or hospitalization for IBD PPD/CCI

13. AST, ALT, and Total Bilirubin concentrations above the allowed cut-offs PPD/CCI

14. International normalized ratio (INR) ≥ 1.2

15. PPD/CCI

16. PPD/CCI

17. PPD/CCI

18. PPD/CCI

19. Any active malignant disease (within 3 years), other than non-melanomatous skin cancer

20. Human immunodeficiency virus (HIV) infection

21. Existing or intended pregnancy, and/or breast feeding

22. Has received any study medication in the context of another clinical trial within the past the 30 days prior to screening

23. PPD/CCI

24. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

PPD/CCI

[redacted]

PPD/CCI

[redacted]

- DUR 928 10 mg PO daily for 28 days
- DUR 928 50 mg PO daily for 28 days

6.0 TRIAL CONDUCT

6.1 Investigative Sites

This will be a multicenter study with approximately 12 clinical sites (hospitals) 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 safety laboratory services will be transferred to one or more contract research organizations (CROs).

6.3 Duration

The first patient, first [screening] visit (FPFV) has been planned for October 2017. Patient participation will last for up to 100 days.

6.4 Discontinuation of Trial

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

See Section 7.4 regarding study stopping criteria.

7.0 TRIAL PROCEDURES

The study procedures are listed below PPD/CCI [redacted]

7.1 Patient Randomization

Oral DUR-928 will be administered daily for 28 days. Subjects will be randomly assigned with equal allocation to one of two treatment groups.

- DUR 928 10 mg PO daily for 28 days
- DUR 928 50 mg PO daily for 28 days

7.2 Trial Test Drug

7.2.1 Administration of Test Drug

The test drug will be self-administered by study subjects daily from Day 1 through Day 28 (with up to 2 extra doses if patient returns to site at Day 30) according to the instructions provided by the study staff. The first dose will be administered in the clinic where the staff will instruct the subjects on how to take their study drug. See Appendix 1.

7.2.2 Packaging and Labeling of Test Drug

The Sponsor will supply the investigational product (DUR-928) in PPD/CCI labeled with the product name, lot number, and quantity.

7.2.3 Storage of Test Drug

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7.2.4 Preparation of Test Drug

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7.2.5 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 dispensed to subjects, 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 group, 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. In the event that the clinical study unit is unable to dispose of the investigational product, unused drug will be returned to DURECT.

7.3 Trial Visits and Study Procedures

Refer to Table 1 for Schedule of Events by Visit.

7.3.1 Visit 1: Screening (Day -42 to Day 0)

All screening procedures will be performed after obtaining informed consent. After obtaining informed consent, subjects will be assigned a patient screening number and screening procedures will be performed. For the patient screening number, subjects will be numbered consecutively within each site in order of their consent into the trial. Only their assigned patient screening number and date of birth will identify subjects to the Sponsor in order to maintain anonymity.

Screening procedures include completion of:

- Demographic information
- Medical and surgical history
- Complete Physical examination (including height and weight)
- Vital signs (BP, HR, RR and T)
- Review of inclusion / exclusion criteria
- Safety laboratory tests (fasted: chemistry, hematology, urinalysis)
- sBA test, HIV-1, HIV-2, Hepatitis B, Hepatitis C and IgG4 (if absence of evidence of IgG4-related sclerosing cholangitis) testing
- Urine pregnancy test (females of childbearing potential)
- 12-lead ECG
- Record prior and concomitant medications (taken within 30 days of screening)
- Biomarker sample collection (see Section 9.6)
- VAS-itch score and 5-D pruritus itch scale diaries given to subjects for completion
- Transient Elastography/FibroScan® (only required if not performed within 3 months of screening)
- MRC or ERC (only required if not performed within 12 months of Day 1)
- Collection of partial Mayo score for IBD flare assessment

7.3.2 Visit 2: Day 1 and Randomization

7.3.2.1 Visit 2 – Prior to Randomization

The following procedures will be performed

- Review of inclusion/exclusion criteria
- Vital signs (BP, HR, RR and T)
- Complete Physical exam (excluding height)
- Safety laboratory tests (fasted: chemistry, hematology, urinalysis)
- sBA Test
- Biomarker sample collection
- PK samples (at selected sites)
- Urine pregnancy test (females of childbearing potential)
- 12-lead ECG
- Concomitant medications
- Adverse events
- VAS-itch score and 5-D pruritus itch scale diaries collected by study staff
- Collection of partial Mayo score for IBD flare assessment

7.3.2.2 Visit 2 - Randomization

After verification that patient meets entrance criteria (as noted in sections 5.3.2), the patient can be randomized to study treatment.

Subjects will be randomly assigned with equal allocation to one of two treatment groups.

- 10 mg DUR 928 administered for 28 days
- 50 mg DUR 928 administered for 28 days

Study drug administration PPD/CCI :

- [redacted]
- [redacted]
- The subject will be sent home with enough study drug (7 days + 2 extra back up doses) to allow for daily dosing between study visits.
- [redacted]

7.3.3 Treatment Period visits: Day 8 PPD/CCI , Day 15 PPD/CCI , Day 22 PPD/CCI and Day 28 PPD/CCI

Subjects will return to clinic weekly for the following study procedures:

Day 8, 15 and 22 PPD/CCI :

- Vital signs (BP, HR, RR and T)
- Safety laboratory tests (fasted: chemistry, hematology, urinalysis)
- Biomarker sample collection
- Limited Physical exam (excluding height)
- sBA test (only on Day 15)
- Collection of unused drug and accountability check
- Concomitant medications
- Adverse events
- Dispensing of new drug supply (7 days + 2 extra back up doses) PPD/CCI
- Transient Elastography/FibroScan® (only on Day 8 and Day 15)
- 12-Lead ECG
- Collection of partial Mayo score for IBD flare assessment

Day 28 PPD/CCI

- Vital signs (BP, HR, RR and T)
- Safety laboratory tests (fasted: chemistry, hematology, urinalysis)
- Biomarker sample collection
- sBA test
- PK samples (at selected sites)
- Collection of unused drug and accountability check
- Concomitant medications
- Adverse events
- Complete Physical exam (excluding height)
- 12-Lead ECG
- Transient Elastography/FibroScan®
- Collection of partial Mayo score for IBD flare assessment
- Urine Pregnancy Test for Females
- VAS-itch score and 5-D pruritus itch scale diaries given to subjects

7.3.4 Day 42 PPD/CCI : Follow-up Visit

The following procedures will be performed

- Vital signs (BP, HR, RR and T)
- Limited Physical exam (excluding height)
- Safety labs (fasted- chemistry, hematology, urinalysis)
- Biomarker sample collection

- sBA test
- 12-lead ECG
- Transient Elastography/FibroScan®
- Collection of partial Mayo score for IBD flare assessment
- VAS-itch score and 5-D pruritus itch scale diaries collected by study staff
- Unused drug return and accountability check
- Concomitant medications
- Adverse events

7.3.5 Day 56 PPD/CCI : Trial Completion / Early Termination

- Complete Physical examination (excluding height)
- Vital signs (BP, HR, RR and T)
- Safety laboratory tests (fasted: chemistry, hematology, urinalysis)
- Biomarker sample collection
- sBA test
- 12-lead ECG
- Collection of partial Mayo score for IBD flare assessment
- Urine pregnancy test (females of childbearing potential)
- Unused drug return and accountability check
- Concomitant medications
- Adverse events

7.4 Study Stopping Criteria

In the event a subject experiences grade 5 CTCAE toxicity, the study will be paused and safety reports will be submitted to FDA for review and agreement prior to dosing any further subject.

If more than 2 subjects develop a CTCAE grade 3 or higher in the same category, the study will be paused and safety data will be evaluated to determine the next step.

Based on the above evaluations, the study may proceed or may be stopped in accordance with the SAC Charter (see Section 13.6, Safety Assessment Committee).

7.5 Concomitant Medication(s)

All medications taken since 30 days prior to screening will be recorded on the appropriate source document and concomitant medication (CM) CRFs. Any required treatment deemed necessary for treatment of the patient will be under the treating physician's discretion, given as medically required, and documented on the CRFs

7.5.1 Prohibited Concomitant Medications

PPD/CCI [redacted] prednisolone PPD/CCI [redacted] or other investigational drugs are prohibited during the course of the study.

8.0 ASSESSMENT OF EFFICACY

8.1 Efficacy Assessments

The primary efficacy endpoint is:
% change of serum ALP from baseline through the end of study treatment and throughout the follow-up period.

The secondary efficacy endpoints are:

- % of subjects with ≥ 20% reduction of serum ALP from baseline
- % of subjects with ≥ 30% reduction of serum ALP from baseline
- % of subjects with ≥ 40% reduction of serum ALP from baseline
- % change of liver enzymes, including ALT, AST, GGT, bilirubin, from baseline through the end of study treatment and throughout the follow-up period.
- % change of selected biomarkers from baseline through the end of study treatment and throughout the follow-up period.
- % change of serum bile acids (sBA) from baseline through the end of study treatment and throughout the follow-up period.

PPD/CCI [redacted]

9.0 ASSESSMENT OF SAFETY

9.1 Safety Assessments

- AEs: Spontaneously reported AEs; either volunteered by the patient, prompted by non-directed questioning or reported by an investigator will be documented on the eCRF.
- Standard 12-lead ECG
- Safety Laboratory Tests (Serum chemistry, hematology, urinalysis)
- Vital Signs and Physical Examination

9.1.1 Discontinuation of Study Drug

Study drug will be discontinued for any subject who experiences:

- a diagnosed IBD flare up based on clinical judgment or the partial Mayo score

- cholangitis
- biliary strictures
- drug-induced liver injury (DILI, see below)

Drug-induced liver injury (DILI)

Cholestatic markers (ALP/GGT) need to be monitored closely for emergent complications of PSC and/or disease progression. To protect patient safety, sites will be instructed to closely monitor for DILI of all subjects as defined by the following criteria:

- Normal total bilirubin throughout the trial and only transaminase elevations are observed:
  - ALT or AST increase ≥ 5X baseline levels AND the patient doesn't have liver-related symptoms or immunological reaction, e.g. anorexia, nausea, vomiting, right upper quadrant pain, rash and pruritus (but not confined to these clinical features only)
  - ALT or AST increase ≥ 3X baseline levels AND are associated with liver-related symptoms or immunological reaction, e.g, anorexia, nausea, vomiting, right upper quadrant pain, rash and pruritus (but not confined to these clinical features only)

- Increase in total bilirubin ≥ 2X baseline AND exceeds 2X ULN with or without liver-related symptoms or immunological reaction, e.g. anorexia, nausea, vomiting, right upper quadrant pain, rash and pruritus (but not confined to these clinical features only)

- ALP or GGT that increase to 3X baseline without OR 2X baseline with liver-related symptoms or immunological reaction, e.g. anorexia, nausea, vomiting, right upper quadrant pain, rash and pruritus (but not confined to these clinical features only)

- INR increased by at least 50% above baseline level to abnormal value.

For the subjects described above, the study drug will be discontinued, the liver profile tests (ALT, AST, bilirubin and PT/INR) will be repeated within 2-3 days along with a physical examination. The AE will be followed per adverse event reporting instructions and a report form will be completed accordingly. All cases will be reviewed by the DURECT Safety Assessment Committee (SAC), see Section 13.6.

9.2 Interim **Safety Profile**

There is no interim safety analysis planned for this study.

9.3 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.

9.3.1 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.

9.4 12-Lead ECGs

Standard resting 12-lead ECGs will be obtained according to the schedule of events. Overall interpretation will be recorded on the eCRF. Clinically significant ECG findings that emerge after treatment will be recorded on the AE eCRF.

9.5 Laboratory Tests

All routine laboratory analyses will be conducted by a central laboratory and have been listed below. Laboratory tests will be obtained as indicated on the Schedule of Events table. Instructions on sample collection, processing and shipment will be provided in a separate laboratory manual.

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[redacted]

Female subjects of childbearing potential will have a urine pregnancy test at Screening, Day 1, Day 28 and at the end of the study. The urine pregnancy test will be performed locally at the investigative site.

9.5.1 Safety Laboratory Tests

***Chemistry*:** Sodium, potassium, chloride, bicarbonate, serum bile acids (total and sub-speciation), serum creatinine, urea, glucose, albumin, calcium, uric acid, alanine aminotransferase, alkaline phosphatase, aspartate transaminase, creatine kinase (CPK), bilirubin (total and conjugated), cholesterol (total, LDL and HDL), triglycerides and gamma-glutamyl transpeptidase (GGT).

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, red cell distribution width.

Coagulation: PT (INR)

Urinalysis: Macroanalysis by dipstick for glucose, bilirubin, ketones, blood, pH, protein, and urobilinogen.

Other: Hepatitis B surface antigen, Hepatitis C antibody *HIV 1/HIV 2 and IgG4.

Laboratory values that are out of range for the central lab will be identified and may be repeated at the Investigator's discretion. The Investigator will classify laboratory values outside the normal range as either clinically significant or not clinically significant. Clinically significant laboratory values outside the normal range (i.e. any clinical abnormality or change that suggests a disease and/or organ toxicity and is of a severity that requires active management) that emerge after signature of the Informed Consent Form will be considered and recorded as an AE. Clinically significant out of range laboratory values that emerge after treatment will be followed and treated (if appropriate) by the Investigator until resolution or lost to follow-up.

9.6 Biomarkers

A PPD/CCI sample will be collected at screening visit PPD/CCI and at pre-dose at Day 1, Day 8, Day 15, Day 22, Day 28, Day 42 and Day 56 (or early termination visit) for assessment of selected exploratory biomarkers.

PPD/CCI

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

- Vital Signs
- ECG
- Biomarkers (serum)
- PK (plasma- at selected sites)
- Safety lab tests

Details on sample collection, processing, storage and shipment will be provided in the study specific Study Reference Manual.

9.7 Vital Signs

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be measured. Blood pressure and heart rate will be measured after the patient has been resting (supine or sitting) for 5 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.

9.8 Physical Examination

A Complete Physical Examination will be conducted at Screening, ,Day 1, Day 28, and at the Trial Completion Visit (Study Day 56) or Early Termination Visit. Day 1 Complete Physical Exam will establish a baseline for comparison with findings at subsequent study visits.

The Complete Physical Exam includes the following assessments:

- Weight
- Height (at screening only)
- General Appearance: head, eyes, ears, nose, mouth, throat, neck (including thyroid)
- Cardiovascular System
- Respiratory System
- Gastrointestinal and Liver System, including rectal examination where indicated
- Skin
- Musculoskeletal System
- Lymph Nodes
- Neurological System

A Limited Physical Exam (excluding height) will be conducted at Day 8, Day 15, Day 22, and Day 42. It includes the following assessments:

- Weight
- General Appearance: head, eyes, ears, nose, mouth, throat, neck (including Thyroid)
- Gastrointestinal and Liver System, including rectal examination where indicated
- Any other body system at the PI's discretion

For unscheduled visits, complete or limited physical exam will be conducted at the PI's discretion.

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

9.9 Partial Mayo score

The partial Mayo score (Rutgeerts et al, 2005) will be collected at each study visit (Appendix 5). This score consists of stool frequency, rectal bleeding, and Physician's Global Assessment (PGA). It aids in the assessment of an IBD flare.

9.10 Blood and Urine Sampling

Blood and urine samples will be collected for safety and biomarker tests from all subjects as per target sample times PPD/CCI

A urine pregnancy test (for female with childbearing potential) will be collected at screening visit, Day 1 visit, Day 28 visit and end of study/early termination visit.

PPD/CCI

9.11 VAS Itch Score and 5-D Pruritus Itch Scale

The VAS (Visual Analogue Scale) Itch Score evaluates the subject's severity of itching (Appendix 3). The 5-D Pruritus Itch Scale is developed as a brief but multi-dimensional questionnaire designed to be useful as an outcome measure in clinical trials (Appendix 4).
PPD/CCI [redacted]

At Day 1 and Day 42 visits, patients will bring in and hand over their itch diaries to the study staff.

9.12 Transient Elastography (TE) or FibroScan®

Transient elastography (TE) e.g. FibroScan® will be conducted at the screening visit for subjects PPD/CCI [redacted] If result shows a value ≥14.4 kPa, the subject won't be enrolled in the study. PPD/CCI [redacted]

9.13 Adverse Events

9.13.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject 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 baseline. 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.

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 clinical 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).

9.13.2 Classifications

Severity

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

- Mild: An event that is easily tolerated by the subject, 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 sponsor for follow-up steps.

An AE that is 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 is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.13.1.

Causality

A blinded 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).

9.13.3 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 subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

DURECT 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.

9.13.3.1 Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal clinical laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition described above. Abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

9.13.4 Reporting of Serious Adverse Events

Regardless of causality, the investigator must complete and submit an SAE form to PPD/CCI within 24 hours of knowledge of the event for all serious adverse events.

PPD/CCI

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 subject 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 subject 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.

If a clinically relevant SAE related to PSC progression occurs, a blood sample (approximately 8 mL) will be collected as soon as possible for measurement of plasma DUR-928 concentration. The collection date and time should be documented. Refer to the sample processing, shipping and handling instructions provided within the laboratory manual.

9.13.5 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 the 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 subject 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 subject is lost to follow-up, or died and until all queries related to the AEs have been resolved. If a subject 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 histopathology.

9.14 Pregnancy

A urine pregnancy test (for female with childbearing potential) will be collected at screening visit, Day 1, Day 28 and Day 56 (end of study/early termination visit).

Female subjects 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

At selected center(s), blood samples will be collected for drug concentration measurements in approximately 5 subjects from each dose group). These samples will be collected on Day 1 and Day 28 of dosing. PPD/CCI

For details on sample collection please refer to Appendix 2, for sample collection, processing and shipping details.

If a clinically relevant SAE related to PSC disease progression occurs, a blood sample (approximately 8 mL) will be collected as soon as possible for measurement of plasma DUR-928 concentration. The collection date and time should be documented, in addition to the date and time of last 2 doses taken. Refer to the sample processing, shipping and handling instructions provided within the laboratory manual.

11.0 STATISTICAL METHODS AND DATA ANALYSIS

11.1 Sample Size Determination

A sample size estimation was performed for the primary efficacy endpoint 'Percentage change from baseline to week 4 in the serum alkaline phosphatase (ALP) level.

Forty subjects will be randomized in total. Considering an early withdrawal rate of 10%, a sample size of 36 subjects (18 subjects per dose group) provides a statistical power of 80% to detect a 15% decrease (with a standard deviation of 35%) compared to baseline in serum ALP after 4 weeks of treatment using a one-group t-test. PPD/CCI

Details of statistical measures and data analysis will be further specified in the Statistical Analysis Plan for this study.

11.2 Patient Randomization

Subjects will be randomized into DUR-928 10 mg and 50 mg treatment groups at a 1:1 ratio, without stratification.

11.3 Definition of Analysis Populations

Intent-to-Treat (ITT) Population: The ITT population will include all randomized subjects independent of their exposure to test drug.

Safety Population: The Safety population will include all subjects who received any amount of test drug. The Safety population will be used for all safety analyses.

Modified Intent-to-Treat (mITT) Population: The mITT population will include all randomized subjects who receive any test drug.

All efficacy endpoints will be analyzed using the mITT population. The disposition data will be summarized using ITT population.

11.4 General Statistical Analysis Considerations

Study data will be summarized by treatment group and overall using descriptive statistics. Categorical variables will be reported with frequencies and percentages. Continuous variables will be reported with number of subjects, mean, standard deviation (SD), median, minimum, and maximum. 95% confidence intervals will also be provided when appropriate. All summaries, statistical analyses, and individual patient data listings will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

The primary efficacy endpoint of detecting a signal with regards to the decrease of the percentage change from baseline in ALP will be tested in the 'pooled group' of both dose levels. The comparison between the dose levels will be performed by exploratory testing. Secondary and other endpoints will be analyzed and explored in a descriptive manner.

11.5 Methodology for Dropouts and/or Missing Data

Missing data will not be imputed except missing date of concomitant medication. Missing dates of concomitant medication may be imputed according to rules to be specified in the SAP. Subjects who discontinued the study early will be summarized by reasons and treatment group.

11.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics specified in section 11.5. Baseline is defined as the last non-missing value before the first dose of study drug.

11.7 Statistical Analyses of Efficacy Endpoints

11.7.1 Primary Efficacy Endpoint

- % change from baseline of serum ALP to the end of the study treatment
- % change from baseline of serum ALP at all post-baseline visits and throughout the follow-up period

11.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- % of subjects with ≥ 20% reduction of serum ALP from baseline to the end of the study treatment
- % of subjects with ≥ 30% reduction of serum ALP from baseline to the end of the study treatment
- % of subjects with ≥ 40% reduction of serum ALP from baseline to the end of the study treatment
- Mean and % change from baseline of bilirubin (total and direct) to the end of the study treatment
- % change from baseline of ALT to the end of the study treatment
- % change from baseline of AST to the end of the study treatment
- % change from baseline of GGT to the end of the study treatment
- % of subjects with ≥ 20% reduction of serum ALP from baseline at all post-baseline visits and throughout the follow-up period
- % of subjects with ≥ 30% reduction of serum ALP from baseline at all post-baseline visits and throughout the follow-up period
- % of subjects with ≥ 40% reduction of serum ALP from baseline at all post-baseline visits and throughout the follow-up period
- % change from baseline of bilirubin (total and direct) at all post-baseline visits and throughout the follow-up period
- % change from baseline of ALT at all post-baseline visits and throughout the follow-up period

- % change from baseline of AST at all post-baseline visits and throughout the follow-up period
- % change from baseline of GGT at all post-baseline visits and throughout the follow-up period
- % change of selected biomarkers (to be specified in the Statistical Analysis Plan (SAP) from baseline and throughout the follow-up period
- % change of serum bile acids (sBA) from baseline and throughout the follow-up period

PPD/ CCI [redacted]

11.7.4 Adjustment for Multiple Hypotheses Testing

Only the primary efficacy criterion will be tested confirmatorily, thus no adjustment for multiple testing is required.

11.7.5 Subgroup Analysis

No subgroup analysis is planned for this study.

11.7.6 Analyses Strategy for Pooling Trial Centers

All trial centers will be pooled for statistical summary.

11.8 Interim Analyses and Data Monitoring

No interim analyses have been planned for this study.

11.9 Statistical Analysis of Safety Endpoints

11.9.1 Safety Variables and Descriptive Summaries

Safety variables include incidence of AEs, results of ECG recordings, laboratory test results (chemistry, hematology, urinalysis and other tests specified in section 9.1.4), and physical examination findings.

Safety variables will be summarized descriptively based on the safety analysis population. No formal statistical testing will be performed for the safety analyses.

Adverse Events (AEs) will be recorded from signing the informed consent through the end of study or early termination. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) is defined as any AE that emerges on or after first dosing of study drug or worsens relative to the pretreatment state. Various TEAEs will be summarized by MedDRA system organ class, prefer term and treatment.

Summary statistics of clinical laboratory test values at all applicable study visit and change from baseline to each post-baseline study visit will be calculated by treatment.

Vital sign results at each time point and change from baseline to each post-baseline study visit will be summarized by treatment.

ECG results at each study visit and change of these parameters from baseline to each post-baseline study visit will be summarized by treatment.

PE results will be displayed in by-patient listings.

11.10 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 SAP and as a protocol amendment, if applicable. The amended SAP will be submitted to the FDA. If amended, the protocol will be submitted to the IRB and to the FDA.

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

PPD/CCI

PPD/CCI [redacted]

12.2 Data Identification

Safety laboratory results from the central safety laboratory will be considered source data. All other 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, and other factors. 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 violation is "a serious non-compliance that may lead to exclusion of a subject from analyses and/or discontinuation from the trial."
- A protocol deviation is "related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment."

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 subject's rights, safety, or well-being"

The Investigator should not deviate from the protocol. Except for changes intended to eliminate any immediate hazard to subjects, 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 open-label trial. Periodic reviews of safety data will be performed by the Sponsor's medical monitor.

13.6 Safety Assessment Committee

In accordance with the Guidance for Industry, Safety Assessment for IND Safety Reporting, DURECT implemented a Safety Assessment Committee (SAC) to closely monitor all safety parameters PPD/CCI [redacted]

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 subjects for this trial will be provided a consent form describing this trial and providing sufficient information for subjects 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 subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any trial procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. Each subject 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 subjects 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 under development and has not been approved for commercial use.

14.4 Patient Information and Informed Consent

Prior to participation in the trial, the Investigator or designee will obtain written consent from each patient 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

Subjects 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. 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 7.3.5 and Section 9.1.1 unless the patient withdraws consent. If a patient withdraws consent they will be

encouraged to complete an early termination visit and AE follow-up. Subjects 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 subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve. Subjects 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.

Subjects who withdraw prior to assignment of test drug will be considered as screen failures and will not be considered randomized (See Section11.2).

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 subjects 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.

PPD/ CCI [redacted]

PPD/CCI

[redacted]

18.0 REFERENCES

PPD/CCI

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