DURECT

Official Title:	A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Safety and Efficacy of DUR-928 in Subjects Infected with SARS-CoV-2 with Acute Lung, Liver or Kidney Injury
NCT Number:	NCT04447404
Document Date:	December 08, 2020

Clinical Protocol

Protocol No.	C928-020
Title:	A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Safety and Efficacy of DUR-928 in Subjects Infected with SARS-CoV-2 with Acute Lung, Liver or Kidney Injury
Phase	2
IND:	149343
Versions:	**Original:** 22 April2020 **Amendment 1:** 11 May 2020 **Amendment 2:** 08 Dec 2020

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 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:

Principal Investigator: Date
Title and Institution:

Sponsor Approval:

PPD/CCI [redacted]

09-Dec-2020
Date

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1.0 TRIAL SYNOPSIS

Title of Trial:	A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Safety and Efficacy of DUR-928 in Subjects Infected with SARS-CoV-2 with Acute Lung, Liver or Kidney Injury
Sponsor:	DURECT Corporation
Phase of Development:	Phase2
Objectives and Primary Endpoints:	Primary: • Evaluate safety in subjects treated with DUR-928 as evidenced by treatment-emergent serious adverse events (TESAEs), including 1. Respiratory failure events 2. Liver failure events 3. Renal failure events 4. Heart failure events 5. Secondary infection (regardless viral or non-viral) • Evaluate efficacy of DUR-928 in treatment of acute organ failure, including acute liver or kidney injury, in subjects infected with SARS-CoV-2. The primary efficacy endpoint is the composite of being alive and free of acute organ failure at Day 28. This is specifically defined as being: o Alive at Day 28 o Free of mechanical ventilation at Day 28 o Free of acute liver failure (i.e., free of the simultaneous presence of: jaundice, coagulopathy, ascites, and hepatic encephalopathy) at Day 28 o Free of renal replacement therapy at Day 28 Secondary: • Alive at Days 28 and 60 • Alive, out of ICU, at Day 28 • Alive, out of hospital, at Days 28 and 60 PPD/CCI [redacted]

[redacted]

Trial Design: This is a Phase 2, randomized, double-blind, placebo control study to evaluate safety and efficacy of DUR-928. A total of 80 subjects will be enrolled into the following 2 study treatment groups in a 3:1 (DUR-928:Placebo) ratio:

- DUR-928: 150 mg PPD/CCI on Day 1 and on Day 4
- Placebo: Sterile Water for Injection PPD/CCI on Day 1 and on Day 4

Subjects will be followed for 60 days. During the trial, subjects should receive standard of care as determined by the site PI. Should any drug product be determined to be safe and effective for the treatment of COVID-19 at the time of study execution, such treatments should be offered to any remaining and future subjects in this trial.

Trial Population: Subjects diagnosed with SARS-CoV-2 infection with acute lung, liver injury or acute kidney injury (AKI)

Inclusion Criteria:

1. Age 18-80 years old and able to provide written informed consent (either from subject or subject's legally acceptable representative)
2. Hospitalized with documented COVID-19 infection diagnosed by standard RT-PCR or equivalent testing other than anti-COVID-19 antibody testing (either upon entry into the hospital, in the hospital, upon admission to the ICU, or in the ICU)
3. Hospitalized with moderate, severe, or early critical COVID-19 illness:
   a. Mean arterial pressure (MAP) ≥ 60 mm Hg, including patients who require no more than one intravenous pressor at the time of enrollment;
   b. If the subject is on ventilator at the time of Day 1 dosing, the total days on ventilator should be < 5 days (120 hours).
4. Subject meets one (lung only) or two (lung with liver or kidney) of the following criteria at the time of enrollment:
   a. Acute liver injury irrespective of known, suspected, or unknown hepatic fibrosis or cirrhosis:
      - In subjects without a known history of liver disease and with a documented normal ALT level within past 12 months, acute liver injury will be defined as ALT > 2 ULN and bilirubin <2.5 mg/dL
      - In subjects with a known history of liver disease and/or a known baseline ALT level within past 12 months, acute liver injury will be defined as ALT >2x baseline level and bilirubin <2.5.

b. AKI:

- Creatinine increase ≥ 0.3 mg/dL (26.52 μmol/L) in 48 hours or increase ≥ 1.5 times baseline within the prior 7 days.

c. Moderate COVID-19 pneumonia defined by the following:

- Severe bilateral diffuse infiltrates & ground glass opacities involving more than 50% of the lung fields

  OR

- PaO2 to FiO2 ratio 100 to 300.

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

Exclusion Criteria:

1. Critical COVID-19 illness:
   - MAP < 60 mm Hg
   - On mechanical ventilator for ≥ 5 days
2. On maintenance (chronic) hemodialysis or peritoneal dialysis
3. History of end stage renal disease (ESRD) or CKD with eGFR <15 mL/min/1.73 m^2
4. Child Pugh C cirrhosis or cirrhosis with any decompensation event (ascites, hydrothorax, hepatic encephalopathy, or clinically significant variceal bleed) within the past 3months.
5. The presence of acute liver AND kidney injury defined as meeting criteria for AKI in the presence of ALT >1.5x ULN and bilirubin >1.5 mg/dL
6. Participant of other clinical trials
7. Receipt of other concomitant experimental therapies except antiviral drugs
8. Underlying diseases that, in the opinion of the principal investigator, might be complicated or exacerbated by proposed treatments or might confound assessment of study drug
9. Any active malignancies other than skin cancer (basal cell carcinoma or squamous cell carcinoma) amenable to local curative therapy. Patients with other potentially curable malignancies that have been treated and are in

remission for at least three years shall be eligible for enrollment in the study. Women who are pregnant or breast feeding

Efficacy Evaluations

Evaluate efficacy of DUR-928 in treatment of acute organ failure, especially acute liver or kidney injury, in subjects infected with SARS-CoV-2. The primary efficacy endpoint is the composite of being alive and free of acute organ failure at Day 28. This is specifically defined as being:

1. Alive at Day 28
2. Free of mechanical ventilation at Day 28
3. Free of acute liver failure (i.e., free of the simultaneous presence of jaundice, coagulopathy, ascites, and hepatic encephalopathy) at Day 28
4. Free of renal replacement therapy at Day 28

Safety Evaluation: Each subject will be followed up for 60 days for safety assessment. Day 60-assessment will be conducted by phone interview.

Safety will be determined based on clinical and laboratory monitoring.

Clinical: Vital signs, and physical examination (when feasible) should be recorded and examined daily while in hospital or during scheduled clinical visits with specific attention to pulmonary abnormalities, worsening liver and kidney functions. Other decompensation events, including ascites and hepatic encephalopathy, will be monitored clinically.

Laboratory: Biochemical parameters that are monitored daily while in hospital or during scheduled clinical visits include liver biochemistry (daily assessment of PT in subjects with coagulopathy may be affected), hematology, creatinine, urinalysis, and serum chemistries. MELD Na, Child's Pugh Turcotte, and CLIF scores in subjects with acute on chronic liver disease will also be monitored when feasible and available.

Viral Test: Viral RNA will be monitored for as long as it continues to be shed in nasopharyngeal oropharyngeal and stool samples of each subject by the standard quantitative RT-PCR.

Data Monitoring Committee (DMC): The mission of the DMC will be to safeguard patient interests and to enhance trial integrity. To address this mission, DMC will meet on a regular basis to review unblinded data on efficacy, safety and quality of trial conduct.

Monitoring Process: During the trial, individual subjects will be evaluated by the site PI if any of the following SAE occurs. The PI and medical monitor, based on the nature and severity of the event(s), will determine if the event(s) warrants

the early termination of the study therapy in the best interest of the subject. The DMC may also provide recommendations as needed.

1. Appearance of DILI:
   a) If baseline measurements (BLM) were <2x ULN, discontinue if ALT or AST increases to >5x BLM;
   b) If BLM ≥2x ULN but <5x ULN, discontinue if ALT or AST increases to >3x BLM;
   c) If BLM ≥ 5x ULN, discontinue if ALT or AST increases to >2x BLM;
   d) Discontinue if ALT or AST increase > 2x BLM AND the increase is accompanied by a concomitant increase in TBL to >2x BLM OR the INR concomitantly increases by >0.2 in absence of COVID-19 coagulopathy;
   e) In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% or > 500/μL)
2. Worsening of COVID-19 severity
3. SAE events associated with cardiac, kidney, liver, or secondary infection.

The PI and medical monitor, based on the nature and severity of the event(s), will determine if the event(s) warrants the early termination of the study therapy in the best interest of the subject. The DMC may also provide recommendations as needed.

The DMC also will be contacted on an as needed basis by the medical monitor to review available data, unblinded by intervention group, providing insights about whether any unexpected SAE (or SUSAR) could be due to study drug rather than the underlying COVID-19 disease and to provide advice regarding study conduct.

In accordance with the Charter, the DMC review of unblinded data will occur promptly to address situations listed in Section 11.5, for example,

1. PPD/CCI [redacted]
2. more than 2 subjects have an AE grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the medical monitor;
3. more than 3 deaths, and the overall percentage of study patients with deaths within 60 days exceeds 10%.

Based on data review, DMC could recommend termination of the trial, pausing of randomization, discontinuation of treatment, or continuation of the trial.

Refer to Section 11.5.

The following parameters will be recorded daily for the safety evaluation:

1. Serious adverse events
2. Standard 12-lead ECG
3. Safety Laboratory Tests (clinical chemistry, hematology, coagulation, and urinalysis)
4. Vital Signs
5. Physical examination (when feasible)

Refer to Section 9.4.1.

Statistical Considerations:

In this Phase 2 randomized placebo-controlled study, the principal objectives are to provide screening evaluations of safety and efficacy of DUR-928.

Safety analyses

Treatment emergent SAEs will be listed and summarized. All SAEs reported in this study will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA).

Particular attention will be given to assessment of treatment emergent SAEs in the domains of respiratory failure events, liver events, and renal events.

The overall incidences of SAEs in each system organ class (SOC) and preferred term (PT) will be tabulated. In addition, incidences 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 treatment group.

Safety will be evaluated by assessment of serious adverse events, clinical laboratory tests, and vital signs, starting at Screening.

Status and severity of comorbid conditions such as diabetes (e.g. last known HbA1C, medications), cardiac disease (e.g. previous MI, Stroke, echocardiogram, 12 lead EKG, baseline troponin, WHO heart failure definition), and immunocompromised status will be documented.

Data regarding the use of experimental anti-viral therapies will be collected.

Data on other supportive measures, such as proning, received by subjects who are on invasive mechanical ventilation will be collected.

For subject deaths, data will be collected on whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care.

For each subject, the reason for hospital admission, the standard of care followed for each subject/site, and if care decisions are made based on resource limitation will all be document.

Refer to Section 9.0.

Efficacy analyses

While this trial will provide important exploratory analyses of efficacy, particular attention will be given to the pre-specified primary endpoint and to the pre-specified secondary endpoints.

The primary endpoint is the composite of being alive and free of acute lung, liver or kidney organ failure at day 28.

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Power Calculations:

A Pearson chi-square statistic will be used to compare the proportion of responders between treatment groups for the primary endpoint, 'alive and free of acute lung, liver or kidney organ failure at day 28'.

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See Section 9.2.

Pharmacokinetics	Pharmacokinetic sampling will only be performed on the first 10 subjects enrolled in the study. Plasma concentration data of DUR-928 from each patient will be used to calculate relevant PK parameters with an appropriate PK data analysis program. PK parameters for DUR-928 will be summarized by dose group using descriptive statistics. Method and Timing: The time points for PK sample collection will be (after only one of the 2 doses administered [Day 1 or Day 4]) as follows: PPD/CCI [redacted] A total of up to 4 samples will be collected, frozen and stored for subsequent processing to determine the concentration of DUR-928 and its major metabolite in plasma.
Test drug, dosage and mode of administration:	DUR-928 at 150 mg PPD/CCI [redacted] and infused over approximately 2 hours. Refer to Section 5.1 for detailed instructions.
Comparator, dosage and mode of administration:	Sterile Water for Injection PPD/CCI [redacted] and infused over approximately 2 hours. Refer to Section 5.1 for detailed instructions.
Schedule of Events:	Refer to Table 1below.

Table 1: Schedule of Events

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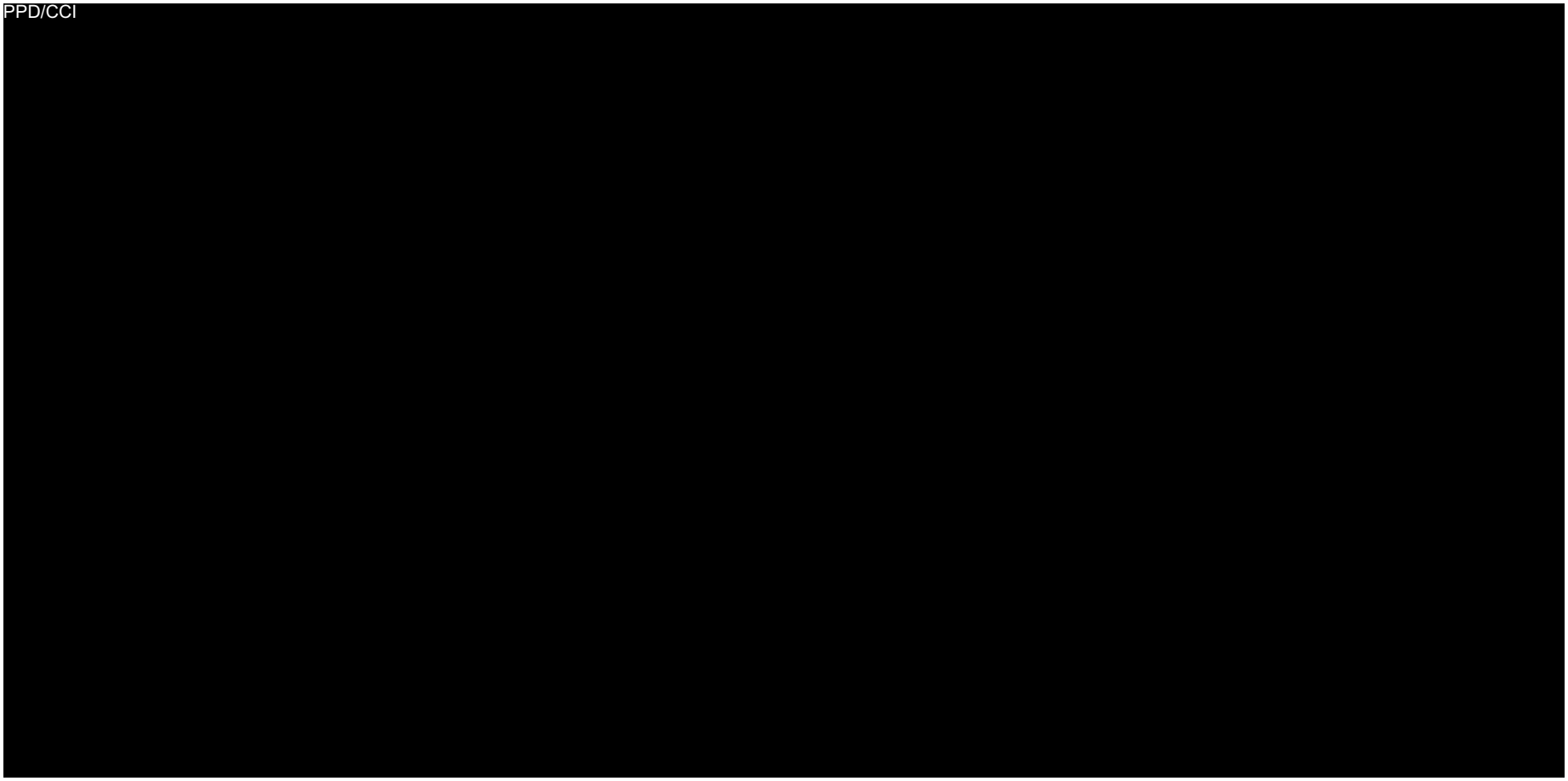
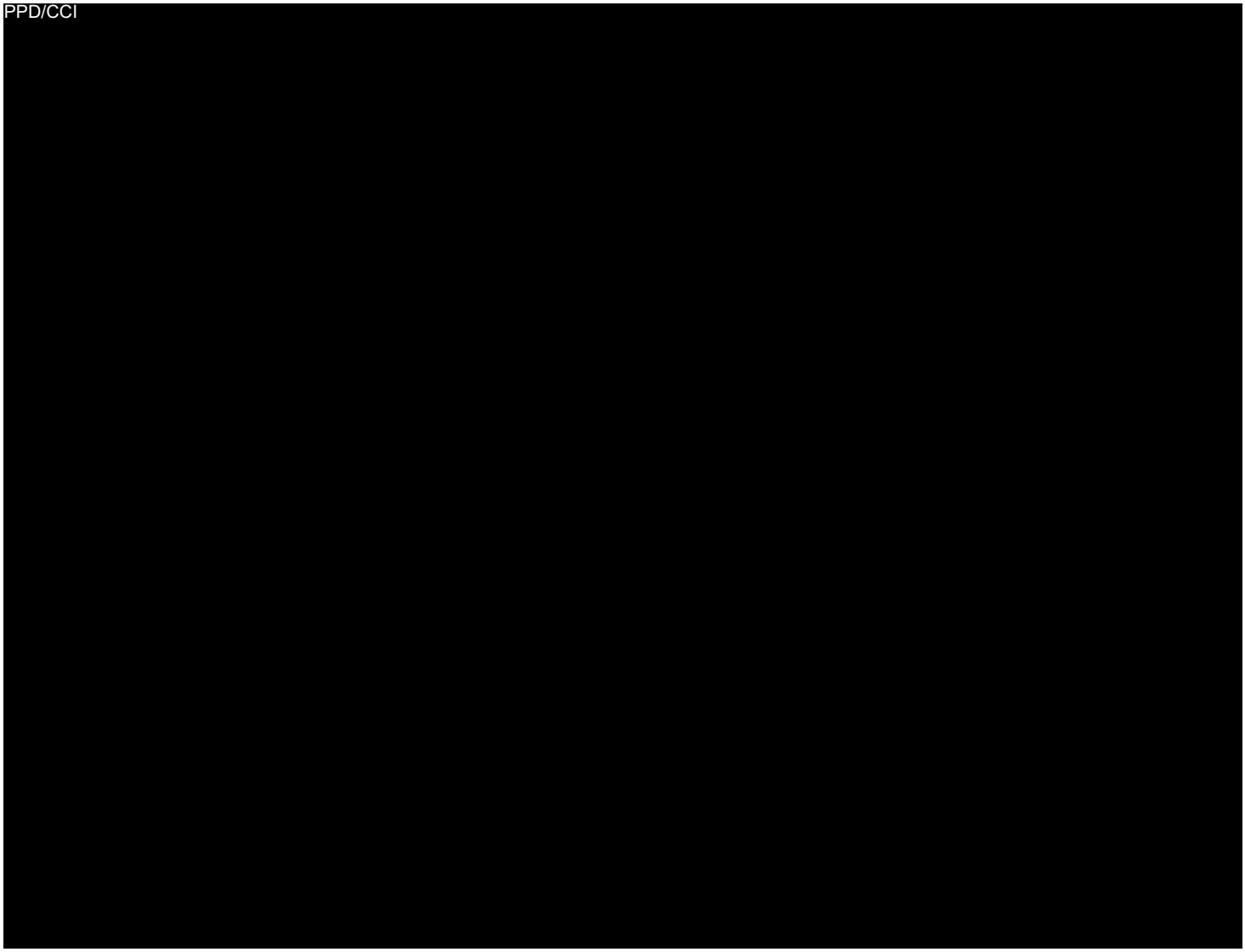


Footnotes for Schedule of Events Table



2.0 LIST OF ABBREVIATIONS

AE	Adverse event
AH	Alcoholic Hepatitis
AKI	Acute kidney injury
ALD	Alcoholic Liver Disease
ALT	Alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	Maximum serum concentration
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus 2019
Cr	Creatinine
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESRD	End stage renal disease
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
hERG	Human ether-a-go-go related gene
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
MELD	Model for End Stage Liver Disease

NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
PI	Principal Investigator
PK	Pharmacokinetic
PO	Oral
PPARγ	Peroxisome proliferator activated receptor-gamma
PT	Prothrombin time
RR	Respiratory rate
SAH	Severe Alcoholic Hepatitis
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SC	Subcutaneous
sCr	Serum creatinine
SST	Serum Separating Tube
$T^{1/2}$	Half-life
T_{max}	Time to maximum serum concentration
ULN	Upper limit of normal
USAE	Unexpected serious adverse event
Vd	Volume of distribution
Wt	Weight

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

PPD/CCI

[redacted]

3.8 **CURRENT TRIAL**

3.9 **Trial Objectives and Primary Endpoints**

Primary:

- Evaluate safety in subjects treated with DUR-928 as evidenced by treatment-emergent serious adverse events (TESAEs), including
    1. Respiratory failure events

2. Liver failure events
3. Renal failure events
4. Heart failure events
5. Secondary infection (regardless viral or non-viral)

- Evaluate efficacy of DUR-928 in treatment of acute organ failure, especially acute liver or kidney injury, in subjects infected with SARS- CoV-2. The primary efficacy endpoint is the composite of being alive and free of acute organ failure at Day 28. This is specifically defined as being:
  - Alive at Day 28
  - Free of mechanical ventilation at Day 28
  - Free of acute liver failure (i.e., free of the simultaneous presence of: jaundice, coagulopathy, ascites, and hepatic encephalopathy) at Day 28
  - Free of renal replacement therapy at Day 28

Secondary:

- Alive at Days 28 and 60
- Alive, out of ICU, at Day 28
- Alive, out of hospital, at Days 28 and 60

PPD/CCI

[redacted]

3.10 Trial Design

This is a Phase 2, randomized, double-blind, placebo control study to evaluate safety and efficacy of DUR-928. A total of 80 subjects will be enrolled into the following 2 study treatment groups in a 3:1 (DUR-928:Placebo) ratio:

- DUR-928: 150 mg PPD/CCI [redacted] on Day 1 and on Day 4
- Placebo: Sterile Water for Injection PPD/CCI [redacted] on Day 1 and on Day 4

Subjects will be followed for 60 days. During the trial, subjects should receive standard of care as determined by the site PI. Should any drug product be determined to be safe and effective for the treatment of COVID-19 at the time of study execution, such treatments should be offered to any remaining and future subjects in this trial.

Figure 1: Trial Schema

3.11 Population

Subjects diagnosed with SARS-CoV-2 infection with acute liver or kidney injury will be enrolled. The target number of participants to complete the study is 80. During the trial, subjects should receive standard of care as determined by their PI.

3.11.1 Inclusion Criteria

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

1. Age 18-80 years old and able to provide written informed consent (either from subject or subject's legally acceptable representative)
2. Hospitalized with documented COVID-19 infection diagnosed by standard RT-PCR or equivalent testing other than anti-COVID-19 antibody testing (either upon entry into the hospital, in the hospital, upon admission to the ICU, or in the ICU)
3. Hospitalized with moderate, severe, or early critical COVID-19 illness:
    c. Mean arterial pressure (MAP) ≥ 60 mm Hg, including patients who require no more than one intravenous pressor at the time of enrollment;
    d. If the subject is on ventilator at the time of Day 1 dosing, the total days on ventilator should be < 5 days (< 120 hours).
4. Subject meets one (lung only) or two (lung with liver or kidney) of the following criteria at the time of enrollment:
    a. Acute liver injury irrespective of known, suspected, or unknown hepatic fibrosis or cirrhosis:
        - In subjects without a known history of liver disease and/or with a documented normal ALT level within past 12 months, acute liver injury will be defined as ALT > 2x ULN and bilirubin <2.5.

- In subjects with a known abnormal baseline ALT level within past 12 months, acute liver injury will be defined as ALT >2x baseline level and bilirubin <2.5.

b. AKI:

- Creatinine increase ≥ 0.3 mg/dL (26.52 μmol/L) in 48 hours or increase ≥ 1.5 times baseline within the prior 7 days

c. Severe COVID-19 pneumonia defined by the following:

- Severe bilateral diffuse infiltrates & ground glass opacities involving more than 50% of the lung fields

OR

- PaO2 to FiO2 ratio 100 to 300.

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

3.11.2 Exclusion Criteria

To participate in this study, subjects must NOT meet any of the following exclusion criteria:

1. Critical COVID-19 illness:
   - MAP < 60 mm Hg
   - On mechanical ventilator for ≥ 5 days
2. On maintenance (chronic) hemodialysis or peritoneal dialysis
3. History of end stage renal disease (ESRD) or CKD with eGFR < 15 mL/min/1.73 m^2
4. Child Pugh C cirrhosis or cirrhosis with any decompensation event (ascites, hydrothorax, hepatic encephalopathy, or clinically significant variceal bleed) within the past 3 months.
5. The presence of acute liver AND kidney injury defined as meeting criteria for AKI in the presence of ALT >1.5x ULN and bilirubin >1.5 mg/dL
6. Participant of other clinical trials
7. Receipt of other concomitant experimental therapies except antiviral drugs
8. Underlying diseases that, in the opinion of the principal investigator, might be complicated or exacerbated by proposed treatments or might confound assessment of study drug

9. Any active malignancies other than skin cancer (basal cell carcinoma) amenable to local curative therapy. Patients with other potentially curable malignancies that have been treated and are in remission for at least five years shall be eligible for enrollment in the study.
10. Women who are pregnant or breast feeding

3.11.3 Number of Subjects

A total of 80 subjects will be enrolled.

3.11.4 Dosage and Regimen

Assigned study treatment (DUR-928 or placebo) will be administered on Day 1 and on Day 4 in PPD/CCI by intravenous infusion over approximately 2 hours PPD/CCI until entire dose is given.

4.0 TRIAL CONDUCT

4.1 Investigative Sites

This will be a multi-center study with up to 8 clinical sites located in the United States.

4.2 Sponsor Obligations of Trial Conduct

Sponsor responsibilities such as data management site management, site monitoring, and medical monitoring may be transferred to one or more contract research organizations (CROs).

4.3 Duration

Subject participation is approximately 60 days.

4.4 Discontinuation of Trial

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

5.0 TRIAL PROCEDURES

The study procedures are listed in Section 5.0and in the Schedule of Events (Table 1).

5.1 Trial Test Drug

5.1.1 Randomization

Subjects will be assigned randomly at a 3:1 ratio to the following treatment groups:

- **DUR-928**, 150 mg in PPD/CCI administered over approximately 2 hours via IV infusion.
- **Sterile Water for Injection**, 5mL (placebo) in PPD/CCI administered over approximately 2 hours via IV infusion

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

5.1.2 Maintenance of the Blind

For the best chance of achieving a valid and reliable test of efficacy, the blind must be maintained despite the fact that the site pharmacist will be unblinded to treatment assignment for the purpose of treatment preparation.

The un-blinded pharmacist must not disclose which test drug the subject received, or bias the subject or blinded staff by discussing the group assignments with them. Any documentation in the medical records must not reveal treatment assignment by indicating the specific study treatment and/or dose volumes added to the PPD/CCI IV bag.

If in a medical emergency knowledge as to which treatment assignment has been administered is critical for the supportive therapy of the subject or will influence further medical treatment of the subject, the Investigator or designee should obtain the subject's test drug treatment assignment from the pharmacist, medical monitor, or Sponsor.

The date, time, reasons for breaking the blind and person doing so must be documented in the source record as it will be reviewed by Sponsor representatives. Unless medically indicated, the treatment should not be disseminated further or shared with the subject to prevent introduction of bias.

5.1.3 Administration of Test Drug

The 1st dose, or Day 1 dose, of the assigned study treatment (test drug) will be administered in a hospital setting immediately after the subject is enrolled.

The second dose of the assigned study treatment (test drug) will be given on Day 4, or 3 days after the 1st dose.

A total of no more than two doses of study treatment (test drug) will be given.

5.1.4 Packaging and Labeling of Test Drug

The sponsor will supply the sterile ready to use DUR-928for Injection:

- PPD/CCI

The concentration of the DUR-928 Injection product to be used in this study is PPD/CCI

The sponsor will supply 5 mL vials of Sterile Water for Injection, USP (placebo).

Each vial is labeled with product name, lot number, and quantity.

5.1.5 Storage of Test Drug

Both DUR-928 Injection and Sterile Water for Injection, USP (placebo) should be stored at PPD/CCI [redacted]

5.1.6 Preparation of Test Drug

The assigned study treatment (DUR-928 Injection or placebo) will be diluted into a PPD/CCI [redacted]

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

5.1.7 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 (e.g. unblinded pharmacist) must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from PPD/CCI [redacted] the amount administered 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 subject to whom the drug was dispensed;
- Date(s), study treatment, and quantity of the drug dispensed to each subject.

The inventory must be available for inspection by the unblinded 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.

5.2 Trial Visits and Study Procedures

Refer to Table 1for an overview of the schedule of events by visit.

5.2.1 Screening (Day -4 to Day-1)

The screening visit will be performed up to 4 days prior to the day of dosing. After obtaining informed consent, subjects will be assigned a subject number and screening procedures will be performed. For the subject number, subjects will be numbered consecutively within each site in order of their consent into the trial. Only their assigned subject number and date of birth will identify subjects to the Sponsor in order to maintain anonymity.

Screening procedures include completion of:

- Informed Consent
- Demographic information
- Medical and surgical history
- Review of inclusion / exclusion criteria
- Physical examination (including height and weight)
- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature)
- Safety laboratory tests (chemistry, hematology, urinalysis, coagulation)
- Urine or serum pregnancy test (females of childbearing potential) performed locally
- 12-lead ECG
- Record prior and concomitant medications (taken within 30 days of screening)

5.2.2 Day 1 (In-hospital, Study Treatment)

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

- Review of inclusion / exclusion criteria to confirm eligibility
- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature) pre-dose
- Physical exam (including weight) when feasible
- PPD/CCI [redacted]
- Safety labs (chemistry, hematology, urinalysis, coagulation) at pre-dose
    - NOTE: If a subject is screened and dosed on the same day, only the safety labs for Screening should be collected. An additional collection for Day 1 Pre-dose safety labs does **not** need to be performed.
- 12-lead ECG (post-dose completion/end of infusion)
- Adverse events and concomitant medications
- Biomarker samples collection (blood) at pre-dose when feasible
- Randomization

- Study Drug Dosing

5.2.3 **Day 2**

- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature)
- Physical exam (including weight) when feasible
- PPD/CCI [redacted]
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- 12-lead ECG (when feasible)
- Adverse events and Concomitant medications

5.2.4 **Day 3**

- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature)
- Physical exam (including weight) when feasible
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- 12-lead ECG (when feasible)
- Adverse events and concomitant medications

5.2.5 **Day 4**

- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature) pre-dose
- Physical exam (including weight) when feasible
- Safety Labs (chemistry, hematology, urinalysis, coagulation) pre-dose
- 12-lead ECG (post-dose completion/end of infusion)
- Adverse events and Concomitant medications
- Biomarker samples collection (blood) at pre-dose when feasible
- PPD/CCI [redacted]
- Study drug dosing (Dose 2 of assigned study drug)

5.2.6 **Day 5 and Day 6**

Subjects will not be kept in the hospital longer than is medically required. If subjects remain hospitalized on Day 5 and Day 6, the following procedures will be performed and, *regardless*

of hospitalization, occurrence of AEs, and intake of concomitant medications will be assessed (in person or via phone contact):

- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature)
- Physical exam (including weight) when feasible
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- PPD/CCI [redacted]
- 12-lead ECG (when feasible)
- Adverse events and Concomitant medications

5.2.7 Day 7 (± 1 day)

The following procedures will be performed via clinic visit on Day 7, or in the hospital if the subject has not been 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 the Day 6 visit should **not** be completed and the Day 7 visit should be completed per visit window.

- Vital signs (BP, HR, respiratory rate, oxygen saturation, and temperature)
- Physical exam (including weight) when feasible
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- 12-lead ECG
- Adverse events and Concomitant medications

5.2.8 Days8-14 (±3 days)

Subjects will not be kept in the hospital longer than is medically required. If subjects remain hospitalized on Day 8-14, the following procedures will be performed, and, *regardless of hospitalization, occurrence of AEs, and intake of concomitant medications will be assessed* (in person or via phone contact). A clinic visit will be performed on Day 14.

- Vital signs (BP, HR, respiratory rate, temperature)
- Physical exam (including weight) when feasible
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- Adverse events and Concomitant medications

5.2.9 Day 28 (±3 day) Trial Completion / Early Termination

The following procedures will be performed via clinic visit on Day 28:

- Physical Exam (including weight) when feasible

- Vital signs (BP, HR, respiratory rate, temperature)
- Urine or serum pregnancy test (females of childbearing potential) performed locally
- Safety labs (chemistry, hematology, urinalysis, coagulation)
- Biomarker samples collection (blood) when feasible
- 12-lead ECG
- Adverse events and Concomitant medications

5.2.10 Day 60 (±3 day) End of Study Follow up

The following procedures will be performed by phone:

- Adverse events and Concomitant medications

5.3 Concomitant Medication(s)

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

6.0 ASSESSMENT OF EFFICACY

6.1 Efficacy Assessments

Primary:

- Evaluate safety in subjects treated with DUR-928 as evidenced by treatment-emergent serious adverse events (TESAEs), including
    1. Respiratory failure events
    2. Liver failure events
    3. Renal failure events
    4. Heart failure events
    5. Secondary infection (regardless viral or non-viral)
- Evaluate efficacy of DUR-928 in treatment of acute organ failure, especially acute liver or kidney injury, in subjects infected with SARS-CoV-2. The primary efficacy endpoint is the composite of being alive and free of acute organ failure at Day 28. This is specifically defined as being:
    - Alive at Day 28
    - Free of mechanical ventilation at Day 28
    - Free of acute liver failure (i.e., free of the simultaneous presence of: jaundice, coagulopathy, ascites, and hepatic encephalopathy) at Day 28
    - Free of renal replacement therapy at Day 28

Secondary:

- Alive at Days 28 and 60
- Alive, out of ICU, at Day 28
- Alive, out of hospital, at Days 28 and 60

PPD/CCI

[redacted]

6.2 Method and Timing of Assessments

Safety Labs will be collected at:

- Screening
- Pre-dose on Day 1
- Pre-dose on Day 4
- Daily during hospitalization, Day 7,14, and Day 28

See Table 1 for further details and timing of study procedures.

7.0 ASSESSMENT OF SAFETY

7.1 Safety Assessments

Each subject will be followed up for 60 days for safety assessment. Day 60 assessment will be conducted by phone interview.

Safety will be determined based on clinical and laboratory monitoring.

Clinical: Vital signs, and physical examination (when feasible), should be recorded and examined daily while in hospital or during scheduled clinical visits with specific attention to pulmonary abnormalities, worsening in liver and kidney functions. Other decompensation events, including ascites and hepatic encephalopathy, will be monitored clinically.

Laboratory: Biochemical parameters that are monitored daily while in hospital or during scheduled clinical visits include liver biochemistry (daily assessment of PT in subjects with coagulopathy may be affected), hematology, creatinine, urinalysis, and serum chemistries. MELD Na, Child's Pugh Turcotte, and CLIF scores in subjects with acute on chronic liver disease will also be monitored when feasible and available.

Viral Test: Viral RNA will be monitored for as long as it continues to be shed in nasopharyngeal oropharyngeal and stool samples of each subject by the standard quantitative RT-PCR.

Data Monitoring Committee (DMC): The mission of the DMC will be to safeguard patient interests and to enhance trial integrity. To address this mission, DMC will meet on a regular basis to review unblinded data on efficacy, safety and quality of trial conduct.

Monitoring Process and Individual Subject Stopping Rule: During the trial, individual subjects will be evaluated by the site PI if any of the following SAE occurs. The PI and medical monitor, based on the nature and severity of the event(s), will determine if the event(s) warrants the early termination of the study therapy in the best interest of the subject.

The DMC may also provide recommendations as needed.

1. Appearance of DILI:
   a. If baseline measurements (BLM) were <2x ULN, discontinue if ALT or AST increases to >5x BLM;
   b. If BLM ≥2x ULN but <5x ULN, discontinue if ALT or AST increases to >3x BLM;
   c. If BLM ≥ 5x ULN, discontinue if ALT or AST increases to >2x BLM;
   d. Discontinue if ALT or AST increase > 2x BLM AND the increase is accompanied by a concomitant increase in TBL to >2x BLM OR the INR concomitantly increases by >0.2 in absence of COVID-19 coagulopathy;
   e. In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% or > 500/μL)
2. Worsening of COVID-19 severity
3. SAE events associated with cardiac, kidney, liver, or secondary infection.

The DMC also will be contacted on an as needed basis by the medical monitor to review available data, unblinded by intervention group, providing insights about whether any unexpected SAE (or SUSAR) could be due to study drug rather than the underlying COVID-19 disease and to provide advice regarding study conduct.

In accordance with the Charter, the DMC review of unblinded data will occur promptly to address situations listed in Section 11.5, for example,

- PPD/CCI
- more than 2 subjects have an AE grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the medical monitor;
- more than 3 deaths, and the overall percentage of study patients with deaths within 60 days exceeds 10%.

Based on data review, DMC could recommend termination of the trial, pausing of randomization, discontinuation of treatment, or continuation of the trial.

Refer to Section 11.5.

The following parameters will be recorded daily for the safety evaluation:

- Serious adverse events

- Standard 12-lead ECG
- Safety Laboratory Tests (clinical chemistry, hematology, coagulation, and urinalysis)
- Vital Signs
- Physical examination (when feasible)

7.2 Method and Timing of Assessments

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

Where time-points of different measurements and/or blood samples coincide, the following sequence applies:

1. Vital Signs
2. ECG
3. Safety labs
4. Biomarkers (blood)
5. Pharmacokinetic sample collection

7.2.1 Adverse Event Recording

Adverse events will be recorded from the time the subject signs the informed consent form through trial completion final visit/early termination.

7.2.2 Spontaneously Reported Adverse Events

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

7.2.3 12-Lead ECGs

Standard resting 12-lead ECGs will be obtained after subject is resting in the supine position for 10 minutes at the time points listed in Table 1.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, per the Investigator's clinical judgment, that emerge after treatment will be recorded on the AE CRF.

7.2.4 Safety Laboratory Tests

All safety laboratory analyses will be conducted at local laboratory and have been listed below. Laboratory tests will be obtained as indicated on the Schedule of Events (Table 1).

Female subjects of childbearing potential will have a urine or serum pregnancy test performed locally at Screening and on Day 28.

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

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

Urinalysis: Macroanalysis for bilirubin, blood, specific gravity, pH, protein, glucose, ketones,urobilinogen. Dipstick urinalysis is permitted.

Coagulation: PT, INR

7.2.5 Vital Signs

Systolic/diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature will be measured with specific attention to pulmonary abnormalities. Vital signs will be measured prior any blood collection. Measurements will be taken at the times specified in the Schedule of Events (Table 1) and will be recorded on the appropriate source document and CRF.

7.2.6 Physical Examination

Due to restrictions in patient contact related to COVID-19infection, a physical examination will only be performed when feasible. The exam includes general appearance, evaluation of head, eyes, ears, nose, throat, neurological exam, weight with specific attention to worsening in liver function as noted by increasing jaundice, ascites (based on International Ascites Club Criteria), or hepatic encephalopathy (based on West Haven Criteria) and presence of infection. The Physical Exams will be taken at the times specified in the Schedule of Events (Table 1) and will be recorded on the appropriate source document and CRF. Any changes from baseline outside the normal range that emerge after treatment will be recorded on the AE CRF.

7.2.7 Biomarkers

Biomarkers will only be assessed when feasible. PPD/CCI [redacted]

The time window for sample collection can be within 12 hours. Serum samples should be stored at -65^{0}C to -80^{0}C until analysis or according to local laboratory instruction.

The following is a list of planned biomarkers. However, additional non-genetic biomarkers may be included if warranted.

- Subset of cytokines: PPD/CCI [redacted]

- High-sensitivity C-reactive protein (hsCRP)
- Lactate dehydrogenase (LDH)
- Ferritin and D-dimer
- Soluble urokinase plasminogen activator receptor (suPAR)

The biomarker data at baseline and at each post-dose time point will be plotted and listed for each subject for evaluation of any change from baseline over time. Since the baseline level of each marker may vary from subject to subject, percent change from baseline will be derived at each post-dose time points for each subject.

See Section 7.2 for sequencing when time-points of different measurements and blood sample types coincide.

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

Blood Volume to be taken during the study:

No more than PPD/CCI of blood will be collected for protocol-related samples collection.

7.3 Adverse Events

7.3.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject 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 subject's medical history, unless the condition for which the procedure was planned has worsened since subject's informed consent. 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 subject 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**≥ 24 hours or prolongation of existing hospitalization
  Prolongation of hospitalization as determined by the Investigator
- 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed above.*

Unexpected Serious Adverse Event

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

Adverse Reaction

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

Suspected Unexpected Serious Adverse Reaction

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

Abnormal Laboratory Value as an AE

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

7.3.1.1 **Classifications**

Severity

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

Mild - Transient symptoms, no interference with the subject's activities of daily living

Moderate – Marked symptoms, moderate interference with the subject's activities of daily living

Severe – Considerable interference with the subject's activities of daily living

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 Section7.3.1.

Toxicity Grade

The Investigator will also provide AE severity grading per CTCAE (Version 5.0)

Causality

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

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

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

Possibly related – A causal relationship is conceivable

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

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

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

7.3.2 Adverse Event Reporting

All events that meet the definition of an AE and occur in the period from when the subject has signed the informed consent form (ICF) through trial completion (final visit), or early termination, must be recorded on the adverse event CRF. All SAEs will be recorded on the appropriate CRF 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 subject (visit or phone), after the subject 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 subject and recorded on the appropriate CRF. 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 CRF along with the assessment of association.

The Investigator will treat the subject 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 CRF(s). All SAEs, and any possibly/probably related severe AEs will be followed until resolution. Resolution of an AE is defined as that point in time when no further changes in the event are expected, that is, 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'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.

7.3.3 Reporting of Serious Adverse Events

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

Submit SAE Report Forms via facsimile or email to:

The Investigator must indicate the SAE's relationship to test drug and sign the SAE report 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 (See Section 7.3.2). 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.

7.3.4 Adverse Event Follow-up

During and after participation by a subject in a clinical trial, the Investigator will ensure that adequate medical care has been provided to the subject for any AEs including clinically significant laboratory values related to the trial. The Investigator will inform the subject 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 (See Section 7.3.2), 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 autopsy and histopathology.

7.4 Pregnancy

Pregnancy tests will be done at screening visit and on Day 28 for females of child-bearing potential

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.

8.0 PHARMACOKINETICS

Plasma samples will be collected from each of the first 10 patients enrolled. These samples will be used to calculate relevant pharmacokinetic parameters of DUR-928 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.

Additionally, if appropriate, PK/PD analysis will be undertaken. MELD score, serum chemistry, and/or biomarker(s) may be used as PD variables for PK/PD analysis.

PK Sample Timepoints:

PPD/CCI

[redacted]

Sites will have flexibility to collect PK samples around e[PPD/CCI] The time window for [PPD/CCI] time point PK sample collection can be [PPD/] The [PPD/CCI] post-dose initiation sample should be collected [PPD/CCI], as close as possible, since it is the highest drug concentration (Cmax) time point. The [PPD/CCI] sample can be collected within [PPD/CCI] of post-dose initiation timeframe. All samples must be clearly labeled with the actual date and time of collection. A total of up to [PPD/CCI] will be collected and processed for plasma. Plasma samples should be stored at -80 C until analysis.

See [PPD/CCI] for collection, storage, and shipment of samples.

9.0 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Research hypotheses

While this trial will provide important exploratory analyses of efficacy, particular attention will be given to the pre-specified primary endpoint and to the pre-specified secondary endpoints.

The primary endpoint is the composite of being alive and free of acute lung, liver or kidney organ failure at day 28.

- [PPD/CCI]

9.2 Sample Size Determination

A Pearson chi-square statistic will be used to compare the proportion of responders between treatment groups for the primary endpoint, 'alive and free of acute lung, liver or kidney organ failure at day 28'.

[PPD/CCI]

Eighty subjects will be enrolled in this study and will be randomized to receive DUR-928 or placebo in a 3:1 ratio.

9.3 Subject Randomization

A total of 80 subjects will be enrolled into the following 2 study treatment groups in a 3:1 (DUR-928:Placebo) ratio:

- DUR-928:150 mg [PPD/CCI] on Day 1 and on Day 4
- Placebo: Sterile Water for Injection [PPD/CCI] on Day 1 and on Day 4

Above study treatments will be diluted in PPD/CCI and administered at PPD/CCI for approximately 2 hours or until the bag is empty.

9.4 General Statistical Methods

In this Phase 2 randomized placebo-controlled study, the principal objectives are to provide screening evaluations of safety and efficacy of DUR-928.

9.4.1 Safety analyses

Treatment emergent SAEs will be listed and summarized. All SAEs reported in this study will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA).

Particular attention will be given to assessment of treatment emergent SAEs in the domains of respiratory failure events, liver events, and renal events.

The overall incidences of SAEs in each system organ class (SOC) and preferred term (PT) will be tabulated. In addition, incidences 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 treatment group.

Safety will be evaluated by assessment of serious adverse events, clinical laboratory tests, and vital signs, starting at Screening.

Status and severity of comorbid conditions such as diabetes (e.g. last known HbA1C, medications), cardiac disease (e.g. previous MI, Stroke, echocardiogram, 12 lead EKG, baseline troponin, WHO heart failure definition), and immunocompromised status will be documented.

Data regarding the use of experimental anti-viral therapies will be collected.

Data on other supportive measures, such as proning, received by subjects who are on invasive mechanical ventilation will be collected.

For subject deaths, data will be collected on whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care.

For each subject, the reason for hospital admission, the standard of care followed for each subject/site, and if care decisions are made based on resource limitation will all be document.

9.4.2 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by descriptive statistics. When appropriate, 95% confidence intervals will also be provided when appropriate.

9.5 Planned Interim Analyses

Not applicable.

9.6 Tabulation of Individual Subject Data

Listings by subject will be provided of all data collected in this study

9.7 Changes and Deviations to the Protocol and Statistical Analysis Plan

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

10.0 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.

10.1 Confidentiality

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

10.2 Data Identification

Data for each subject will be identified by a unique subject ID number that will be assigned at the time of screening.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 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 CRFs. 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, subject recruiting ads, record-keeping, protocol adherence, data verification and transmission, adverse event reporting. Participating investigators should expect final quality assurance visits by the Sponsor, and possibly by the FDA.

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

11.2 Protocol Deviations

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

Definitions:

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

An important protocol deviation is "a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a 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.

11.3 Case Report Forms

Paper case report forms will be used for this trial. All data will be recorded on a source document prior to being entered into the CRF. Data entry will occur at the investigative site and will be performed by trained and qualified site personnel. The Investigator will ensure all the CRFs are completed after each subject visit in a timely manner. Specific instructions are provided in the CRF completion guidelines.

11.4 Coding

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

11.5 Data Monitoring Committee (DMC)

An independent, external DMC that includes a hepatologist, a nephrologist and an ICU specialist will convene prior to study start, once the PPD/CCI enrolled and their PK data available, once PPD/CCI have been treated and followed for PPD/CCI to monitor the study for safety events including SAEs, death, premature discontinuation of treatment for SAEs, or any treatment-emergent laboratory abnormalities.

DMC will evaluate (based on an unblinded review of safety data) if there is:

1. PK data and safety review of the PPD/CCI ;

2. a >20% of subjects in the DUR-928 group than in the placebo group with treatment-emergent, treatment-related serious adverse event(s) of a specific type;
3. more than 3 deaths, and the overall percentage of study patients with deaths within 60 days exceeds 10%.
4. more than 2 subjects have an AE grade 3 or above on the CTCAE scale that is determined to be possibly or probably attributable to study drug as per the medical monitor.

The DMC also will be contacted on an as needed basis by the medical monitor to review available data, unblinded by intervention group, providing additional insights about whether any unexpected SAE (or SUSAR) to an individual subject could be due to study drug rather than the underlying COVID-19 disease and to provide advice regarding study conduct. The PI and medical monitor, based on the nature and severity of the event(s) under the Individual Subject Stopping Rule as listed below, will determine if such event(s) warrant the early termination of the study therapy in the best interest of the subject. The DMC may also provide recommendations as needed.

Individual Subject Stopping Rule:

1. Appearance of DILI:
   a) If baseline measurements (BLM) were <2x ULN, discontinue if ALT or AST increases to >5x BLM;
   b) If BLM ≥2x ULN but <5x ULN, discontinue if ALT or AST increases to >3x BLM;
   c) If BLM ≥ 5x ULN, discontinue if ALT or AST increases to >2x BLM;
   d) Discontinue if ALT or AST increase > 2x BLM AND the increase is accompanied by a concomitant increase in TBL to >2x BLM OR the INR concomitantly increases by >0.2 in absence of COVID-19 coagulopathy;
   e) In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% or > 500/μL)
2. Worsening of COVID-19 severity
3. SAE events associated with cardiac, kidney, liver, or secondary infection.

The DMC will provide recommendations to DURECT on whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interest of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule. While the DMC will be asked to

advise the sponsor regarding future conduct of the study, including possible early study termination, DURECT retains final decision-making authority on all aspects of the trial.

Based on data review, DMC could recommend termination of the trial, pausing of randomization, discontinuation of treatment, or continuation of the trial.

12.0 ETHICAL CONSIDERATIONS

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

12.1 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 approved by the IRB/IEC.

12.2 Regulatory Compliance

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

12.3 Regulatory Status

DUR-928 is an investigational product.

12.4 Subject Information and Informed Consent

Prior to participation in the trial, the Investigator or designee will obtain written consent from each subject 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 subject 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. This consent discussion will be done using remote communication methods (e.g. video) to maintain social distancing in the efforts to prevent the spread of SARS-CoV-2. Each subject will be given a copy of the signed consent form. The original, signed consent forms will be maintained at the investigative site.

12.4.1 Subject 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 subject'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 subject's early termination, before the scheduled final clinic visit, or on the scheduled final clinic visit as described in Section 5.2.9 unless the subject withdraws consent. If a subject 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. (See Section 7.3.2). 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 subject's last trial visit, whichever comes first.

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

13.0 DATA HANDLING AND RECORD RETENTION

13.1 Data Ownership

The CRFs, 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.

13.2 Retention of Trial Records

The Investigator will retain all trial documents (e.g., approved protocol, copies of completed CRFs, 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]

[redacted]

[redacted]

[redacted]

16.0 REFERENCES

PPD/CCI

PPD/CCI

17.0 Appendices

PPD/CCI

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