DICER (Dipyridamole to prevent Coronavirus Exacerbation of Respiratory Status)

Clinical Research Protocol 6.0

NCT04391179

July 12th, 2021

CLINICAL RESEARCH PROTOCOL

DICER (Dipyridamole to prevent Coronavirus Exacerbation of Respiratory Status)

Protocol Number:	HUM00179783
Version and Version Date:	Internal Ver 6.0; July 12th, 2021
Investigational Product:	Dipyridamole
IND Number:	149516
Development Phase:	Phase II Proof-of-concept and feasibility
IND Holder	Yogendra Kanthi, MD 1150 West Medical Center Drive Ann Arbor, Michigan 48109
Funding Organization:	University of Michigan
National and UM Site Principal Investigator	Name: Jason S. Knight, MD, PhD Telephone: (734) 615-1880 Fax: (734) 763-4151 E-mail: jsknight@med.umich.edu
Medical Monitor:	DSMB (central)

VERSION HISTORY

Version	**Date**
Ver 1.0(Internal version 5.2)	06May2020
Ver 2.0	16Jun2020
Ver 2.1	15Jul2020
Ver 3.0	19Jul2020
Ver 4.0	11Aug2020
Ver 5.0	23Nov2020
Ver. 6.0	12-July-2021

SUMMARY OF CHANGES

Item/Section	Change (s)
	Please see Summary of Changes

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ARDS	Acute respiratory distress syndrome
CBC	Complete blood cell count with differential
COVID-19	Coronavirus disease
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FiO2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IRB	Institutional Review Board
MICHR	Michigan Institute for Clinical and Health Research
PI	Principal Investigator
PMN	Neutrophils
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO2	Peripheral pulse oximetry

PROTOCOL SYNOPSIS

TITLE	DICER (DIpyridamole to prevent Coronavirus Exacerbation of Respiratory status)
IND Holder	Yogendra Kanthi
National and Site Principal Investigator	**Jason S. Knight, MD, PhD**
FUNDING ORGANIZATION	University of Michigan, Taubman Medical Research Institute
NUMBER OF SITES	1
RATIONALE	Immune hyperactivation and thrombophilia appear to predict worse outcomes in individuals with COVID-19. Approximately one-quarter of patients admitted with COVID-19 will develop progressive respiratory dysfunction and require mechanical ventilation. The majority of hospitalized patients infected with COVID-19 develop coagulation dysfunction as indicated by elevated D-dimer, which predicts acute respiratory distress syndrome, venous thromboembolism, and mortality. The intent of this proof-of-concept study is to evaluate whether dipyridamole will reduce D-dimer elevation in participants with moderate COVID-19. Dipyridamole is an adenosinergic drug with a favorable safety profile, that reduces thrombosis, immune hyperactivation, and directly inhibits SARS-CoV-2 virus replication. A small clinical trial of dipyridamole in 31 patients with moderate- and severe-COVID-19 showed safety of dipyridamole and efficacy in reducing D-dimer levels, and a trend toward improved clinical outcomes. This is a proof-of-concept study to evaluate the effect of dipyridamole on participants with moderate coronavirus infection (COVID-19) with respect to increase in D-dimer, respiratory status, ventilation and mortality, and ICU admission. If this novel approach is effective in reducing the progression of D-dimer elevation, it will inform a larger, multi-center trial to determine efficacy in preventing progression of moderate to severe COVID-19 infection. The result may broadly improve care of patients with coronavirus infection.
STUDY DESIGN	This is a proof-of-concept multi-center, randomized, single-blinded, placebo-controlled phase II study. We will recruit female or male patients with moderate COVID-19 and randomize them to treatment with 14 days of dipyridamole, or placebo control.
PRIMARY OBJECTIVE	The first primary objective of this study is to evaluate the effect of dipyridamole on D-dimer changes in patients with moderate COVID-19. The second primary objective, formerly a secondary objective, is to compare the effect of dipyridamole vs. placebo on a composite of clinical outcomes.
PRIMARY OUTCOMES	The first co-primary outcome is increase in plasma D-dimer levels compared to baseline.

	The second co-primary endpoint is a clinical hierarchical composite of time to death, number of days on mechanical ventilation, decrease in daily average SpO2/FiO2 ratio, and cumulative sum of COVID ordinal score.
SECONDARY OUTCOMES	Days alive and free of organ support, where organ support is defined as receipt of invasive mechanical ventilation, vasopressor therapy, ECMO support, or dialysis. Individual components of composite endpoint.
EXPLORATORY OUTCOMES	Time to improvement in oxygenation status, initiation of mechanical ventilation or ICU care, proportion of patients requiring mechanical ventilation, change from baseline in hematology labs (C-reactive protein, LDH, ferritin, leukocyte count, platelet count) among patients with abnormal baseline values, time to hospital discharge, incidence of hospital readmission, proportion of surviving patients requiring supplemental oxygen at discharge, number of days on supplemental oxygen, arterial or venous thromboembolism (separately and pooled), gene expression / function / activation of peripheral blood leukocytes, and decrease in each of the following among patients with elevated baseline values: glomerular filtration rate, neutrophil activation, inflammatory / anti-inflammatory / other cytokines, and coagulant and anti-coagulant cytokines.
NUMBER OF PARTICIPANTS	The original protocol called for the enrollment of 80 participants in order to complete the study, randomized 1:1 to dipyridamole or placebo. However, the standard of care changed with the introduction of anti-inflammatory steroids which suggested an increase in sample size may be necessary, thus it was decided to double the number of participants to 160. During the January DSMB meeting it was decided to halt enrollment at 100 participants due to futility.
PARTICIPANT SELECTION CRITERIA	Inclusion Criteria: 1. Age ≥ 18 years 2. Willing and able to provide informed consent prior to performing study procedures unless they have a legally authorized representative (LAR) 3. Confirmed coronavirus (SARS-CoV-2) infection 4. Currently hospitalized or anticipated hospitalization requiring supplemental oxygen Exclusion Criteria: 1. In the opinion of at least two physicians, unlikely to survive for >48 hours from screening 2. Concurrent enrollment in a clinical trial with a cytokine inhibitor (targeting IL-6, IL-6R, IL-1, or Janus kinase). *Use of remdesivir is permitted*.

	3. Currently on invasive mechanical ventilation 4. Hypotension defined as systolic blood pressure < 90 mmHg on two sequential readings at least 4 hours apart 5. Pregnant or breastfeeding 6. Concurrent ***dual*** antithrombotic therapy (aspirin or P2Y12 inhibitor *plus* anticoagulation to treat deep venous thrombosis or pulmonary embolism (*single antiplatelet or anticoagulant agent at prophylaxis or therapeutic dose is permitted*) 7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5x upper limit of normal, hemoglobin <8 g/dL, or platelets <50,000 per mm^3 8. History of recent major bleeding, defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH). 9. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Dipyridamole, 100 mg four times per day to be taken by mouth Dipyridamole will be administered orally every day for up to 14 days until hospital discharge.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo will be prepared by a local pharmacy by contract.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Treatment phase: 14 days of dipyridamole or placebo Follow-up: 30 days after last dose of drug The total duration of the study is expected to be 6 months. The participant recruitment is expected to be 4.5 months. This timeframe is based upon current COVID-19 projections. Pending actual COVID-19 occurrence and participant recruitment, this duration may be extended.
CONCOMITANT MEDICATIONS	Allowed: Any, except as noted above in Exclusion Criteria or as deemed by the PI to be unsafe or likely to confound analysis
EFFICACY EVALUATIONS	This study is statistically powered to be a proof-of-concept phase II clinical trial
SAFETY EVALUATIONS	Each participant will have a complete blood cell count with differential (CBC), hepatic function panel (LFT) and coagulation panel done. This clinical evaluation will measure hemoglobin, platelet count, partial thromboplastin time, international normalized ratio, AST and ALT. Wherever possible, tests will be performed on blood drawn for clinical care.

	Participants will be excluded from participating if their hemoglobin is < 8 g/deciliter, platelets are < 50,000 / mm3, AST or ALT > 5 times the upper limit of normal at the time of screening. Coagulation panel and CBC will be done every other day. LFT will be done at least every four days. Blood pressure will be measured in study participants at least twice each day per institution protocol for hospitalized patients. Participants will be excluded from participating in this clinical trial if their systolic blood pressure is < 90 mmHg at the time of screening. The medical team will notify the study team if systolic blood pressure is < 90 mmHg on two sequential measurements at least 4 hours apart, and the study drug will be held until systolic BP is ≥ 90 mmHg on two sequential measurements at least 4 hours apart. The study team will review the medical record to determine whether the patient's participation in the study trial should be terminated for the safety of the patient.
PLANNED INTERIM ANALYSES	Interim data analyses will be performed and study conduct reviewed by the DSMB at the specified milestones when the following number of participants have completed the study: 1. Safety and futility will be evaluated after approximately 25% and 50% of participants have completed the study or 10 deaths have occurred (whichever occurs first), 2. Study conduct will be evaluated after approximately 25% and 50% of participants have completed the study, or three months after initiation of enrollment (whichever comes first). 3. Efficacy will be evaluated when 50% of participants have completed the study. 4. A second efficacy analysis will occur for clinical outcomes pursuant to the December 2020 DSMB meeting. The first efficacy endpoint will be the proportion of patients by treatment group whose change in D-dimer levels is at least +5% as estimated by simple linear regression. The efficacy analysis will use the O'Brien-Fleming method to correct for interim analyses. For the futility endpoint, if the lower limit for the 95% confidence interval of the daily change in D-dimer is above 9% at the time of the 50% interim analysis, the trial will be stopped. The second efficacy endpoint will be a hierarchical composite outcome of time to death, days on ventilation, change in SpO_2/FiO_2 ratio, and Ordinal scores. It will be analyzed using nonparametric win ratio analysis (Pocock et al., 2012). Decisions regarding the secondary endpoint will be based on conditional power, which does not require adjustments for Type I error (Lan and Trost, 1999; Siu and Lan, 2001; Lachin, 2006). Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

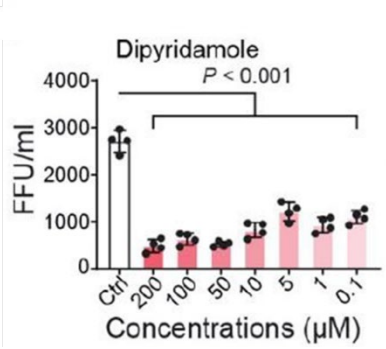
STATISTICS Primary Analysis Plan	For analysis of the first primary endpoint, we will estimate patient-level relative change in D-dimer by fitting a random coefficients regression model to log-scale D-dimer levels. The model will include treatment effects, baseline D-dimer levels, and stratification factors (sex and age), including treatment interactions with stratification factors. The hierarchical composite endpoint will be analyzed using a win ratio algorithm stratified by age and sex**.** In a win-ratio analysis, all treatment patients are compared pairwise to all control patients, and the patient with better outcomes 'wins' (as determined by the hierarchy of the composite endpoint). The algorithm results in a ranking of patients that are analyzed nonparametrically by a Mann-Whitney U test.
SAMPLE SIZE RATIONALE	Decision thresholds and power are based on a preliminary analysis of 147 D-dimer measurements taken on 41 COVID-19 patients in the University of Michigan hospital. We used a simulation approach matching the patient population characteristics learned from the analysis of preliminary data reported above. For power simulation, the intraclass correlation coefficient (ICC) was set to 0.7, somewhat lower than the observed ICC of 0.77, in order to provide a margin for uncertainty in the pilot results. Power is based on a 13% daily increase in D-dimer levels for untreated patients, as observed in preliminary analysis. We posited a 50% reduction in the growth rate for the 100 mg dose. Using 2 arms with 40 subjects per arm (80 subjects in all), power is 0.91 for comparing the pooled dipyridamole participants to the controls. At the December 2020 DSMB meeting, it was decided to promote the hierarchical composite endpoint to a primary endpoint. Sample size for this analysis are calculated according to methods presented in Yosef et al. (2019).

1 BACKGROUND - DIPYRIDAMOLE

SARS-CoV-2 infection (COVID-19) is associated with a thrombophilic state marked by microvascular and macrovascular thrombosis, neutrophilic infiltration in lungs, and development of acute respiratory distress syndrome (ARDS)[1,2]. These form a self-amplifying feedback loop that results in increased immune activation, coagulation, and refractory respiratory failure. Currently there are no therapies for COVID-19, and treatments under investigation are incomplete as they only target specific disease mechanisms (eg. viral replication, individual cytokines, etc.). Treatments that target multiple disease-exacerbating pathways would present unique opportunities to augment current clinically available tools for COVID-19.

Dipyridamole is an FDA-approved drug indicated for use as an antithrombotic agent in combination with vitamin K antagonists following cardiac valve replacement, or with aspirin for prevention of recurrent transient ischemic attacks. Two recent studies conducted in China have shown that dipyridamole suppresses coronaviral replication *in vitro*, and may suppress D-dimer elevation in a small study of patients with COVID-19 [3,4]. Patients with COVID-19-associated pneumonia were treated with dipyridamole 50 mg three times daily for seven days, in addition to treatment with ribavirin. As compared with ribavirin alone-treated controls, the dipyridamole-treated patients demonstrated a significant improvement in D-dimer levels and platelet counts, and a possible trend toward improved clinical outcomes. Dipyridamole increases extracellular adenosine signaling by (1) preventing its reuptake; and (2) stabilizing intracellular cyclic AMP (cAMP) signaling. Dipyridamole potently reduces replication of the novel coronavirus strain (SARS-CoV-2) *in vitro* with EC50 100 nM (**Figure 1**), at plasma drug concentrations significantly lower than typically achieved plasma concentrations in patients treated with dipyridamole (1-4 μM) at the FDA-approved dose[3-5]. Among the cytokine families, Type 1 interferons are the primary drivers of human anti-viral immune responses[6]. Human and animal studies show that dipyridamole induces production of type 1 interferons that are essential in the physiologic antiviral response[7,8]. Induction of protective type 1 interferons may be an additional mechanism by which dipyridamole exerts anti-viral effects[9]. Importantly, in a phase I/II randomized clinical trial, dipyridamole decreased chronic inflammation in patients with HIV on antiretroviral therapy by suppressing T cell activation and cytokine production[10].

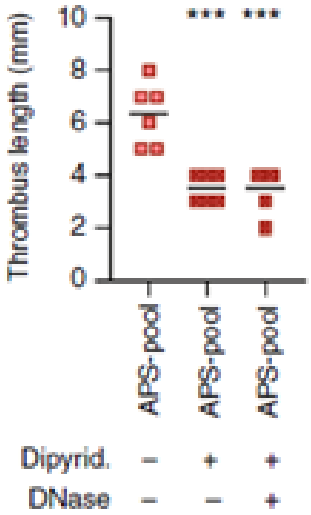
Figure 1: Suppressive effects of DIP on SARS-CoV-2 replication in Vero cells[4]



Elevated levels of both D-dimer (indicating thrombophilia) and neutrophils now also appear to predict severe disease and worse outcomes in individuals with COVID-19[11]. D-dimer, a

byproduct of fibrin formation and degradation, is used clinically as a highly sensitive biomarker of venous thromboembolism (VTE), and other thrombotic and inflammatory conditions. A recent, small clinical trial of dipyridamole in 31 patients with severe COVID-19 suggested potential efficacy of dipyridamole in reducing D-dimer levels and improving platelet counts[4]. Our group previously discovered that dipyridamole reduces venous thrombosis in an animal model by activating the adenosine 2A receptor ($A_{2A}R$) (Figure 2)[12]. This adds further support to the rationale of this study as VTE is present in up to 40% of patients with COVID-19[13].

Figure 2: Dipyridamole reduces venous thrombosis in mice treated with human immune-activating (APS) antibodies.[12]



The acute, exudative phase of ARDS is characterized by an increased immune response with high production of pro-inflammatory cytokines and chemokines, increased neutrophil infiltration and accumulation in the alveoli, and disruption of the alveolar epithelial-capillary barrier, which leads to increased vascular permeability and edema[14]. Neutrophil mediators such as reactive oxygen species, proteinases, and neutrophil extracellular traps (NETs) are potentially toxic to host cells and can result in thrombosis and bystander tissue damage. NETs are extracellular tangles of DNA, histones, microbicidal proteins, and oxidant enzymes that are released by neutrophils to corral infections, but which—when not properly regulated—can amplify inflammation and venous thrombosis. We have recently found that dipyridamole reduces human neutrophil activation and NET formation *ex vivo*[12].

Severe cases of COVID-19 appear to be defined by neutrophilia, lymphopenia, thrombocytopenia, and elevated levels of IL-1β, IL-6, TNF-alpha, and D-dimer[16], the latter suggesting a coagulopathy. All these abnormalities could be potentially explained in part by increased levels of netting neutrophils. NETs license macrophages to produce IL-1β production in many cardiovascular conditions. The same is true for IL-6, either directly[15], or via IL-1β-mediated signaling[16]. Examples of NETs as drivers of coagulopathy are myriad, as intravascular NETosis have been shown to drive thrombotic events in all vascular beds. Of particular relevance here, we have discovered that dipyridamole inhibits human NET formation[12]—a critical effector of thrombo-inflammation[5] and ARDS[1,2]. We have recently identified markedly

elevated indicators of NETosis in COVID-19 patients (**Figure 3A**)[17]. Our data show that the degree of NETosis measured in serum correlated with severity of COVID-19 respiratory illness and mechanical ventilation (**Figure 3B**). We also determined that serum from COVID-19 patients is capable of inducing NETosis in healthy human neutrophils **(Figure 4**) suggesting the presence of a potentially self-amplifying loop of inflammation and thrombosis.

Figure 3: Levels of NETs in serum associate with (A) COVID-19 infection and (B) COVID-associated mechanical ventilation.[17]

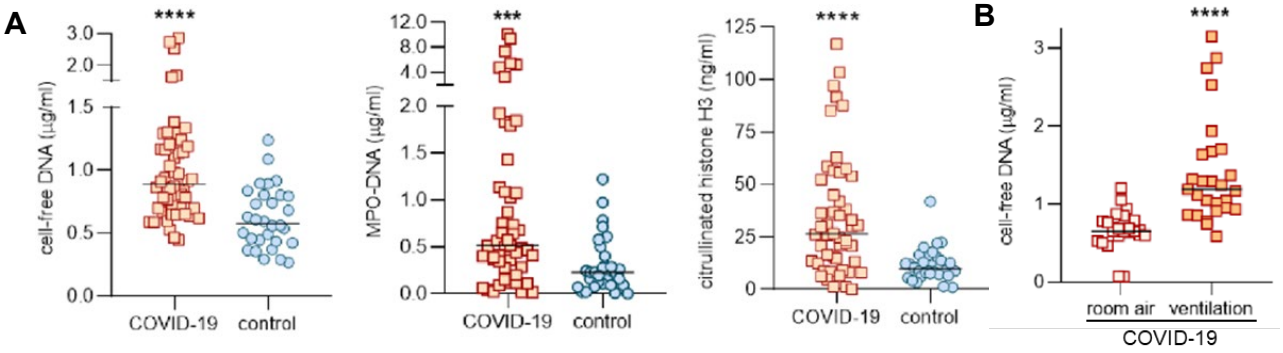
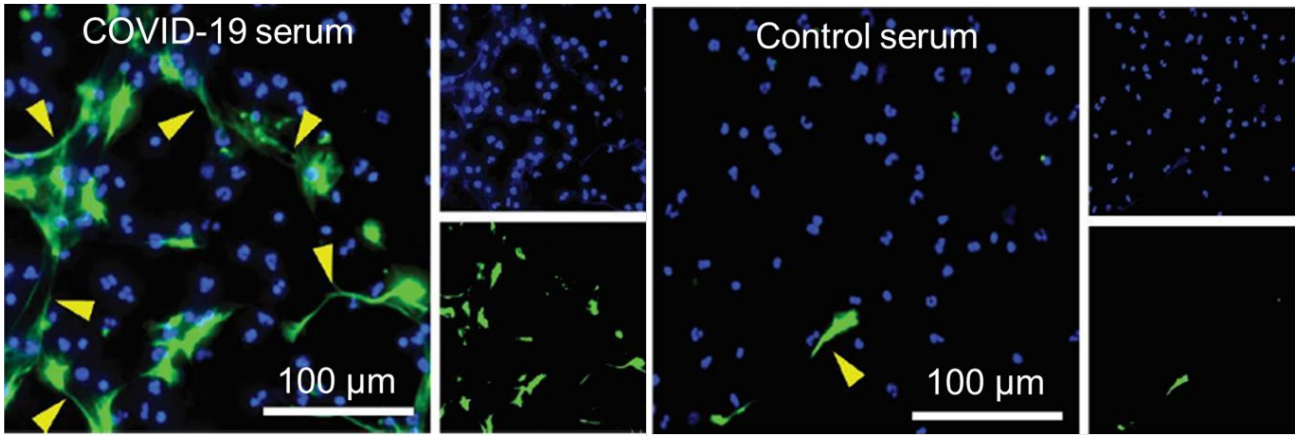


Figure 4: Serum from patients with COVID-19 infection triggers NETs (yellow arrowheads) in healthy neutrophils (green-neutrophil elastase, blue-DNA).[17]



Thus, dipyridamole may be beneficial in patients with COVID-19. Given that the majority of hospitalized patients with COVID-19 develop coagulation dysfunction as indicated by elevated D-dimer[18], and many will also develop ARDS and VTE[18], it is critical to better understand the appropriate management of patients with COVID-19.

Participants in this study will be administered dipyridamole or placebo.

1.1 Non-Clinical Studies Overview

From FDA-approved USPI for dipyridamole[19]

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5-1.9 μg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A -receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'- adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP).

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMPPDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

Hemodynamics

In dogs intraduodenal doses of dipyridamole of 0.5 to 4.0 mg/kg produced dose-related decreases in systemic and coronary vascular resistance leading to decreases in systemic blood pressure and increases in coronary blood flow. Onset of action was about 24 minutes and effects persisted for about 3 hours.

Similar effects were observed following intravenous dipyridamole in doses ranging from 0.025 to 2.0 mg/kg.

In humans the same qualitative hemodynamic effects have been observed. However, acute intravenous administration of dipyridamole may worsen regional myocardial perfusion distal to partial occlusion of coronary arteries.

Pharmacokinetics and Metabolism

Following an oral dose of dipyridamole capsules, the average time to peak concentration is about 75 minutes. The decline in plasma concentration following a dose of dipyridamole capsules fits a two-compartment model. The alpha half-life (the initial decline following peak concentration) is approximately 40 minutes. The beta half-life (the terminal decline in plasma concentration) is approximately 10 hours. Dipyridamole is highly bound to plasma proteins. It is metabolized in the liver where it is conjugated as a glucuronide and excreted with the bile.

1.2 Clinical Studies Overview

From current FDA-approved USPI for dipyridamole[19]

It is believed that platelet reactivity and interaction with prosthetic cardiac valve surfaces, resulting in abnormally shortened platelet survival time, is a significant factor in thromboembolic complications occurring in connection with prosthetic heart valve replacement.

Dipyridamole tablets have been found to lengthen abnormally shortened platelet survival time in a dose-dependent manner.

In three randomized controlled clinical trials involving 854 patients who had undergone surgical placement of a prosthetic heart valve, dipyridamole tablets, in combination with warfarin, decreased the incidence of postoperative thromboembolic events by 62 to 91 % compared to warfarin treatment alone. The incidence of thromboembolic events in patients receiving the combination of dipyridamole tablets and warfarin ranged from 1.2 to 1.8%. In three additional studies involving 392 patients taking dipyridamole tablets and coumarin-like anticoagulants, the incidence of thromboembolic events ranged from 2.3 to 6.9%.

In these trials, the coumarin anticoagulant was begun between 24 hours and 4 days postoperatively, and the dipyridamole tablets were begun between 24 hours and 10 days postoperatively. The length of follow-up in these trials varied from 1 to 2 years.

Dipyridamole tablets do not influence prothrombin time or activity measurements when administered with warfarin.

2 STUDY RATIONALE

The purpose of this study is to evaluate the putative benefit of dipyridamole to prevent progressive D-dimer elevation in COVID-19 severity. By protecting against the COVID-19 thrombo-inflammatory storm and reducing platelet activation and NETs, dipyridamole may also protect against respiratory failure.

Adverse reactions at therapeutic doses are usually minimal and transient. On long-term use of dipyridamole tablets, initial side effects usually disappear. The following reactions in Table 1 were reported in two heart valve replacement trials comparing dipyridamole tablets and warfarin therapy to either warfarin alone or warfarin and placebo.

Table 1: Adverse reactions reported in 2 heart valve replacement trials

Adverse Reaction	Dipyridamole Tablets/ Warfarin	Placebo/ Warfarin
Number of patients	147	170
Dizziness	13.6%	8.2%
Abdominal distress	6.1%	3.5%
Headache	2.3%	0.0%
Rash	2.3%	1.1%

For patients taking dipyridamole, there is a 2% risk for the development of transient hypotension with systolic blood pressure < 90 mmHg with IV administration[20]. This study will administer only the oral tablet formulation, for which hypotension has not been described as a side effect. In a small clinical trial, patients with endotoxemia who were randomized to receive dipyridamole

(total 400 mg daily) or placebo control had no difference in blood pressure[21]. Participants in this clinical trial will receive 400 mg total daily dose of dipyridamole. The blood pressure of each participant will be measured to determine eligibility before randomizing the participants at screening. Patients will be ineligible for this clinical trial if their systolic blood pressure is less than 90 mmHg on two consecutive measurements > 4 hours apart at the time of screening. In order to ensure safety of our participants, blood pressure will be monitored at least twice daily throughout the study for clinical care. If while reviewing blood pressure values, the study team finds that the blood pressure is less than 90 mmHg on two sequential measurements at least 4 hours apart, the study team will review the medical record to determine whether the patient's participation in the study trial should be terminated for the safety of the patient.

Participants taking dipyridamole may be at higher risk of bleeding complications secondary to its antithrombotic effect. In clinical studies, dipyridamole did not increase risk of bleeding when added to aspirin or vitamin K antagonists[22,23]. Importantly, no excess bleeding was reported in a clinical trial with endotoxemic patients randomized to a received randomized clinical trial of dipyridamole in endotoxemia using the maximum recommended daily dose recommended by the FDA [21]. Medical records will be reviewed daily for ISTH-defined major bleeding.

For participants taking dipyridamole, there is a risk of developing other reactions from uncontrolled studies including diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely and there have been rare reports of liver dysfunction. As per the USPI, on those uncommon occasions when adverse reactions have been persistent or intolerable, they have ceased on withdrawal of the medication.

In post-marketing reporting experience, there have been rare reports of hypersensitivity reactions (such as rash, urticaria, severe bronchospasm, and angioedema), larynx edema, fatigue, malaise, myalgia, arthritis, nausea, dyspepsia, paresthesia, hepatitis, thrombocytopenia, alopecia, cholelithiasis, hypotension, palpitation, and tachycardia.

3 STUDY OUTCOMES

3.1 Primary Outcome

1. **Title**: D-dimer
   Description: Change in plasma D-dimer level compared with baseline at enrollment
   Time Frame: Data gathered through day 14
2. **Title**: Hierarchical composite rank score
   Description: Hierarchical composite rank score of death, days on ventilation, decline in daily average SpO2/FiO2 of 50 or more compared to enrollment, cumulative COVID ordinal score
   Time Frame: Data gathered through 28 ± 1 day

3.2 Secondary Outcomes

1. **Title:** Data
   Description: Days to mortality.
   Time Frame: Data gathered through 28 ± 1 day

2. **Title:** Mechanical ventilation days
   Description: Days spent on mechanical ventilation.
   Time Frame: Data gathered through 28 ± 1 day
3. **Title: Change** in SpO2/FiO2
   Description: Dichotomized outcome of decrease in daily average SpO2/FiO2 of 50 or greater compared to enrollment SpO2/FiO2.
   Time Frame: Data gathered through day 14
4. **Title:** Cumulative sum of Ordinal scores
   Description: Sum of daily Ordinal scores during hospitalization. This is a rough approximation of duration and severity.
   Time Frame: Data gathered through day 14
5. **Title:** Days alive and free of organ support
   Description: Organ support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, ECMO support, or dialysis.
   Time Frame: Data gathered through day 14

3.3 Safety Outcomes

1. **Title:** Incidence of serious adverse events
   Description: Incidence of serious adverse events as defined in the study protocol.
   Time Frame: Data gathered through 30 days after administration of last drug dose
2. **Title:** Incidence of severe hypotension
   Description: Hypotension with systolic blood pressure < 90 mmHg requiring more than a 1-L IV fluid bolus
   Time Frame: Data gathered through day 14 ± 1 day
3. **Title:** Incidence of major bleeding
   Description: Incidence of major bleeding defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH) as bleeding that is associated with a decrease in the hemoglobin level of 2 g per deciliter or more, leads to a transfusion of 2 or more units of blood, occurs in a critical site, or contributed to death
   Time Frame: Data gathered through day 28 ± 1 day

3.4 Exploratory Outcomes

1. **Title:** C-reactive protein, LDH, ferritin, leukocyte count, platelet count in blood
   Description: Improvement for participants with abnormal levels at day 1 (>standard laboratory cutoff)
   Time Frame: Data gathered through 28 ± 1 day
2. **Title:** Incidence of mechanical ventilation or ICU care
   Description: Incidence of mechanical ventilation initiation or ICU care
   Time Frame: Data gathered through 28 ± 1 day
3. **Title:** Time to hospital discharge
   Description: Time to hospital discharge will account for death and lost to follow up as a competing risk and censoring event, respectively.
   Time Frame: Data gathered through 30 days after last study drug administration

4. **Title:** Proportion of participants requiring supplemental oxygen
   Description: Incidence of participants alive without requirement for ongoing oxygen supplementation.
   Time Frame: Data gathered through 28 ± 1 day
5. **Title:** Number of days of supplemental oxygen use
   Description: Number of days of supplemental oxygen use
   Time Frame: Data gathered through 28 ± 1 day
6. **Title:** Time to improvement in average daily oxygenation
   Description: Time to first improvement in average daily SpO2/FiO2 ratio of 50 or greater compared to the nadir SpO2/FiO2 ratio
   Time Frame: Data gathered through 28 ± 1 day
7. **Title:** Neutrophil activation studies
   Description: Decrease for participants with elevated levels at day 1 (>2 SD above established healthy-controls)
   Time Frame: Data gathered through day 14 ± 1 day
8. **Title:** Inflammatory, anti-inflammatory, and other cytokines and molecules in blood
   Description: Increase or decrease for participants (>2 SD above established healthy-control mean)
   Time Frame: Data gathered through day 14 ± 1 day
9. **Title:** Coagulant and anticoagulant cytokines and molecules in blood
   Description: Increase or decrease for participants (>2 SD above established healthy-control mean)
   Time Frame: Data gathered through day 14 ± 1 day
10. **Title:** Incidence of arterial or venous thromboembolism
    Description: Arterial or Venous thromboembolism diagnosed by imaging study
    Time Frame: Data gathered through 28 ± 1 day
11. **Title:** Incidence of venous thromboembolism
    Description: Venous thrombosis diagnosed by imaging study
    Time Frame: Data gathered through 28 ± 1 day
12. **Title:** Incidence of arterial thrombosis
    Description: Arterial thrombosis diagnosed by imaging study
    Time Frame: Data gathered through 28 ± 1 day
13. **Title:** Estimated glomerular filtration rate
    Description: Decrease for participants from day 1 (>1 SD laboratory cutoff)
    Time Frame: Data gathered through 28 ± 1 day
14. **Title**: Leukocyte transcriptomics
    Description: Gene expression, function, and activation of peripheral blood leukocytes following treatment with dipyridamole.
    Time Frame: Days 1 and 5

4 STUDY DESIGN

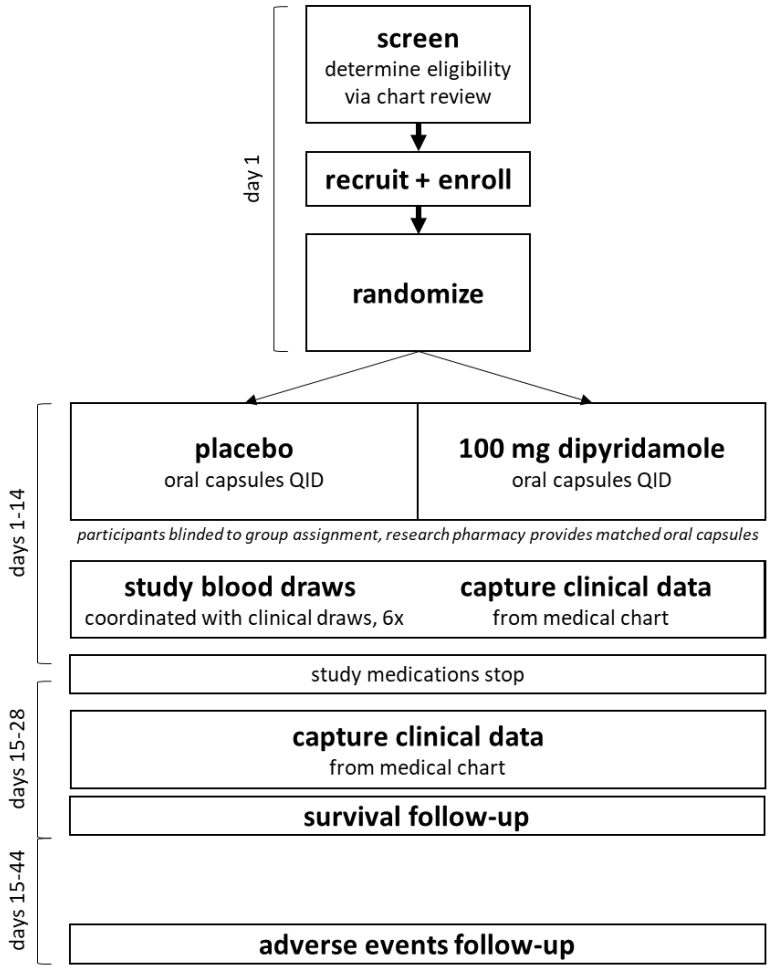
This is a proof-of-concept, single-center, single-blinded, placebo-controlled, randomized, 14-day trial. Participants who meet all inclusion criteria and none of the exclusion criteria will be offered the opportunity to complete the study.

plan to enroll 160 participants. If an interested patient is eligible for this study, the participant will begin a 14-day treatment period when they will be administered a study drug or placebo control for 14 days.

Participants will be assigned to receive the treatments in a stratified, random blocks based on sex and age (above/below 65).Stratified blocks were generated using the 'blockrand' package in R. Clinical evaluations will be made daily. If lab studies from any of these days are abnormal to a clinically significant extent, the study investigator will further evaluate whether the abnormality is attributed to the study drug.

Total treatment of participant is planned for 14 days, but patients will be followed for 30 days after their last dose of study drug. Total duration of the study is expected to be 6 months. Study Schematic is in Figure 5.

Figure 5: Schematic Representation of Study Design



5 CRITERIA FOR EVALUATION

5.1 Safety Evaluations

Each participant will have a complete blood cell count with differential (CBC), and hepatic function panel done on the day of admission per institutional protocol for all patients admitted with confirmed COVID-19 infection. This clinical evaluation will measure hemoglobin, and platelet count, AST and ALT. Hemoglobin and platelets will be measured every 2 days. AST and ALT will be measured every 4 days. Whenever possible, clinical tests will be added to blood already drawn for clinical care.

Patients will be excluded from entering the study if their hemoglobin is < 8 g/deciliter, platelets are < 50,000 / mm3, AST or ALT > 5 times the upper limit of normal. These will be checked at least every 5 days in hospitalized participants per institutional and study protocol and will be reviewed by the study team for changes. If, after randomization, a participant develops hemoglobin < 7 g/deciliter, platelets < 50,000 / mm3, or AST or ALT > 5 times the upper limit

of normal, the study drug will be withheld and restarted if repeat lab testing shows resolution of the abnormality within 24 hours.

Blood pressure will be measured in study participants at least twice daily. Participants will be excluded from participating in this clinical trial if their systolic blood pressure is < 90 mmHg on two sequential measurements at least four hours apart at the time of screening. If, after randomization, a participant develops hypotension with systolic blood pressure < 90 mmHg on two sequential measurements at least four hours apart, the study drug will be held and restarted if repeat blood pressure measurements show systolic blood pressure ≥ 90 mmHg on two sequential measurements at least 4 hours apart.

Participation in the trial will be terminated at the discretion of the medical team attending physician or the PI if deemed important for the safety of the participant.

5.2 Other Evaluations

We plan to evaluate participants' blood samples for circulating, cellular, transcriptional, and genetic biomarkers of coagulation and immune responses in COVID-19.

6 PARTICIPANT SELECTION

6.1 Study Population

Participants with a laboratory test-confirmed diagnosis of COVID-19 who meet the inclusion and have no exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Age ≥ 18 years
2. Willing and able to provide informed consent prior to performing study procedures unless they have a legally authorized representative (LAR)
3. Confirmed coronavirus (SARS-CoV-2) infection
4. Currently hospitalized or anticipated hospitalization requiring supplemental oxygen

6.3 Exclusion Criteria

1. In the opinion of at least two physicians, unlikely to survive for >48 hours from screening
2. Concurrent enrollment in a clinical trial of a cytokine inhibitor (targeting IL-6, IL-6R, IL-1, or Janus kinase). ***Use of remdesivir is permitted.***
3. Currently on invasive mechanical ventilation
4. Hypotension defined as systolic blood pressure < 90 mmHg on two readings at least 4 hours apart
5. Pregnant or breastfeeding
6. Concurrent *dual* antithrombotic therapy (aspirin or P2Y12 inhibitor (eg. clopidogrel, ticagrelor) *plus* anticoagulation to treat deep venous thrombosis or pulmonaryembolism

(***single antiplatelet agent, or anticoagulant agent at prophylaxis or therapeutic dose is permitted***).

7. Presence of any of the following abnormal laboratory values: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 x upper limit of normal (ULN), platelets <50,000 per mm^3, hemoglobin <8 g per deciliter
8. History of recent major bleeding, defined in accordance with the criteria of the International Society on Thrombosis and Hemostasis (ISTH) as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site within 30 days.
9. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.

7 CONCURRENT MEDICATIONS

All participants' non-study medications will be at the discretion of the treating medical provider.

7.1 Allowed Medications and Treatments

Any medications and supplements are allowed except as noted in the exclusion criteria and in the prohibited medications or as deemed by the PI to be unsafe or likely to confound analysis. If a prohibited medication would benefit the participant, the medical attending physician and PI will decide together whether the participant's involvement in the clinical trial should be terminated.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

1. Dual antithrombotic therapy (aspirin or P2Y12 inhibitor *plus* anticoagulation to treat deep venous thrombosis or pulmonary embolism (***single antiplatelet agent, or anticoagulant agent at prophylaxis or therapeutic dose is permitted***).

8 STUDY TREATMENTS

8.1 Method of Assigning Participants to Treatment Groups

Up to 160 eligible participants will be randomly assigned to dipyridamole or placebo control in a 1:1 ratio using stratified, random blocks based on sex and age (above/below 65). Stratified blocks will be generated using the 'blockrand' package in R.

8.2 Blinding

The study will be conducted as a single-blinded trial.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

Active drug: FDA-approved generic dipyridamole tablets

The generic dipyridamole tablets will be over-encapsulated to ensure it looks identical to the matching placebo.

8.3.2 *Formulation of Control (Placebo) Product*

Placebo capsules will be prepared by pharmacy. The placebo capsules will look identical to the dipyridamole capsules.

8.3.3 Packaging and Labeling

Packaging: the study drug will be delivered to the medical ward per routine institutional protocols. The medical team will administer the study drug per routine institutional protocols.

Labelling example: label contents are compliant with Federal laws and state pharmacy laws for prescription and investigational drug labeling. Label contains required language, for example: "Caution: New Drug Limited by Federal (or United States) law to investigational use"

8.4 Supply of Study Drug at the Site

8.4.1 Generic study drugs will be purchased by the pharmacy. Dosage/Dosage Regimen

Pharmacy and medical teams will be instructed to administer the study medication four times daily. If a research participant for some reason misses a dose of their study medication, pharmacy and medical team are encouraged to administer the dose as soon as possible. However, if it is ≤ 2 hours from their next dose, they will be asked to skip the missed dose and go back to their regular dosing schedule. Pharmacy and medical providers will be informed to not double the doses.

8.4.2 Dispensing

Roles delegated to pharmacy are documented on the study-specific Delegation of Authority Log, which is signed by the lead pharmacist for the study. The lead pharmacist determines who or what specific pharmacy areas will perform the delegated roles. Staff performing delegated activities will sign or initial documents and/or forms as indicated in the Dispensing Guidelines and on other study-specific documents. Both research pharmacist and pharmacy technician will be involved in dispensing of study drug.

8.4.3 Administration Instructions

The pharmacy will dispense study drug after randomization has been completed. The medical team will administer the study drug four times per day in both study groups (dipyridamole 100

mg QID, placebo QID). If a participant is discharged during the 14-day treatment period, the study drug will be disposed of per local institute policy.

8.4.4 Supply of Study Drug at the Site

Initial shipment of generic dipyridamole tablets has been purchased by the pharmacy. Subsequent study drug purchase will be made depending on the enrollment rate.

8.4.5 Storage

Generic dipyridamole tablets will be stored at USP controlled room temperature according to the package insert. If the temperature of study drug storage in the pharmacy exceeds or falls below this range, study drugs will be physically quarantined, and a temperature excursion report will be submitted to PI or designee for evaluation.

Medical team will be instructed to store the study drug at room temperature.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing will be maintained. Due to COVID -19 pandemic, return drug may not be counted by the research pharmacist or study staff. After treatment is complete, the remaining study medications will be counted by two clinical staff. If the count cannot be verified by another staff, the single staff member should count twice before final disposal per local institutional guidelines

Administration records of study drug will be verified in the medical record at the end of the study. Compliance below 80% compliance will be documented.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent containing Health Insurance Portability and Accountability Act (HIPAA) authorization will be signed and dated by the participant.

9.1 Clinical Assessments

9.1.1 Concomitant medications

All concomitant medications will be documented during the study, including early termination when applicable. Dose, route, unit frequency of administration, indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (race, ethnicity, sex, date of birth, height and weight) will be recorded at the time of enrollment.

9.1.3 Medical history

Relevant medical history, including history of current disease and information regarding underlying diseases will be obtained from the patient and/or by chart review, and recorded at the time of enrollment.

9.1.4 Social history

Relevant social history, including history of pregnancy, tobacco and alcohol use, will be obtained from the patient and/or by chart review, and recorded at the time of enrollment.

9.1.5 Physical examination

A complete physical examination will be performed by the medical team during the hospitalization. Abnormal physical exam findings will be documented, and the principal investigator will incorporate this information into consideration of continued eligibility from a safety perspective.

9.1.6 Electrocardiogram

Electrocardiogram (ECG) will be performed by the medical team if clinically appropriate and documented in the eCRF if obtained.

9.1.7 Chest imaging

Chest imaging will be performed by the medical team if clinically appropriate and documented in the eCRF if obtained. Imaging findings will be coded in binary variables for infiltrates, pneumonia, pleural effusion, consolidation, pulmonary embolism, RV strain, and cardiomegaly.

9.1.8 Vital signs

Temperature, blood pressure, heart rate, respiration rate, and weight will be performed per institutional protocol. Blood pressure readings and pulse oximetry will be measured at least twice daily.

9.1.9 Oxygen requirements

Pulse oximetry (SpO_2), oxygen requirements (mode of delivery), fraction of inspired oxygen (FiO_2), oxygen flow rate, and mode of mechanical ventilation will be recorded at least daily alongside vital signs measurement. Pulse oximetry will be measured at least twice daily.

9.1.10 Modified WHO COVID-19 8-point Ordinal scale assessment

Ordinal scale assessments will be made daily and on Day 28 as below:

Modified COVID 8-point Ordinal Scale

PATIENT STATE	DESCRIPTOR	SCORE
Dead	Death	8
Hospitalized – severe disease	Ventilation + additional organ support (pressors, renal replacement therapy, ECMO)	7
	Intubation and mechanical ventilation	6
	Non-invasive ventilation or high-flow oxygen	5
Hospitalized – mild disease	Oxygen by mask or nasal prongs	4
	Hospitalized, no oxygen therapy	3
Ambulatory	Limitation of activities	2
	No limitation of activities	1

9.1.11 National Early Warning Scores (NEWS2)

The NEWS2 score will be made daily and on Day 28.

9.1.12 Adverse events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded on the source document.

9.2 Clinical Laboratory Measurements

9.2.1 D-dimer, Ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), complete blood cell count with differential (CBC), fibrinogen, partial thromboplastin time (PTT), international normalized ratio (INR) arterial blood gases (ABG), basic metabolic panel (BMP), hepatic function panel (LFT)

We anticipate blood will be drawn for clinical care at least every other day, and anticipate that most research blood studies will be performed on blood already drawn for clinical care. We will also extract data for any studies done for clinical care purposes. Blood will be obtained and sent to the clinical laboratory to measure LDH, CBC, CRP, D-dimer for standard of care at the

discretion of the medical team. D-dimer, fibrinogen, PTT, INR, ferritin, CBC, LFT, LDH, CRP, BMP will be measured on day 1 on blood drawn for clinical care. Although daily measurement of D-dimer would be ideal for the primary endpoint of this research study, we will measure D-dimer every other day given ongoing medical resource constraints. D-dimer, fibrinogen, PTT, INR and CBC will be measured on days 3, 5, 7, 9, 11, 13 and 14 during hospitalization. CRP, ferritin, LDH, BMP will be measured on day 1, 5, 9, and 13, during hospitalization for research study using blood drawn for clinical care wherever possible. LFT will be measured on day 1 for clinical care, and at least every 4 days until end of drug treatment phase in blood drawn for clinical care wherever possible during hospitalization. ABG will only be recorded if performed for clinical care purposes.

9.2.2 Pregnancy test

A urine pregnancy test, if not already performed for clinical care, will be obtained from female patients who are of childbearing age by the medical team prior to obtaining informed consent.

9.3 Pharmacokinetic measurements

Not applicable.

9.4 Research Laboratory Measurements (see Schedule of Events)

9.4.1 Coagulation potential

Blood will be obtained to investigate potential mediators of COVID-19 and novel parameters of coagulation and platelet activity measured in the study team's research laboratories.

9.4.2 Biomarkers of blood cell activation

Blood will be collected in sodium citrate, heparin, EDTA or serum separator tubes. The blood sample will be labeled and processed at the local sites before shipping to the study team's research laboratories at the University of Michigan to evaluate novel biomarkers of blood cell activation, coagulation, and cytokines.

9.4.3 Leukocytes

Blood will be collected in EDTA, sodium citrate, or heparin tubes. The blood sample will be labeled and sent for processing to the clinical and research labs.

10 EVALUATIONS BY DAY OF HOSPITALIZATION

10.1 Screening Enrollment Visit (24 hour)

1. Chart review to determine eligibility
2. Review the study with the participant and obtain electronic or written informed consent
3. Obtain urine pregnancy test in females of child-bearing potential, if not already performed for clinical care.
4. Assign the participant a unique study number.
5. Randomize participant

10.2 Day 1 Treatment

(Screening Enrollment visit and Day 1 can be on same day)

1. Record demographics data.
2. Record social history.
3. Record medical history
4. Record concomitant medications.
5. Record vital signs, physical examination and oxygen requirements obtained by the medical team.
6. Record clinical laboratory tests performed for routine clinical care
    a. 1x citrate tube
    b. 1x SST tube
    c. 1x EDTA tube
7. Record chest imaging and electrocardiogram if performed by the medical team for routine clinical care.
8. Collect blood for research laboratory tests. This will be coordinated with a clinical draw whenever possible.
    a. 5x citrate tubes
    b. 1x SST tube
    c. 1x PAXgene RNA tube
9. Start study drug according to randomization
10. Review and record any Adverse Events.

10.3 Day 2 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.

10.4 Day 3 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review

3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 3 (± 1 day)
    a. 1x citrate tube
    b. 1x SST tube

10.5 Day 4 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.

10.6 Day 5 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x SST tube
    c. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 5 (± 1 day)
    a. 5x citrate tubes
    b. 1x SST tube
    c. 1x PAXgene RNA tube

10.7 Day 6 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.

10.8 Day 7 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review

3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 7 (± 1 day)
    a. 1x citrate tube
    b. 1x SST tube

10.9 Day 8 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.

10.10 Day 9 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x SST tube
    c. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 9 (± 1 day)
    a. 1x citrate tube
    b. 1x SST tube
    c. 1x EDTA tube

10.11 Day 10 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.

10.12 Day 11 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review

3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 11 (± 1 day)
    a. 1x citrate tube
    b. 1x SST tube

10.13 Day 12 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants assigned to study drug arms.
5. Review and record any Adverse Events.
6. Administer study drugs to participants according to randomization
7. Collect blood for clinical laboratory tests

10.14 Day 13 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube
    b. 1x SST tube
    c. 1x EDTA tube
7. Collect blood for research laboratory tests on Day 13 (± 1 day)
    a. 1x citrate tube
    b. 1x SST tube

10.15 Day 14 Treatment

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Concomitant medications review
3. Review medical records to record data for endpoints.
4. Administer study drugs to participants according to randomization
5. Review and record any Adverse Events.
6. Collect blood for clinical laboratory tests (can be used for clinical care)
    a. 1x citrate tube

b. 1x EDTA tube

10.16 Early Withdrawal Interaction

1. Record vital signs, oxygen requirements, and physical examination findings.
2. Review medical records to record data for endpoints
3. Concomitant medications review.
4. Review and record any Adverse Events.
5. Collect blood for clinical laboratory tests as described in the informed consent document.
   a. 1x citrate tubes
   b. 1x SST tube
   c. 1x EDTA tube
6. Collect blood for research laboratory tests as described in the informed consent document.
   a. 1x citrate tubes
   b. 1x SST tube
7. Follow up call to participant for adverse events, 30 days after last dose of study drug

10.17 30 Days after last dose of study drug (± 2 day)

Chart review and follow up call to participant for AEs assessment up to 30 days after last dose of study drug (maximum of 44 days from initiation of trial participation).

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current protocol or of greater severity or frequency than expected based on the information in the protocol.

The Investigator or designee will probe, via medical record review, for the occurrence of AEs during each study day for the duration of study drug administration, and record the information in the source documents. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

11.2 AE Severity

The guidelines shown in below Table 2 should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 2: AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

11.2.1 AE Relationship to Study Drug

The relationship of an AE to the study drug will be assessed using the following the guidelines.

Table 3: AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes: major bleeding as defined by ISTH, AST or ALT > 10 times the upper limit of normal.

Other important medical events may also be considered a SAE when, based on appropriate medical judgement, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

11.2.3 Serious Adverse Experience Reporting

Study personnel will document all SAEs that occur (whether or not related to study drug). The collection period for all SAEs will begin after informed consent is obtained and end 30 days after administration of the last dose of study drug.

In accordance with the standard operating procedures and policies of the local IRB, the study team will report SAEs to the IRB.

11.3 Protocol Defined Important Medical Findings Requiring Real Time Reporting

Not applicable.

11.4 Medical Monitoring

A DSMB has been established and a DSMB charter formed. Details are noted in the Data Safety section below.

12 DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

12.1 Early Discontinuation of Study Drug

A participant may be discontinued from study treatment at any time if the participant, medical team, or the Site-Investigator feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Participant withdrawal of consent
- Participant is discharged earlier than 14 days
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the study team until the abnormal parameter or symptom has resolved or stabilized.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

The reason for the participant's withdrawal from the study will be specified in the participant's source documents. Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Participants from the Study

A participant may be withdrawn from the study at any time if the participant, the medical team, or the Site-Investigator feels that it is not in the participant's best interest to continue.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

The reason for the participant's withdrawal from the study will be specified in the participant's source documents. Refer to Section 10 for early termination procedures.

12.3 Replacement of Participants

Participants who withdraw from the study treatment will not be replaced.

Participants who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the participant, study coordinator or the investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Use of a prohibited concomitant medication
- Non-compliance with study drug regimen

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The National Investigator in consultation with IND Sponsor will determine if a protocol violation will result in withdrawal of a participant.

When a protocol deviation occurs, a protocol deviation form detailing the deviation will be completed. A copy of the form will be filed in the study's regulatory binder.

14 DATA SAFETY MONITORING

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including clinical trials, thrombosis

expertise, clinical pharmacology, biostatistics. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The study's DSMB will review data relating to safety and efficacy, to conduct and review an interim analysis, and to ensure the continued scientific validity and merit of the study. The DSMB has been formed and includes experts in clinical trials, statistics, thrombosis, and pharmacology. A Charter has been written to guide the DSMB's activities. There will be at least two interim review(s) conducted by the DSMB for the purpose of monitoring study conduct and assessing participant safety. Study conduct will be evaluated by the DSMB when approximately 25% and 50% of participants have completed the study, or three months after initiation of enrollment (whichever comes first). When approximately 25% and 50% of participants have completed the study or 10 deaths have occurred (whichever occurs first), an interim data analysis to evaluate safety and futility will be conducted by an independent data monitoring committee. The interim analyses for efficacy will be limited to the review after 50% of participants have completed the study to limit the cost to power from multiple interim analyses.

Further details regarding the timing and content of the interim reviews is included in the statistical section below.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

Analyses will follow a modified intent to treat (mITT) paradigm. All eligible participants who are randomized into the study and receive at least one dose of the study drug will be included in the analysis.

Based on interim analysis for futility, it was decided to halt recruitment beginning January 19th, 2021. The final data analysis will begin:

- after all 30-day post drug follow-up has been completed for all randomized patients,
- after chart review and data cleaning are complete, and
- after approval of the SAP by the study team.

15.2 Demographic and Baseline Characteristics

The following demographic variables at enrollment will be recorded: race, ethnicity, sex, date of birth, height and weight.

15.3 Analysis of Primary Endpoints

Due to changes in standard of care, the initial D-dimer endpoint may no longer be clinically meaningful. Standard care of treatment for COVID-19 has changed to include anti-inflammatory

steroids which decrease D-dimer levels. Looking for an impact of dipyridamole to further reduce already diminished D-dimer levels is of limited value. In light of the changes to standard of care, it was decided to evaluate the effect of dipyridamole on clinical outcomes more directly by elevating the hierarchical composite outcome from a secondary endpoint to a primary endpoint.

The first primary endpoint is the relative change in D-dimer level over time during up to 14 days of hospitalization. We will assess the trend across D-dimer measurements obtained every second day, but we anticipate that some patients will have fewer measures (e.g. due to discharge before day 14). Linear mixed effects regression will be used to assess the longitudinal trend in log-transformed D-dimer values. The regression model will have a fixed intercept and fixed slope for each treatment arm, and a random intercept and random slope for each subject. The model will also include treatment interactions by stratification factor (sex and age). The primary hypothesis is that the treatment arm will have a smaller fixed slope than the control arm, indicating that treated subjects' D-dimer levels either increase more slowly or decrease relative to those of the control subjects.

Mixed effects regression makes use of all available information for each subject -- even a subject with a single D-dimer measurement can be included. This technique efficiently makes use of the partial or full data observed from each subject, implicitly weighting subjects more if they have more observed points. We note that subjects who do well and are discharged relatively earlier will be somewhat down-weighted due to having fewer measurements, but this is appropriate since our primary aim is to assess moderation of D-dimer increase in-hospital. Discharge and other outcomes are discussed below as secondary aims. We also note that this approach quantifies the change in D-dimer as a linear trend on the log scale. Our preliminary analysis of D-dimer levels in patients with COVID-19 supports this simple approach to quantifying D-dimer variation. Although D-dimer can fluctuate from day-to-day, the longer-term trend is primarily linear, but we acknowledge that some patients may exhibit other patterns of change.

The second primary endpoint is a hierarchical composite of:

- Time of death from any cause during study duration
- Number of days on mechanical ventilation during study hospitalization
- Decrease in SpO_2/FiO_2 ratio of at least 50 units relative to baseline at any time during the observation period, and
- The cumulative sum of COVID ordinal scores during study hospitalization.

The composite endpoint will be nonparametrically assessed by comparing global composite rank score outcomes[24] across pairs of patients and evaluating a 'win ratio' using the Mann-Whitney U statistic. Each pair consisting of one treated and one untreated subject is ranked as defined below:

1. If both subjects die, then the subject who lives longer wins.
2. If exactly one subject dies, then the subject who does not die wins.
3. If the subjects are tied after step 2 (neither subject dies), then the subject with fewer days on ventilator wins.
4. If the subjects are tied after step 3, and only one of the subjects has a decrease in SpO2 of 50 or greater, then the subject who does not have the decrease in SpO2 wins.

5. If the subjects are tied after step 4, then the subject with lower Ordinal score wins.
6. If the subjects are tied after step 5, then their final result is a tie

The win proportion is the probability that a treatment patient experiences better outcomes when compared to a placebo patient, thus representing the effect size. The analysis is powered to a 0.67 win proportion. For the efficacy endpoint using the O'Brien-Fleming method to correct for interim analyses, we will use a P value cutoff of 0.006 for the midway point analysis and 0.044 for the final analysis, yielding an overall alpha (type I error rate) of 0.05.

15.3.1 Interim Analyses of Primary Endpoints

When approximately 25% and 50% of participants have completed the study or 10 deaths have occurred (whichever occurs first), an interim analysis for safety and futility will be conducted by the DSMB. The interim analyses for efficacy will be limited to the review after 50% of participants have completed the study to limit the cost to power from multiple interim analyses.

The interim analysis of benefit for the primary endpoint will be conducted on a binary version of patient-level D-dimer change rates. Rates will be estimated separately for each patient by simple linear regression and dichotomized by whether the rates was above a 5% daily increase. Treatment groups will be compared by a Fisher's exact test. We will use the O'Brien-Fleming method and Lan-DeMets alpha spending functions to preserve an overall Type I error rate of 0.05. Thus, the interim analysis will use a significance threshold of $\alpha = 0.006$ (based on 45 patients), and the remaining 0.044 of alpha will be divided evenly between the final analyses of the two primary endpoints.

For futility of the D-dimer endpoint, if the lower limit for the 95% confidence interval of the daily change in D-dimer is above 9% *for the dipyridamole population* at the time of the 50% interim analysis, the trial will be stopped.

It was decided in the December 2020 DSMB meeting to conduct benefit and futility analyses of the composite hierarchical primary endpoint for all patients with study completion as of December 31, 2020. We proceed with the win ratio analysis described above but base futility and benefit decisions on the conditional power approach described in Lan and Trost (1999) and advanced in Siu and Lan (2001) and Lachin (2006). This approach calculates the condition power (CP), defined as the probability of finding a significant result at the end of the study given the interim results and a presumption that the data reflect the true effect size. Decision thresholds are predetermined as:

- CP $\geq$ 0.9 : Stop study for benefit
- 0.8 $\leq$ CP < 0.9 : Continue study to planned N = 127
- 0.3 $\leq$ CP < 0.8 : Continue study to with re-estimated sample size not to exceed 160
- CP < 0.3 : Stop study for futility

15.4 Analysis of Secondary Endpoints

We will conduct secondary analyses on each component of the hierarchical composite endpoint:

- Time to death
  - *Analysis:* Cox proportional hazards regression
- Number of days on mechanical ventilation during study hospitalization
  - *Analysis:* Poisson regression with subject-level random effects
- Dichotomized (yes/no) decrease in SpO_2/FiO_2 ratio of at least 50 units relative to baseline at any time during the observation period
  - *Analysis:* Logistic regression
- Cumulative sum of COVID ordinal scores during study hospitalization
  - *Analysis:* Mann-Whitney U-test (nonparametric)

We will analyze an additional secondary endpoint:

- Days free of organ support, where organ support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, ECMO support, or COVID-related dialysis, and
- Death at any time is assigned a value of 0 days.
  - *Analysis:* Mann-Whitney U-Test (nonparametric)

Each analysis will include interactions of the study drug by stratification factor.

15.5 Analysis of Exploratory Endpoints

The DICER study contains four major kinds of exploratory endpoints (listed in Section 3.5): continuous, change over time (continuous), binary, and time to event. All analyses will be based on the mITT population except where specified in the definition of the endpoint.

We will analyze continuous endpoints by ANOVA with treatment and stratification factors (sex and age) as predictors.

We will analyze continuous change over time endpoints by mixed linear effect models using the same methodology described in Section 10.1 for the D-dimer primary efficacy endpoint.

We will analyze binary endpoints by logistic regression with treatment and stratification factors (sex and age) as predictors.

We will analyze time-to-event by Cox proportional hazards regression with treatment and stratification factors (sex and age) as predictors.

In all analyses, the only estimate of interest will be the difference between treatment arms. We will include treatment interactions by stratification factor in all models, and we will fit separate models where age is continuous versus where age is represented by an indicator variable for age ≥ 65 years. Hypothesis tests will be two-sided.

15.6 Power analysis

Decision thresholds and power are based on a preliminary analysis of 147 D-dimer measurements taken on 41 COVID-19 patients admitted to Michigan Medicine. Using variance

components regression on log-transformed D-dimer levels, we found that the intraclass correlation coefficient (ICC) for participants (between-participant variance to total variance) was 0.77 in a model controlling for days since admission and ICU status (binary) as fixed effects. ICU status serves as a proxy for case severity. An increasing trend in D-dimer levels (~13% per day) was common to both groups. The moderately high ICC reflects the contributions of around 90% within-participant variation (day-to-day) relative to around 300% between-participant variation. Thus, D-dimer levels largely behave as a stable participant-level trait that may indicate the underlying extent of disease. Defining the endpoint in terms of the least squares slope of D-dimer level using up to 7 measurements reduces the impact of daily D-dimer fluctuations and thereby increases statistical power.

To assess power for the proposed design, we used a simulation approach matching the patient population characteristics learned from the analysis of preliminary data reported above. For power simulation, the ICC was set to 0.7, somewhat lower than the observed ICC of 0.77, in order to provide a margin for uncertainty in the pilot results. Power is based on a 13% daily increase in D-dimer levels for untreated participants, as observed in preliminary analysis. We posited a 50% reduction in the growth rate for the 100 mg dose. Using 2 arms with 40 participants per arm (100 participants in all), power is 0.91 for comparing the dipyridamole-treated participants to the controls. However, the standard of care treatment has changed with introduction of anti-inflammatory steroids which suggests an increase in sample size may be necessary to complete the study.

15.7 Sample Size and Randomization

We will enroll 100 participants to complete this study based on the power calculation. Patients will be recruited for this study and randomized in a 1:1 ratio using stratified random blocks. This study is a proof-of-concept multi center, single-blinded, randomized, controlled trial to evaluate the effectiveness of dipyridamole to reduce progressive coagulation dysfunction associated with coronavirus infection.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Site-Investigator or trained delegates will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study drug.

Study personnel will enter data from source documents corresponding to a participant's visit into secured, central databases. Participants will not be identified by name in the study database or on any study documents to be collected by the designee but will be identified by a participant number and initials.

If a correction is made on a paper source document, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The site investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator.

16.2 Data Management Procedures

The data will be entered into a HIPAA compliant database.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

16.4 Availability and Retention of Investigational Records

The Site Investigator will make study data accessible to the IRB and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant will be maintained that includes the signed Informed Consent with HIPAA Authorization and source documentation related to that participant. The Site Investigator will ensure the reliability and availability of source documents.

All study documents (participant files, signed informed consent forms, copies of source documents, etc.) will be kept secured for a period of 7 years following the completion of the study.

16.5 Monitoring

The PI will be primarily responsible for monitoring data integrity. Monitoring is intended to protect participants' rights and safety, and to ensure the integrity and quality of the data collected. The PI will ensure that all relevant IRBMED and FDA policies, procedures, and stipulations are followed by the study team. This study will be monitored by MICHR monitor. Monitoring will be conducted prior to the initiation of study enrollment and throughout the life cycle of the study.

16.6 Participant Confidentiality

In order to maintain participant confidentiality, only a participant study ID number and participant initials will identify all study participants on source documents and other documentation submitted to the IRB. Bio specimen samples that will be analyzed in a collaborator's research laboratory will only contain the participant study ID number.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a participant's name to a participant identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA.

The Site Investigator will also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor, National-Investigator or designee. Protocol amendments will not be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to participants. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the Institutional Review Boards at each institute prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Site-Investigator will keep the IRB informed as to the progress of the study.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Site-Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved will be obtained.

The IRB will be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the participants of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

The Investigator or designee will prepare the informed consent form containing HIPAA authorization and the investigator will provide the documents to the IRB. The consent form generated by the Site-Investigator will be approved by the IRB. The Site-Investigator will store an IRB-approved copy of the Informed Consent Form in the study regulatory binder.

A properly executed informed consent will be obtained from each participant prior to entering the participant into the trial. Information will be given in both oral and written form and participants will be given ample opportunity to inquire about details of the study. A copy of the

signed consent form will be given to the participant and the original will be maintained with the participant's records.

17.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

PROTOCOL REFERENCES

1. Perlman, S. & Dandekar, A.A. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol* **5**, 917-27 (2005).
2. Blondonnet, R., Constantin, J.M., Sapin, V. & Jabaudon, M. A Pathophysiologic Approach to Biomarkers in Acute Respiratory Distress Syndrome. *Dis Markers* **2016**, 3501373 (2016).
3. Li, Z. *et al.* FEP-based screening prompts drug repositioning against COVID-19. *bioRxiv*, 2020.03.23.004580 (2020).
4. Liu, X. *et al.* Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. *Acta Pharm Sin B* (2020).
5. Gregov, D. *et al.* Dipyridamole: pharmacokinetics and effects on aspects of platelet function in man. *Br J Clin Pharmacol* **24**, 425-34 (1987).
6. Perry, A.K., Chen, G., Zheng, D., Tang, H. & Cheng, G. The host type I interferon response to viral and bacterial infections. *Cell Res* **15**, 407-22 (2005).
7. Galabov, A.S. & Mastikova, M. Dipyridamole induces interferon in man. *Biomed Pharmacother* **38**, 412-3 (1984).
8. Galabov, A.S. & Mastikova, M. Interferon-inducing activity of dipyridamole in mice. *Acta Virol* **27**, 356-8 (1983).
9. Tonew, E., Indulen, M.K. & Dzeguze, D.R. Antiviral action of dipyridamole and its derivatives against influenza virus A. *Acta Virol* **26**, 125-9 (1982).
10. Macatangay, B.J.C. *et al.* A Randomized, Placebo-Controlled, Pilot Clinical Trial of Dipyridamole to Decrease Hiv-Associated Chronic Inflammation. *J Infect Dis* (2019).
11. Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* (2020).
12. Ali, R.A. *et al.* Adenosine receptor agonism protects against NETosis and thrombosis in antiphospholipid syndrome. *Nat Commun* **10**, 1916 (2019).
13. Chen, J. *et al.* Findings of Acute Pulmonary Embolism in COVID-19 Patients. *SSRN Electronic Journal* (2020).
14. Matthay, M.A. *et al.* Acute respiratory distress syndrome. *Nat Rev Dis Primers* **5**, 18 (2019).
15. Merza, M. *et al.* Neutrophil Extracellular Traps Induce Trypsin Activation, Inflammation, and Tissue Damage in Mice With Severe Acute Pancreatitis. *Gastroenterology* **149**, 1920-1931 e8 (2015).
16. Ridker, P.M. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. *Circ Res* **118**, 145-56 (2016).
17. Zuo, Y. *et al.* Neutrophil extracellular traps in COVID-19. *JCI Insight* (2020).
18. Chen, J. *et al.* Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19. *medRxiv*, 2020.03.09.20033068 (2020).
19. Persantine (dipyridamole) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. (December 2019).
20. Lette, J. *et al.* Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. *J Nucl Cardiol* **2**, 3-17 (1995).
21. Ramakers, B.P. *et al.* Dipyridamole augments the antiinflammatory response during human endotoxemia. *Crit Care* **15**, R289 (2011).

22. Group, E.S. *et al.* Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* **367**, 1665-73 (2006).
23. Mok, C.K. *et al.* Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. *Circulation* **72**, 1059-63 (1985).
24. Ramchandani, R., Schoenfeld, D.A. & Finkelstein, D.M. Global rank tests for multiple, possibly censored, outcomes. *Biometrics* **72**, 926-35 (2016).

APPENDIX 1. Schedule of Study Events

See attached SOE document

APPENDIX 2. Summary of Changes