Clinical Research Protocol

Title:	A randomized, open-label study of the vascular and microbiologic efficacy of dipyridamole plus standard care vs. standard care in hospitalized COVID19 patients.
Study Phase:	Phase 2 Proof of concept
Drug Name:	Dipyridamole
Indication:	Upper and lower respiratory tract infection in patients hospitalized with SARS-CoV-2
Multiple Principal Investigators:	Single Center, Dr. Liang (PI), Co-PIs: Drs. Kevin Dieckhaus, Jeffrey R. Aeschlimann, Mark Metersky, Eric Mortensen, Christopher Pickett
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Protocol Version: 2 Date: May 26, 2021

Sponsor:

UConn School of Medicine

Name of Finished Product:

Dipyridamole

Study Title:

A randomized, open-label study of the vascular and microbiologic efficacy of dipyridamole plus standard care vs. standard care in hospitalized COVID19 patients.

Study Number: 100

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1.1 Indication

Oral dipyridamole is being evaluated to treat respiratory tract infection and circulatory dysfunction due to SARS-CoV-2 coronavirus.

1.2 Background and Rationale

Rationale for Study

Infection with SARS-CoV-2 causes human COVID-19 (HCoV-19). In severe illness, COVID 19 infection results in lymphopenia, elevated D-dimer levels, hypercoagulation, hypertension, acute respiratory distress syndrome (ARDS), and acute cardiac injury.[1] Dipyridamole (DIP) is an FDA-approved drug which inhibits adenosine uptake that leads to increased extracellular adenosine which in turn stimulates adenosine receptors-mediated vasodilator, anti-platelet and anti-inflammatory effects. These effects are also augmented by DIP's inhibition of phosphodiesterase (PDE).

Pan-PDE inhibition may prevent lung (fibrosis) as well as acute heart, liver, and kidney injury.[2]

In addition, by virtually screening an FDA approved drug library, Liu, et. al[3] have recently shown that DIP appears to bind to the HCoV-19 3c-like protease enzyme (nsp5 or Mpro) and also suppresses HCoV-19 (SARS-CoV-2) proliferation in Vero E6 cells with an IC50 ≤100 nM. The inhibitory activities compared favorably to those of chloroquine (which served as a positive control. Plasma concentrations in humans from routine dosing regimens (regimen of 50 mg three times per day) should exceed this IC50 value for the duration of the 7 day treatment interval proposed in this investigation. In vivo anti-viral effect of dipyridamole has been demonstrated in vesicular stomatitis virus-induced pneumonia with prolongation of survival.

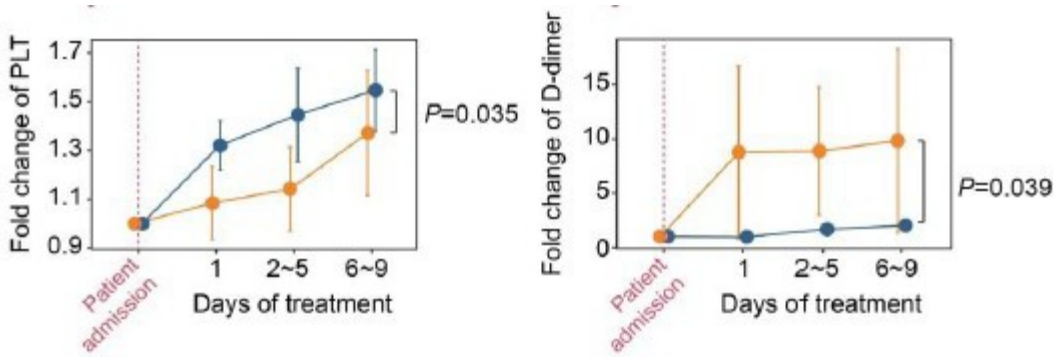
In 12 COVID-19 patients, treated with prophylactic anti-coagulation therapy, the addition of DIP led to increased platelet and lymphocyte counts and reduced D-dimer levels as compared to standard-of-care patients[3].

Reference 3 Liu, X. et al.
Figure 3,Excerpt Panel A

[1] Guan W, et.al, Clinical Characteristics of Coronavirus Disease 2019 in China. NEJM 2020 Feb 28, 2020.
[2] Insel PA, Murray F, Yokoyama U, et al. cAMP and Epac in the regulation of tissue fibrosis. Br J Pharmacol 2012; 444 **166**(2): 447-56.

3 Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction

Xiaoyan Liu, Zhou, Hai-Bin Luo, et. al
doi: https://doi.org/10.1101/2020.02.27.20027557



Additionally, 2 weeks after DIP treatment, 3 of the severe cases and all 4 of the mild-to-moderate cases were discharged from the hospital. One patient died while 3 remaining patients were in remission in the hospital. In the control group, 3 of the 3 mild-to-moderate cases and 1 of 4 severe cases were discharged and only 1 was in remission in the severe group with 1 death. However, the trial was not randomized and was small in size, hence there was no statistical analysis for clinical outcomes.

Nevertheless, the combination of laboratory data indicating direct anti-SARS-CoV-2 activity and encouraging patient laboratory and clinical outcome data do advocate for the scientific basis for evaluating DIP in COVID-19 patients in a larger, randomized trial.

Profile of Patient Cohort Outcomes, Reference 3-

Table 2. Clinical outcomes of 27 enrolled patients

	Severity of illness — no. (%)	**Outcomes (up to 2/26)**	**Total discharge — no. (%)**
Dipyridamole group (n=12)	Mild — 4 (33.3%)	4 discharged (100%)	7 (58.4%)
	Severe — 6 (50.0%)	3 discharged (50%) 2 in remission (33%)	
	Critical ill — 4 (33.3%)	1 in remission (50%) 1 death (2/09)	
Control group (n=10)	Mild — 4 (40.0%)	3 discharged (75%)	4 (40.0%)
	Severe — 4 (40.0%)	1 discharged (25%) 1 in remission (25%)	
	Critical ill — 2 (20.0%)	1 death (2/18)	

2. Study Objectives

Primary Outcome:
Primary objective is to evaluate an effect of DIP on 2 biomarkers- D-dimer and platelet count in hospitalized Covid-19 patients treated with DIP plus standard care vs. those treated with standard care alone.

Secondary Outcome:
The secondary objective is to evaluate the detection of SARS-CoV-2 RNA by RT-PCR (ThermoFisher EUA Test) for DIP treatment vs no treatment (over 9 days, 3 time points) as determined by analyses of coded research nasal or nasopharyngeal swabs or other validated respiratory specimens by the Jackson Laboratory (JAX) CLIA Laboratory. We will determine whether the treatment will alter the stool microbiome. We will also associate the microbiome compositions in treatment and no treatment patients with clinical outcome

Mortality will also be a secondary endpoint. Mortality will be assessed at 30 and 60 days after enrollment.

The safety of DIP therapy vs standard of care will be evaluated using tabulation of standard adverse events by body region.

Exploratory Outcomes:
To evaluate clinical outcome improvement or resolution of clinical parameters such as: fever (≥100.5° F), cough, sputum production, imaging evidence of pneumonia, and Sp02 ≤ 93% on room air until hospital discharge or day 9, whichever occurs last. Those discharged before day 9 will have telephone follow- up call pending patient's consent for the call except for the DOC enrollees due to preservation of their confidentiality. No calls are made to DOC Subjects, after their discharge for follow up.

Other exploratory endpoints will be determined with datapoints as part of the standard clinical care lab work of our COVID-19 infected hospitalized patients. These will include C-reactive protein (CRP), lymphocyte count (LC), prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen (FIB), serum ferritin (FER), thromboembolic event, cardiac Troponin I (cTnI), lactate dehydrogenase (LDH).

In collaboration with University of Michigan, -DICER (NCT#NCT04391179- DIP Trial), other investigational biomarkers from blood such as chemokines and neutralizing antibodies and isolated PBMCs will be studied. In collaboration with UConn Engineering exploratory basic science BioPhotonic analyses of opto-biological blood cell signatures in COVID-19 will be conducted.

3. Study Design

This study is a randomized, open-labeled Phase 2, proof-of-concept single-center trial of the vascular and microbiologic efficacy of dipyridamole plus standard care vs. standard care in hospitalized COVID-19 patients.

Approximately 100 patients with symptoms of a respiratory tract infection who test positive for SARS-CoV-2 by polymerase chain reaction (PCR) will be enrolled to receive dipyridamole 100 mg three times per day for seven consecutive days plus standard care (N=50) or receive standard care (N=50).

The rationale for dosing DIP at 100 mg three times daily is that it is below the maximum daily dosage approved by the FDA as adjunct therapy for preventing cardiac valve-associated thromboembolism

but yet this regimen should still achieve concentrations that will be above the IC50 values described in the Background and Rationale section.

Based on UConn Health hospitalization impact ongoing with COVID-19, it is anticipated that the 100 participants can be met during the proposed enrollment period. Research blood (total 30 cc over study), stool & nasal or nasopharyngeal swab PCR (JAX) are to be obtained in the course of clinical care of COVID-19 care.

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Standard of Care:

Standard supportive care for COVID-19 pneumonia is provided at UConn Health to all study participants. Non-study therapy is allowed with the exception of concurrent usage of any other investigational trial/drug therapy for SARS-CoV-2 while on DIP. Convalescent plasma which is not a drug therapy or investigational treatment can be given concomitant with DIP administration and will not be an exclusion. Other anti-platelet agents such as aspirin or NSAID are permitted. All standard care data that we anticipate analyzing for this proposed study are recorded on subject's EPIC medical record by care providers as part of routine clinical care. A subject discharged early (before day 9) shall have Safety and SOC lab values/tests obtained for their research dataset completion.

Subject Selection and Screening:

Each new COVID-19 patient admitted at UConn Health to their isolation/ biocontainment care unit will be considered for enrollment with the exception of those pregnant. Department of Corrections- DOC patients at UCH for care and those from Nursing Home/Assisted living, shall be included.
Consent may be conducted with pre-qualified prospects as well as those with designated-legally authorized representatives- LARs.

The Principal and above named, Co-Investigators, who are attending these patients or study appointed designees, will review in EPIC their record for the inclusion/exclusion criteria below and introduce the study to the prospects via attending or Nursing caregiver. When asked, if subject has interest, they will be provided with a Consent Form to review. They shall be consented by designated study staff, in a private manner after sufficient time for review has been offered and all questions have been asked. They will be provided a copy of the Consent form which they retain because of biocontainment needs. Fax transmission of completed document images, per policy, from the care area is to be utilized for subject and staff to complete. Phone image scanning and transmittal of images is acceptable from care areas, as necessary with use of UCH issued phone to UCH email. For those unable to read, an audio file can be reviewed and the consent procedure can be securely recorded to the study phone for both their reference and secured study file documentation.

For LAR consent process, the study team may share consent materials with the LAR by email. The LAR can print, sign and scan or send an image (fax or photo) of the signed signature pages to the study team. The LAR would also send back the original wet-ink signature pages by mail or bring them to the site later, to be retained in the research record, but the documentation is valid even if only the image is recorded.

The study coordinator receives copies of the study documents, as above and then verifies and files, the consent and an audio file if used and then assigns the subject's study number and randomized status. Random #s list has been generated for REDCap and is applied to subjects- DIP+ (those receiving DIP- 100mg, po, tid as an addition to standard care) or DIP-, (standard of care, only).

The study coordinator will transmit consents to Pharmacy, of all enrolled subjects and activates the EPIC order set to order DIP (100mg, tid X 7 days) from research pharmacy.

4. Study Population

A total of approximately 100 COVID-19 infected hospitalized patients are planned-50 will be randomized to receive dipyridamole and 50 will not.

Inclusion Criteria:

1. Adults ≥18 years of age.
2. COVID-19 positive by PCR and hospitalized for vascular dysfunction, conditions related or unrelated to COVID-19, or respiratory infection with a range of respiratory severity as follows:

Moderate

- Diagnosed with SARS-CoV-2 infection by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include:

o Fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms; shortness of breath with exertion

- Clinical signs suggestive of moderate illness with COVID-19, such as:

o RR ≥ 20, HR ≥ 90, SaO2 ≥93% on room air or requires ≤2L oxygen by nasal cannula (NC) in order maintain SaO2 ≥93%, fever >38.3 Celsius

Severe

- Diagnosed with SARS-CoV-2 infection by standard RT-PCR assay or equivalent testing
- Symptoms suggestive of severe systemic illness with COVID-19, which could include:

o any symptom of Moderate Illness; shortness of breath at rest or respiratory distress

- Clinical signs indicative of severe systemic illness with COVID-19, such as

o RR ≥ 30, HR ≥ 125, requires > 2L oxygen by NC in order maintain SaO2 ≥93%, PaO2/FiO2<300

Critical

- Diagnosed with SARS-CoV-2 infection by standard RT-PCR assay or equivalent testing
- Evidence of critical illness, defined by at least 1 of the following:

o Respiratory failure defined based on resource utilization requiring at least 1 of the following:

, Endotracheal intubation and mechanical ventilation. Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20L/min with fraction of delivered oxygen ≥0.5), noninvasive positive pressure ventilation, ECMO,

or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
o Shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg or requiring vasopressors)

3. Able to provide documented written informed consent to participate in the study-
   a. To be conducted and witnessed over telephone, by patient (per UCH Policy),
   b. By use of Legal Authorized Representative, as qualified and designated in EPIC.

Exclusion Criteria:

1. Inability to swallow or ingest oral medication in either tablet form or in suspension form including per NG tube.
2. Patient is known to be pregnant.
3. Patients with a history of allergy or hypersensitivity to dipyridamole.
4. Patient is unable to consent in their language or does not have a designated LAR (per UCH Policy).
5. Bleeding disorders (e.g. thrombocytopenia with platelet counts < 50,000; on Warfarinwith INR>3).
6. Existing severe medical illnesses unrelated to Covid-19 infection such as end stage heart, kidney, liver disorders or hepatic insufficiency defined as liver enzymes ≥5 times upper limit normal if baseline is normal or 5 times baseline if baseline is abnormal.
7. Metastatic cancer.
8. Those with severe coronary artery disease, unstable angina, STEMI, Type 1 NSTEMI, hypotension (systolic blood pressure <90mmHg), myocarditis or 2nd degree Mobitz Type II or 3rd degree atrioventricular block without pacemaker.
9. Bradycardia with persistent resting heart rate less than 60 bpm not due to cardio depressant medications such beta blocker or calcium channel blocker.
10. Those with myasthenia gravis and those treated with cholinesterase inhibitors.
11. Patient is enrolled in a clinical trial for another investigational drug designed to test for efficacy for SARS-CoV-2. [consent or infusion for convalescent plasma is not an exclusion].

Women of child-bearing Potential:

If the patient is a woman of childbearing potential, a negative pregnancy test will need to be recorded from standard of care information, prior to enrollment.

Consent by Use of Legally Authorized Representative:

Due to the current visitor restrictions with COVID-19, telephone consent will be obtained from the LAR (those intubated and without decision making capacity) with the following steps:

1. A provider overseeing the care of the patient calls the LAR and explains the patient's condition. The provider informs the LAR about a potential trial that might be suitable for the patient.
2. If the LAR is interested, the provider tells the LAR that a member of the study team will call shortly.
3. A study team member calls, has a preliminary discussion with the LAR, and then asks if the LAR can receive a blank copy of the ICF on a fax machine or computer.
4. The study team member transmits the ICF and allows the LAR time to read it and print a copy.
5. At an agreed time, the study team member calls the LAR to discuss the ICF material with Another UConn Health employee on the line as a witness
6. If the LAR agrees to consent on behalf of the patient, the study team member asks the LAR to sign, date and note the time on his or her copy, fax the signature page back (or scan by use of cell phone and/or email it to study UCH email), and mail the original complete signed document, keeping a copy for him or herself.
7. At the time of the call, the team member writes, "phone consent by [name and telephone number]" in the LAR signature area with the date and time on a copy of the ICF. The study team member also completes the section for the person obtaining consent. The witness signs and dates the document. The study team member also writes a standard informed consent progress note utilizing documentation worksheet.
8. The copy signed by the LAR, the copy signed by the team member and witness, and the signature page faxed by the LAR are all placed in the research record with the progress note.

Test Product, Dose, and Mode of Administration:

The Study Drug is dipyridamole for those randomized to receive it. Patients will receive-100 mg dose (2 tablets of dipyridamole 50 mg each tablet) to be taken by mouth 3 times daily for 7 days.
Suspension may be used if such is necessary after enrollment. Drug dose will not be given when SBP
< 90 mmHg. Based on availability of product to purchase, the total dose of 100mg may also be given by taking 1 tablet of dipyridamole 25mg and one tablet of dipyridamole 75mg.

5 Study Treatments, Procedures and Laboratory Testing

This is a randomized, open-label trial in which patients will be assigned randomly to either DIP plus standard care or standard care only. A patient is eligible after meeting enrollment criteria and once all inclusion criteria are met while no exclusion criteria exist, this includes negative pregnancy test of standard care, for females of childbearing potential. Subjects identified to enrollment log, are assigned study group, based on the REDCap random number list following their consent- Standard care plus DIP for 7 days (DIP+) or Standard care (DIP-).

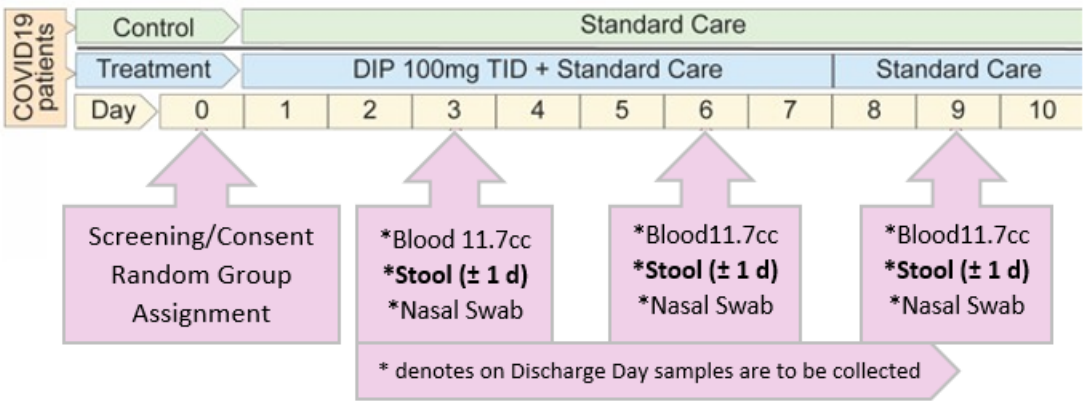
Formulation and Packaging:

The site Investigator/Research Pharmacy will provide patients randomized to the DIP therapy arm with the medication via standard drug distribution methods used in the hospital. The inpatient nursing staff will administer the drug but will hold for SPB<90mmHg. The total

amount of dosing completed and the duration of treatment period will be documented in the EPIC medical record and used for Research data additionally throughout the study.

Other concomitant, non-study medications:
For UConn Health COVID-19 hospitalized subjects, all concomitant medication used at and from the time of Consent, will be recorded. Any study drug designed to test for efficacy for SARS-CoV-2 will not be permitted during the period of DIP use in this protocol.

Treatment Period:



Screening (day 0): All patients that have met enrollment criteria will be approached for informed consent. Standard care and all medical information will be documented in UConn Health's electronic medical record (EPIC). A review of EPIC record for previous drug and non-drug treatments (within past 30 days) and current medications will be conducted. Adverse events going forward from review of EPIC record and by inquiry of Provider Investigator as warranted will be documented.

Day 1: **DIP 100 mg TID plus standard care or standard care only**
Day 2: **DIP 100 mg TID plus standard care or standard care only**
Day 3: **DIP 100 mg TID plus standard care or standard care only** plus blood (11.7 c.c.), stool and nasal swab collected for research purposes.
Day 4: **DIP 100 mg TID plus standard care or standard care only**
Day 5: **DIP 100 mg TID plus standard care or standard care only**
Day 6: **DIP 100 mg TID plus standard care or standard care only** plus blood (11.7 c.c.), stool and nasal swab collected for research purposes.
Day 7: **DIP 100 mg TID plus standard care or standard care only**
Day 8: **Standard care only**
Day 9: S**tandard care only** plus blood 11.7 cc, stool and nasal swab collected for research purposes. Days 10 through patient discharge from the hospital (or death): S**tandard care only**
Day 30: Follow-up phone call/EPIC review-mortality rate data collection
Day 60: Follow-up phone call/EPIC review-mortality rate data collection

During drug treatment period, that is day 1 through day 7, all medical record information will be recorded in EPIC. Research Specimens (blood, stool and nasal swabs) for viral presence by PCR will

be collected on Day 3, Day 6 and Day 9. Clinical responses as defined in the exploratory endpoints will be recorded throughout. Day 1 EKG is done, this includes within 2 hours of DIP administration. DIP, as above, is orally administered, including when necessary as suspension when standard care for subject includes gastric tube for medications (eg. intubation). During the study, any infection whether viral or non-viral will be captured. The site of infection and source of culture such as tracheal aspirate, sputum, blood or urine will also be recorded.

Patient Withdrawal of Consent:

Patients may withdraw from the study or study drug at any time at their discretion or patients may be withdrawn by the investigator or the sponsor for safety, behavioral or administrative reasons. If patient withdraws, the site investigator and study coordinator should attempt to document the reason and follow up for any adverse events. If patient also withdraws consent for disclosure of future information, no further study evaluation should be performed and no additional data will be collected. Follow up is to be for 2 days after withdrawal when permitted by patient. For those discharged prior to day 9, follow-up is by telephone to solicit information on fever, cough, sputum (exploratory objectives). DOC participants who may be discharged prior to completing the study and will not be contacted for information due to their privacy/confidentiality concerns.

Laboratory Research Studies:

We will collect whole blood (11.7 cc) for research data as well as stool samples and nasal or nasopharyngeal (NP) swabs for detection of SARS-CoV-2 RNA and viral susceptibility studies on Day 3, 6 & 9 (+ or – 1 day).

If study subject is to be discharged, an end of study research sample set- (blood, nasal swab, stool) will be obtained on the discharge day (if not discharged on study Day 3, Day 6 or Day 9) in order to maximize trial & safety data collection and review. Per attached Table of Procedures (pg.25) study team will initiate EPIC order if SOC tests are not ordered/ done with discharge.

Whole blood (PBMCs, serum & plasma (EDTA and Citrate preserved)) will be used for exploring immunological profiles as well as metabolomic profiling including nanoscale bio-photonic data and whole genome sequencing for discovery of new biomarkers/ genomic regions that confer increased severity or susceptibility to infection and DIP treatment efficacy.

There will be basic science collaboration with UConn Health/UConn faculty, Jackson Laboratory and the University of Michigan “DICER” researchers who have DIP expertise. Samples for collaborative studies to aid understanding of SARS-CoV-2 infection, blood cell and immune response as well as possible DIP effect will be shared. Samples shared with Michigan and received from Michigan will include coded subject specific data from each trial for markers such as d-dimer, ferritin, etc. but no PHI or other identifiable information.

In addition, blood samples will be banked for future determination of serum levels of DIP in Liang Lab to ascertain exposure and pharmacokinetics of DIP in Covid-19 patients.

Stool samples will be used to obtain microbiome analyses. These studies will be conducted in collaboration with Jackson Laboratory for Genomic Medicine. Research Nasal/NP swabs analyzed by

Jackson Laboratory CLIA lab are fully utilized as results are reported to the Research staff. Subjects wishing to receive results will be advised by designated study staff. Linda Choquette will be the IRB point person representing JAX-GM.

Confidentiality

Paper research records will be locked in a secure location in the Clinical Research Center, apart from the medical record. The records will include a research code such as "753-XXX" along with the subjects name and medical record number. All electronic files (e.g., database, spreadsheet) containing identifiable information will be password protected and encrypted. Any computer hosting such files will also have password protection. Only research staff will have access to the electronic files. A master list that links the code on the paper records to the subjects name will be kept in our electronic format. The research samples will be labelled with the research code only.

Appointed Study staff shall use access to EPIC to record all subject data to coded Case Report forms. These data are electronically maintained in a secure research REDCap database.

Prior to final study closure, any links between personal identifiers and each subject's unique study ID will be deleted to generate a de-identified dataset.

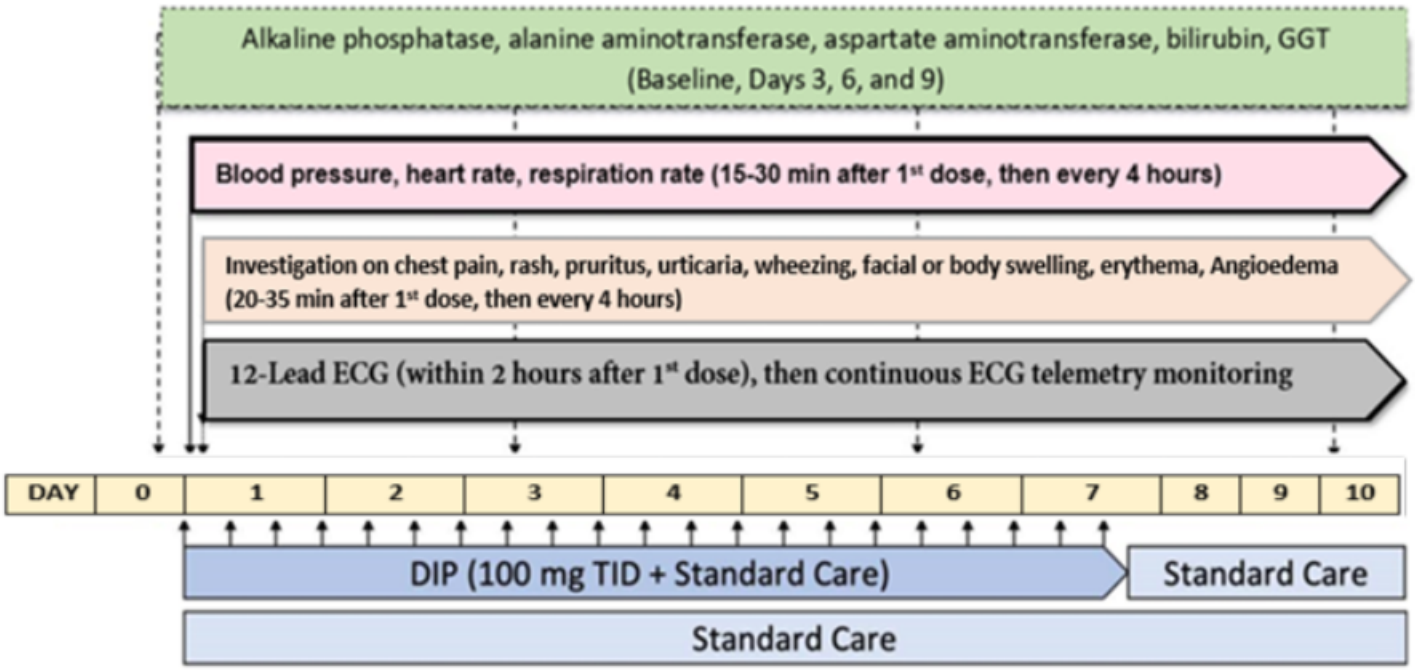
Careful efforts to maintain confidentiality have been effective in our previous research and will be continued.

Safety Assessments:

Safety will be assessed by means of collection of adverse events during the hospitalization.

6 Adverse Events and Reporting:

Study Schedule of Assessments and Procedures for Adverse Events Monitoring



At Day 1, for Safety purpose, EKG is obtained on all subjects including those to be given DIP within 2 hours after first dose.

All adverse events (AEs) will be reported. AEs should be considered to be unrelated only if definitively identified by an alternative explanation. They are defined as any untoward medical occurrence during administration of DIP and 2 days after administration of last dose.

Adverse events need not be causally related to DIP. Any of the protocol-defined primary, secondary or exploratory endpoints, other than mortality, would not be considered an AE.

AEs include hypersensitivity to DIP, drug interactions, overdose or withdrawal. Details of possible adverse effects and drug interactions are provided from extensive literature review in Appendix A-Additional Data on Dipyridamole.

SAEs include but are not limited to death, or life threatening condition leading to pending risk of death or occurrence of disability/incapacity.

Side effects inconsistent with Consent Form will also be recorded as AEs.

Adverse reactions at therapeutic doses of dipyridamole, are usually minimal and transient. With long term use of Dipyridamole tablets, initial side effects usually disappear. With the use of therapeutic warfarin, the following reactions were reported in two heart valve replacement trials, comparing Dipyridamole tablets with ongoing warfarin therapy to either warfarin alone or warfarin with placebo:

Dizziness (13.6% vs. 8.2%)
Abdominal distress (6.1% vs. 3.5%)
Headache (2.3% vs. 0.0%)
Rash (2.3% vs. 1.1%)

Other reported adverse reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely and there have been rare reports of liver dysfunction

We will use National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.5) to grade the severity of adverse events.

The PI or Co-Investigators will timely obtain all information to ascertain the outcomes and determine both severity as well as causality.

The PI, Co-Investigators and designated CRC nursing study staff are responsible for surveillance and grading of toxicities, AE, and SAE during administration of dipyridamole and 2 days after administration of the last dose. Study staff will document AEs using the EPIC Adverse Events Activity. All initial entries by CRC staff will be documented as current grade 0 if not straight forward. The PI or Co-Investigator are responsible for determining the relationship of the AE/SAE and whether its association with the study drug is unrelated, unlikely, possible, probable or definite. The PI or Co-Investigator reviews and manages AEs in EPIC and assesses each AE for causality and required course of action in accordance with the protocol. Study staff will report any such toxicities promptly to the PI or Co-investigator so that action may be taken to remove additional harm to the study participants. The PI assures that protocol specifics for toxicity management and reporting are followed and reported to the regulatory authorities.

Sponsor Investigator with assistance of Co-Investigators will follow up AE's via EPIC Research Event Activity until resolution or stabilization of the AEs.

Per UCH Policy, 2009-001.0 events constituting unanticipated problems involving risk to subjects (or others) must be reported to the IRB as soon as possible but no later than 5 business days from discovery of the event via a Problem Report Form within iRIS .

All AEs will be documented in EPIC Research Adverse Event Activity.

For unexpected fatal or life-threatening suspected adverse reactions the Sponsor Investigator will also report to the FDA as soon as possible but no later than 7 calendar days following discovery of the event via a Med Watch form FDA3500

DSMB will also monitor and receive reports of all AEs and SAEs.

Data and Safety Monitoring Committee (DSMB) and Stopping Rules:

A DSMB will be established prior to enrollment to monitor and be kept informed of AEs and SAEs during the trial. The committee is to review data regarding enrollment, safety and adverse events. The committee will meet after the first 10 subjects are enrolled and again with 25, 50, 75 and 100 enrolled.

The DSMB will also monitor efficacy for the primary endpoints. For example, if during enrollment, a statistically significant difference is reached before the target 100 patient goal is met, the study could be stopped early for evidence of efficacy. Alternately it could be stopped for unacceptable AE profile as deemed by DSMB.

Study suspension / stopping.

A decision to discontinue the study will be based on established study stopping rules defined in the Charter for DSMB.

If supplies of clinical trial such as the drug dipyridamole, supplies to collect research samples or personal protective equipment become unavailable or limited, the study will be suspended.

We do not project that the trial on hospitalized COVID19 patients will interfere with the current public health measures by federal or state. However, any new federal or state public health measurethat would make it not feasible to carry out the study or that continuing study under new public health measures would pose safety to the participating patients. In such a case, the study would be suspended.

Overall, PI/study team will update the IRB per Appendix B (study team meeting after each 10 completed subjects) at Continuation and Sponsor Investigator shall inform the FDA of all situations as needed and then determine continuation of the trial as appropriate.

Subject-specific stopping criteria.

Patients may withdraw from the study or study drug use at any time, at their discretion. Patients may be withdrawn by the Sponsor Investigator for safety, tolerability of the drug, behavioral, or administrative reasons.

If patient withdraws, the site investigator and study coordinator should attempt to document the reason and follow up for any adverse events if permitted for 48 hours by telephone.

If patient also withdraws consent for disclosure of future information, no further study evaluation should be performed and no additional data will be collected.

Any subject treated with DIP who exhibits NCI CTCAE (v.5) grade 3 or higher adverse event or laboratory values will be stopped from further dosing with DIP. EPIC has embedded this grading reference for use by appointed study team to review, assign and collate ongoing AEs for systematic and timely review by Sponsor Investigator and for use by DSMB.

In addition to stopping further DIP treatment, the adverse events will be treated or intervened upon, as per UCH Standard of Care.For example, hypotension will be treated with fluid or pressor if the latter is needed. Hypertension will be treated with anti-hypertensive medications or higher dosage of such existing medication. Particular attention will be given to cardiovascular (hypotension (SBP $\leq$90mmHg), hypertension, bradycardia, acute kidney injury), hepatobiliary toxicity, and allergic or anaphylaxis reaction. Please see attached Appendix B for the severity grade by NCI CTCAE v.5.

Trial-specific stopping criteria

In monitoring the adverse events, we will conduct an assessment of the frequency or the proportion of DIP vs. untreated patients with a serious adverse event, and in this case, with particular attention to cardiovascular, hepatic and hypersensitivity adverse events. We propose to define a reasonable threshold proportion above which DIP treatment will cease. Most of the data were obtained from patients receiving DIP by intravenous administration. Few data exist on those receiving oral DIP. When such oral route data are available, we use them to define the threshold proportion. In addition, the reported frequency of adverse effect was obtained in non-COVID 19 patients who have a higher incidence of cardiovascular complications. We first report the known or expected incidence of cardiovascular, hepatic and hypersensitivity adverse effects. Then, we propose the stopping consideration by the DSMB by the proportion of such effects in treated vs. untreated subjects in a table.

Cardiovascular:

1. Chest pain-19.7% in a study of adjunct IV administration for thallium myocardialperfusion imaging reported chest pain (5). Angina was rare (6).
2. Bradyarrhythmia-0.2% via IV route was reported during myocardial imaging(5).
3. Abnormal ECG such as ST-T segment changes (7.5%) or extrasystoles (5.2%) occurred not uncommonly from the IV experience (5).
4. Hypotension had an incidence of 4.6% by IV route (5).
5. Myocardial infarction frequency was 0.1% (5).
6. Tachycardia had a frequency of 3.2% (5) although in a postmarketing surveillance study, it was rarely found (6). In this proposed protocol, the frequency may not be high given that we will have excluded those with conduction abnormalities or severe coronary artery disease.

Hepatic effects:

Increased liver enzymes have been rarely reported in those taking DIP in postmarking surveillance (6). However, it has been reported that frequency of liver enzyme abnormalities was similar with DIP as with placebo (LiverTox: Clinical and Research Information on Drug-induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2012-Last Update January 4, 2018).

Hypersensitivity reaction:

Rare reports of allergic reaction such as urticarial, pruritus and rash was rarely reported with IV use (5, 7-9). In postmarketing surveillance, hypersensitivity was also rare as was angioedema (6).

Additionally, Based on a review of (1) the dipyridamole product insert, (2) the primary medical literature, (3) FDA Medwatch, and (4) the FDA Adverse Event Reporting System (FAERS) for (a) potentially serious/life-threatening adverse events as described in the DIP product labeling & in the FDA database, and (b) plausible relationships of DIP pharmacologic effects to possible serious/life threatening adverse effects, the DSMB will evaluate the following possible types of adverse effects for **consideration** of possible early termination of the study at the pre-defined interim analysis milepoints:

Adverse Event	Increase in total prevalence (%) in DIP-Treated patients versus Standard—Care Patients at Pre-Specified study analysis milepoints (n=total # of patients enrolled) for **consideration** of premature discontinuation of TOLD study			
	n=10	**n=25**	**n=50**	**n=75**
Severe and/or life-threatening bleeding event[1]	≥ 40%[4]	≥ 25%[5]	≥ 9%[6]	≥ 8%[7]
Severe liver toxicity[2]	> 40%	> 25%	> 9%	> 8%
Severe and/or life-	> 40%	> 25%	> 9%	> 8%

threatening cardiovascular event[3]				
Severe thrombocytopenia (Platelet counts <10/mm^3)	≥40%	≥25%	≥9%	≥8%

1 – Gastrointestinal hemorrhage requiring transfusion, intracerebral hemorrhage,
2 – Asymptomatic elevation of AST, ALT, alkaline phosphatase or Bilirubin to more than 5x upper limit of normal, that is ≥ grade 3 by the NCI CTCAE v.5 criteria.
3 – Acute myocardial infarction, worsening angina symptoms, or ≥ NCI CTCAE v.5 grade 3 hypertension
or hypotension or bradycardia
4 – A prevalence of this event in 2/5 DIP patients versus 0/5 Standard Care patients results in a P=0.22 (***One***-tailed Fisher Exact test)
5 - A prevalence of this event in 3/12 DIP patients versus 0/13 Standard Care patients results in a P=0.096 (***One***-tailed Fisher Exact test)
6 - A prevalence of this event in 3/25 DIP patients versus 0/25 Standard Care patients results in a P=0.117 (***One***-tailed Fisher Exact test)
7 - A prevalence of this event in 3/37 DIP patients versus 0/38 Standard Care patients results in a P=0.115 (***One***-tailed Fisher Exact test)

Other side effects from oral ingestion include dizziness (13.6%), headache (2.3%), abdominal discomfort (6%). The frequencies in DIP-treated vs. untreated COVID-19 patients are not known but will be monitored. The Study will be subject to auditing by UConn Health Human Subject Protection program, prior to enrollment and at any subsequent time.

7. Efficacy Assessments

The assessment of vascular responses will be made based on biomarker (platelet count & D-Dimer) determinations as defined in the primary endpoint at days 3, 6, 9 or at discharge day-premature discontinuation such as patient's withdrawal or occurrence of SAE. The assessment of microbiologic response will be made based on PCR performed on specimens collected on Day 3, 6 & 9 or discharge day,-premature discontinuation such as patient's withdrawal or occurrence of SAE.

Clinical responses of each enrolled subject as defined in the exploratory endpoints will be evaluated at Day 3, Day 6, Day 9 (± 1 day) or at discharge day- premature discontinuation such as patient's withdrawal or an occurrence of SAE that disallows continued participation in the trial. Those who are discharged before day 9 and grant permission for follow-up telephone contact will provide information (48 hrs) on fever, cough and/or sputum. This will not apply to DOC enrollees due to confidentiality concerns.

Statistical Methods and Sample Size Calculation:

The primary outcome measure for efficacy evaluation will be an increase in the platelet counts or a decrease in D-dimer level on day 3, 6 or day 9. For the primary efficacy evaluation, these determinations will be based on a modified intent to treat population (MITT).

The MITT population will be comprised of all randomized patients who received less than one full day or less than 3 doses over 24 hours of the study drug, that is, the study will include patients who received only a single dose of DIP. In Liu et. all, as cited above (pg. 3, ref 3), D-dimer level rose by 9 ± 8 fold (mean and SE) by 6-9 days in hospitalized COVID19 patients who did not receive DIP (1). In order to detect a 6.5 fold reduction in the extent of D-dimer increase in DIP-treated patients, we will need to enroll 25 subjects in each group to have 80% power at a two-sided significance level of 0.05. In order to detect a 6.3 fold reduction in the extent of D-dimer increase in DIP-treated patients, we will need to enroll 35 subjects in each group to have 90% power at a two-sided significance level of 0.05.

Platelet counts rose by 1.35 ± 0.25 fold by 6-9 days in in hospitalized COVID19 patients who did not receive DIP (1). In order to detect a 0.2 fold further increase in the extent of platelet increase in DIP-treated patients, we will need to enroll 25 subjects in each group to have 80% power at a two-sided significance level of 0.05. In order to detect the same 0.2 fold further increase in platelet with 90% power at two-sided level of 0.05, we will need to enroll 35 subjects in each group.

Additionally, the changes in biomarker levels and the number of abnormal biomarkers from baseline to day 6 or day 9, plus the temporal trends will be compared between arms using linear mixed effects models.

The number and percentage of study participants who show clinical improvement will be determined.

The secondary endpoint will be the absence of SARS-CoV-2 in the specimen taken on Day 3, 6 or 9 as assessed by polymerase chain reaction. The number and percentage of those showing disappearance of the virus will be tabulated by treatment assignment.

The secondary endpoint is the non-detection of the SARS-CoV-2 based on PCR of specimens at Day 3, 6 or 9 (± 1 day) in the MITT population.

Based on the efficacy of hydroxychloroquine-azithromycin in eliminating SARS-COv-2 in 20 patients [4]and a potent anti-viral efficacy of DIP in vitro[3], we expect that we will be powered to detect elimination of this virus by DIP should DIP be efficacious in patients. Assuming an attrition of 30%, we plan to enroll 50 subjects in each group. If attrition is less, then fewer than 50 patients will need be enrolled. Nevertheless, the study sample sizes described above will provide power (80% power at an alpha level of 0.05) to detect an absolute reduction of 30-40% in the proportion of patients in the two study groups with positive nasopharyngeal PCR for detection of SARS-CoV-2 virus at the 3 defined evaluation timepoints.

The number and percentage of those showing disappearance of the virus will be tabulated by treatment assignment and compared between arms at day 5 and day 9 using a logistic mixed effects

[4] Gautret, P. et. al Hydroxychloroquine and azithromycin as a treatment of COVID-19:results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents (2020) https://doi.org/10.1016/j.ijantimicag.2020.105949

regression model.

Exploratory clinical endpoints will also be assessed for improvement. The overall combined primary, secondary and exploratory endpoints at each time point in terms of percentage of subjects who show improvement will be calculated. Trend analyses will be conducted.

The exploratory outcome measure of success is defined as improvement or resolution of clinical parameters such as fever <100.5° F, decrease in cough as reported by patient, improvement in chest imaging evidence of pneumonia, Sp02 ≥ 93% on room air until hospital discharge or day 9 whichever occurs last.

Other exploratory endpoints include C-reactive protein (CRP), lymphocyte count, prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen (FIB), and serum ferritin, cTnI, LDH.

Exploratory clinical endpoints will also be assessed for improvement and compared between arms using logistic regression models. We also will assess for the percentages of patients in each study group who: progress to requiring ICU care, needing intravenous vasopressor therapy and/or mechanical ventilation, as well as progression to organ failure such as kidney or liver failure or ARDS. All the statistical analyses will be performed in R version 3.6.1. A p-value smaller than 5% will be considered statistically significant.

General Statistical Considerations:

Each baseline variable will be summarized overall and for the two arms separately, using mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. Baseline variables will be compared between arms by two-sample t-test for continuous variables and by Fisher's exact test for categorical variables. The unbalanced variables in the two arms will be adjusted in the models for outcome comparisons to reduce the confounding effects.

Statistical test comparisons between randomized groups will be made for oral dipyridamole plus standard of care versus standard of care. Analyses of primary and secondary endpoints will be conducted by the modified intention-to-treat approach. If the primary outcome reaches significance, a hierarchical, sequentially rejective process will be followed for the secondary and exploratory endpoints. It is expected that randomization will make the baseline characteristics similar. If not, an analysis of covariance will be conducted for control for baseline differences. There are two primary outcomes (D-Dimer and Platelet count) in this study to evaluate an effect of DIP. In order to control the Type I error, we considered the Bonferroni correction method in the interim analyses of 25 patients to date. In this analysis, the Bonferroni corrected significance level would be 0.025 instead of 0.05 in each hypothesis test. It will be applied to interpret the hypothesis results in primary outcomes in the interim analyses after 50 and 75 patients enrolled

A comprehensive Statistical Analysis Plan (SAP) will be finalized prior to the interim analysis.
Missing data: If a test result from primary or secondary endpoints is not available or that the test is not done, the subject will be included in the MITT population in the statistical analysis. The multiple imputation method will be applied to impute variables in multivariate analyses where the imputed data will be analyzed for sensitivity analyses, compared to the results using available data. Day 3 will be the primary

time endpoint. The two primary endpoints will be analyzed separately as stated. Mortality is considered one of serious adverse events. It will be summarized by frequencies and percentages and will be compared between arms by Fisher's exact test.

Appendix-A

ADDITIONAL DATA ON DIPYRIDAMOLE:

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 were reported in two heart valve replacement trials, comparing Dipyridamole tablets and warfarin therapy to either warfarin alone or warfarin with placebo:

Dizziness (13.6% vs. 8.2%)
Abdominal distress (6.1% vs. 3.5%)
Headache (2.3% vs. 0.0%)
Rash (2.3% vs. 1.1%)

Other reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely and there have been rare reports of liver dysfunction

Contraindications

- Hypersensitivity to dipyridamole or any component of the formulation

Disease-related concerns:

- **Cardiovascular disease:** Use with caution in patients with hypotension, unstable angina, and/or recent myocardial infarction; may enhance exercise induced myocardial ischemia in patients with chronic stable angina.
- **Coronary artery disease:** : Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease, may exacerbate chest pain
- **Hepatic impairment**: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- **Antiplatelet agents/anticoagulants**: Use with caution in patients on other antiplatelet agents or anticoagulation.
    - When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone. In rare cases, increased bleeding during or after surgery has been observed
- **Pharmacologic stress testing:** Interrupt oral dipyridamole therapy for 48 hours prior to stress testing with adenosine, IV dipyridamole, or regadenoson; may increase risk for cardiovascular adverse effects and impair the test sensitivity.
- **Adenosinergic agents** (e.g., adenosine, regadenoson): dipyridamole can increase the plasma concentrations of adenosine, dose adjustment may be necessary

- **Cholinesterase inhibitors:** Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors

Drug Interaction Concerns:

An open-label, randomized, multiple-dose, crossover, drug-interaction study was carried out evaluating the theoretical risk of altered antiplatelet activity of aspirin and extended-release dipyridamole with concomitant use of omeprazole. A total of 6 healthy male and female participants aged 18-50 years were included in the study to evaluate the systemic pharmacokinetic exposure to extended release dipyridamole and aspirin inhibition of arachidonic acid-induced platelet aggregation.

Each participant was randomized to one of two possible treatment sequences where the received either aspirin and dipyridamole first, followed by omeprazole, and vice versa. Each treatment sequence was comprised of four 7-day treatments with a washout of $\geq$ 14 days between the use of aspirin and dipyridamole monotherapy and combination therapy with omeprazole. Investigators reported similar systemic exposure to antiplatelet therapy with and without omeprazole. Using steady-state area under the concentration time curve (AUC) from 0-12 hours and maximum plasma concentration, researchers were able to show that pharmacokinetic and pharmacodynamic behavior of aspirin and extended-release dipyridamole was not altered by concurrent administration of omeprazole (Offman, 2013).

It is thought that dipyridamole has an inhibitory effect on p-glycoprotein exporters, which raises concern for concomitant administration with substrates of P-gp. Shalinski et al investigated how dipyridamole impacts the sensitivity of anticancer drugs, specifically in cell lines that either express the MDR1 (ABC1) gene or do not. MDR1 is the gene that encodes p-glycoprotein. Researchers demonstrated that the presence of p-glycoprotein (multi-drug resistant cell lines) resulted in a much higher level of synergy with dipyridamole and vinblastine compared with cell lines that lack P-gp expression. (Shalinski, 1991)

Pregnancy and Teratogenic Considerations

- There are no well controlled studies in human, pregnant, females
- Dipyridamole should only be used in pregnancy if clearly needed

Breast-Feeding Considerations

- Dipyridamole is excreted in breast milk. The manufacturer recommends that caution be exercised when administering dipyridamole to nursing women

Pediatric Considerations

- Effectiveness in children less than 12 years of age have not been determined

Pharmacokinetics

- Following an oral dose of dipyridamole, the average time to peak concentration isabout 75 minutes.
- The decline in plasma concentration following a dose of dipyridamole tablets 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) isapproximately 10 hours.
- Dipyridamole is extensively protein bound
- It is metabolized in the liver where it is conjugated as a glucuronide and excreted with the bile.

Dipyridamole is metabolized via the liver to a monoglucuronide which is then subject to biliary and fecal excretion and simultaneous enterohepatic circulation. Pharmacokinetic analysis performed in four normal human volunteers found that the serum concentration curve following IV administration follows an open two-compartment model with first order, linear kinetics. Oral dipyridamole pharmacokinetics are described by the use of a corresponding pharmacokinetic model with two consecutive first order steps. The biological half-life of the drug was reported between 85 and 145minutes, with the systemic bioavailability of an oral, 100 mg dose varying from 37-66% (Nielsen-Kudsk, 1979)

Macgregor et al investigated the in vitro protein binding behavior of dipyridamole in plasma and buffered protein solutions. The drug was highly protein bound in heparinized human plasma (~98%) The extent of binding was consistent across the entire therapeutic range of drug concentrations (0.1 – 10 mcg/mL). Comparable binding results were found with a mixture of 80 mg % α-1 acid glycoprotein and 40 g/L human serum albumin in pH 7.4 phosphate buffer solution. Binding in one or the other was significantly lower than in a combination of the two, indicating that both proteins are implicated in dipyridamole protein binding. The binding of dipyridamole to heparinized human plasma or human serum albumin was concentration independent up to 40 mcg/mL, at which point the free fraction of dipyridamole begins to increase (Macgregor, 1991).

Russell et. al investigated pH related changes in 11 healthy elderly adults on the absorption of dipyridamole. The subjects investigated were all over the age of 65 and 6 had a low gastric pH, which served as the control, while 5 had a gastric pH over 5. They all received 50 mg dipyridamole as a single dose. The control subjects were pretreated with 40 mg famotidine while the others were pretreated with 1360 mg glutamic acid. A Heidelberg radiotelemetric capsule monitored the gastric pH and emptying of radiolabeled orange juice was measured. The researchers noticed that an elevated gastric pH had a negative effect of dipyridamole absorption. The Tmax and Ka were slower in subjects with a pH over 5, however, this could be corrected by administration of glutamic acid before treatment. Additionally, gastric emptying seemed to be

slower in patients with a pH above 5. Overall, it would be beneficial for patients with a higher gastric pH to pretreat with glutamic acid HCl before treatment with dipyridamole.

A study by Batista et al (2010) evaluated whether dipyridamole concentrations achieved in the plasma of patients taking an extended-release formulation of the medication through a gastrostomy tube (G-tube) are therapeutic and similar to those achieved in the plasma of patients who receive the drug orally. Patients included were those admitted following an acute cerebral infarction, with an indication for antiplatelet therapy for secondary prevention. Twelve patients with severe dysphagia requiring G-tube placement were cases, and 12 patients who were able to swallow safely served as controls and took the medication orally. The main outcome measure was dipyridamole plasma concentrations on day 5 at all three timepoints. The study found there was no significant difference in dipyridamole plasma concentrations between the groups found at 2 hours ($p = 0.18$), 6 hours ($p = 0.92$) or 12 hours ($p = 0.69$). Dipyridamole plasma concentrations obtained following administration of extended-release dipyridamole through a G- tube in dysphagic patients achieved similar therapeutic levels to those obtained in patients taking the medication orally (Batista, 2010).

Preparation of Dipyridamole Suspension:

For patients who may be unable to swallow tablets or who have a feeding tube in place, the study drug tablets will be crushed and extemporaneous suspension will be prepared as follows:

A 10 mg/mL oral suspension may be made with tablets and one of three different vehicles (cherry syrup, a 1:1 mixture of Ora-Sweet and Ora-Plus, or a 1:1 mixture of Ora-Sweet SF and Ora-Plus). Crush twenty-four 50 mg tablets in a mortar and reduce to a fine powder. Add 20 mL of the chosen vehicle and mix to a uniform paste; mix while adding the vehicle in incremental proportions to almost 120 mL; transfer to a calibrated bottle, rinse mortar with vehicle, and add quantity of vehicle sufficient to make 120 mL. Label "shake well" and "protect from light".
Stable for 60 days when stored in amber plastic prescription bottles in the dark at room temperature or refrigerated.

Reference: Allen LV and Erickson III MA, "Stability of Baclofen, Captopril, Diltiazem, Hydrochloride, Dipyridamole, and Flecainide Acetate in Extemporaneously Compounded Oral Liquids," Am J Health Syst Pharm, 1996, 53:2179-84.8879325

Schedule of Study Procedures

Study Day	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**
Inclusion/exclusion	x											
Consent	x											
Randomization	x											
Vital Signs **(*15-30 mins. after 1st dose)** and then every 4 hours	x Start:20:00	x*	x	x	x	x	x	x	x	x		
Safety Assessments/AEs **(*20-35 mins. after 1st dose)** and then every 4 hours	x Start:20:00	x*	x	x	x	x	x	x	x	x		
DIP (Treatment)		x	x	x	x	x	x	x				
Standard of Care Hospital protocol (Control)		x	x	x	x	x	x	x	x	x		
12 Lead EKG **(up to 2 hrs. after DIP)**		x										
Telemetry	x Start:20:00	x	x	x	x	x	x	x	x	x		
SOC LABs (COVID protocol) Q72 Platelet, D-Dimer, Bilirubin, CRP, PT, APTT, plasma fibrinogen, Serum ferritin, Troponin (cTnI), LD, D-dimer, ***ALT, AST (Safety labs)***	x			x			x			x		
Visit Sample Window				**+/- 1 day**			**+/- 1 day**			**+/- 1 day**		
Research Blood (11.7 cc)				x			x			x		
Research Safety LABs (Alkaline Phosphatase, GGT)	x			x			x			x		
Research Stool				x			x			x		
Research Nasal Swab				x			x			x		
Discharge LABs (Platelet, D-Dimer, Bilirubin, CRP, PT, APTT, plasma fibrinogen, Serum ferritin, Troponin (cTnI), LD, D-dimer, ***ALT, AST Alkaline Phosphatase, GGT (Safety labs)***) ***obtained on D/C day (if not on day 3, 6, 9)**		*	*	x	*	*	x	*	*	x		
Discharge/withdraw follow-up (*for 2 days after withdrawal permitted by patient in ICF except DOC)		x*	x*	x*	x*	x*	x*	x*	x*	x*	x	x

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