PROTOCOL TITLE: Study To antagOnize Plasminogen Activator Inhibitor-1 in Severe COVID-19 (STOP Severe COVID-19)

PRINCIPAL INVESTIGATOR:

Sanjiv J. Shah, MD
Neil J. Stone, MD, Professor, Department of Medicine (Cardiology)
Northwestern University, Feinberg School of Medicine
676 N. St. Clair, Arkes Pavilion, Suite 600
Chicago, IL 60611
Phone: 312 695 0993
Email: sanjiv.shah@northwestern.edu

CO INVESTIGATORS:

Sadiya S. Khan, MD, MSc
Assistant Professor, Department of Medicine (Cardiology) and Preventive Medicine (Epidemiology)
Northwestern University Feinberg School of Medicine
680 N. Lake Shore Drive, Suite 1400
Chicago, IL 60611
Phone: 312 503 2515
Email: s-khan-1@northwestern.edu

Douglas E. Vaughan, MD
Irving S. Cutter Professor and Chairman, Department of Medicine
Northwestern University Feinberg School of Medicine
676 N. St. Clair, Arkes Pavilion, Suite 2300
Chicago, IL 60611
Tel: +1-312-926-9436
Fax: +1-312-926-7260
Email: d-vaughan@northwestern.edu

VERSION NUMBER: 1.2

VERSION DATE: 03 DEC 2020

NCT: NCT04634799

IND: 149959

Table of Contents

Study Summary 4
1. Objectives 6
1.1. Primary Objective 6
1.2. Hypotheses 6
2. Background 6
3. Study Endpoints 8
3.1. Primary outcomes 8
3.2. Secondary outcomes 8
4. Study Design 8
4.1. Study Population 9
5. Study Assessments and Procedures 10
5.1. Schedule of Events 10
5.2. Visit Procedures 11
5.3. Study Visits 13
6. Recruitment Methods 15
7. Risks and Benefits to Participants 15
7.1. Risks of Study Medication- TM5614 15
7.2. Potential Benefits to participants 16
8. Withdrawal of Participants 16
9. Data Management and Confidentiality 16
9.1. Data Management 16
9.2. Confidentiality 18
9.3. Sharing Results with Participants 18
10. Statistical Analysis 18
10.1. Sample Size 18
10.2. Primary Analyses 19
10.3. Additional Secondary Analyses 19
10.4. Planned Subgroup Analyses 19
10.5. Missing Data 20
11. Study Drug 20
11.1. Study Drug Administration 20
11.2. Study Drug Accountability 20
11.3. Labeling and Storage 21
11.4. Dose Adjustment 21
12. Randomization 22
12.1. Unblinding of Treatment Assignment 22
13. Ethics 22
13.1. Ethical Conduct of the Study 22
13.2. Subject Consent 23
14. SAFETY 25
14.1. Safety Definitions 25
14.2. Safety Reporting 27
14.3 Study-specific Events of Interest 28
15. MONITORING 29
15.1. Data & Safety Monitoring Board 29
15.2. Data Monitoring 30
16. Qualifications to Conduct Research and Resources Available 30
17. REFERENCES 32

INVESTIGATOR'S STATEMENT

I agree to conduct the study (STOP SEVERE COVID) in accordance with the protocol and with all applicable government regulations and Good Clinical Practice (GCP) guidance.

_____ _____

Principal Investigator's Signature Date (DD/MMM/YYYY)

_____

Principal Investigator's Name

STUDY SUMMARY

Trial Name	Study To antagOnize Plasminogen Activator Inhibitor-1 in Severe COVID-19 (STOP Severe COVID-19)
Investigational Agent	TM5614: small molecule inhibitor of plasminogen activator inhibitor-1 (PAI-1)
Funding Source	Northwestern University Feinberg School of Medicine
IND #	149959
Trial Design	A single-center, randomized, double-blind placebo controlled trial
Main Objective	Among adult patients (≥65 years OR < 65 with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) with severe coronavirus disease 2019 (COVID-19) requiring supplemental O2, determine whether oral administration of TM5614 up to 180 mg daily (x 7 days) when compared to placebo leads to lower levels of circulating PAI-1 activity, C-reactive protein (CRP), higher ventilator-free days (VFD), venous and arterial thromboembolism, and lower in-hospital mortality.
Sample Size	80
Funding Source	Northwestern University Feinberg School of Medicine
Key Eligibility Criteria	*Key Inclusion Criteria:* 1) Adults ≥65 years old or < 65 years old AND at least one major cardiometabolic comorbidity (diabetes, hypertension, obesity or cardiovascular disease) 2) Established diagnosis of COVID-19 as evidenced by a positive nasopharyngeal or bronchoalveolar lavage viral PCR for SARS-CoV2 3) Requiring supplemental oxygen *Key Exclusion Criteria:* 1) Known contraindication to tissue plasminogen activator (tPA), including a) Active internal bleeding b) History of cerebrovascular accident c) Recent intracranial or intraspinal surgery or trauma d) Intracranial neoplasm, arteriovenous malformation or aneurysm e) Known bleeding diathesis f) Severe uncontrolled hypertension (SBP>200 persistently >12 hours) 2) Currently receiving therapeutic dose anticoagulation (specifically will exclude those with potential drug-drug interaction such as heparin, apixaban, warfarin) 3) Platelets <50,000 platelets/μL 4) Hematocrit <30% 5) Not hemodynamically stable in the preceding 4 hours
Trial Period	Participant Recruitment Period: ~ 6 months Treatment Period: 7 days Safety follow-up period: 30 days

ABBREVIATIONS

AE	Adverse event
ARDS	Acute respiratory distress syndrome
ATE	Arterial thromboembolism
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRP	C-reactive protein
DSMB	Data and safety monitoring board
DSMP	Data and safety monitoring plan
DSQR	Data and Status Quality Reports
DVT	Deep Vein Thrombosis
eGFR	Estimated glomerular filtration rate
NIAID	National Institute of Allergy and Infectious Diseases
PE	Pulmonary Embolism
TM5614	Investigational Drug; Small molecule inhibitor of PAI-1
SAE	Serious adverse event
SOFA	Sequential organ failure assessment score
VFD	Ventilator-free days
VTE	Venous thromboembolism

1. OBJECTIVES

1.1. PRIMARY OBJECTIVE

Determine whether oral administration of TM5614 up to 180mg daily (x 7 days) when compared to placebo leads to lower circulating plasma plasminogen activator inhibitor-1 (PAI-1) activity, C-reactive protein (CRP), higher ventilator-free days (VFD), venous and arterial thromboembolism and lower in-hospital mortality in adult patients (≥65 years OR < 65 with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) with severe coronavirus disease 2019 (COVID-19) requiring supplemental oxygenation

1.2. HYPOTHESES

***Hypothesis 1*:** Adult patients (≥65 years OR < 65 with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) with COVID-19 requiring supplemental oxygen, receiving TM5614 will have greater reduction in PAI-1 activity 7 days after randomization, without increased risk for adverse events, than placebo. 2º outcomes include: CRP level, ventilator-free days (VFDs), sequential organ failure assessment (SOFA) score, renal function, hepatic function, venous and arterial thromboembolism.

***Exploratory Hypothesis*:** Adult patients (≥65 years OR < 65 years with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) requiring supplemental oxygen due to COVID-19 receiving TM5614 will demonstrate lower in-hospital mortality compared with placebo.

Overall Impact: Whether TM5614 can safely improve COVID-19-related lung injury, multi-organ dysfunction syndrome, and functional status compared with usual care is uncertain but is biologically plausible and innovative. This pilot study will generate the necessary and sufficient information to plan a definitive outcomes trial examining TM5614 use among adult patients (≥65 years OR <65 with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) with severe COVID-19 to change the paradigm for these patients.

2. BACKGROUND

In December 2019, a novel virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV) was first identified to cause a severe viral pneumonia, labelled coronavirus disease 2019.[1-3] It has subsequently spread and was declared a global pandemic by the World Health Organization on March 11, 2020. [4-7] The first case in the United States[8] was reported on January 22nd, 2020, but has spread rapidly with over 390,000 known cases and over 12,000 deaths as of April 7, 2020. To date, clinical and epidemiological data published from China, Italy, and early reports from Washington in the United States identify higher rates of symptomatic disease and severity among older adults (>65 years).[1-3, 8-11] The first preliminary national report among patients with COVID-19 in the US was recently published by the Centers for Disease Control

synthesizing data from cases reported between 2/12/20 and 3/16/20.[12] Overall, 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19 were among adults aged ≥65 years. In addition to age being a major risk factor for severity of infection related to COVID-19, history of comorbid pulmonary or cardiovascular disease (CVD) are key risk factors of adverse outcomes.[10, 11, 13-17]

To date, there are no drugs that have been shown to improve outcomes in COVID-19 and there remains limited understanding about potential mechanisms that contribute towards the pulmonary and cardiovascular sequelae of severe disease. While there are highly variable clinical presentations and courses among those infected with COVID-19, altered fibrinolysis appears be a common phenotype manifest by markedly elevated d-dimer levels in the absence of disseminated intravascular coagulation. In addition, anecdotal reports from autopsy demonstrate diffuse microvascular thrombi and high rates of venous thromboembolism, suggesting that altered coagulation may indeed be a mechanism of morbidity and mortality in patients with severe COVID-19. Therefore, targeting the fibrinolytic system and inflammation in those at greatest risk to mitigate cardiopulmonary sequelae is very appealing.

Plasminogen activator inhibitor-1 (PAI-1) is the protein product of the mammalian gene *SERPINE*1 and is the principal inhibitor of tissue plasminogen activator and urokinase. PAI-1 circulates in plasma and is synthesized at a variety of locations in the body, including the liver, the vasculature, visceral fat, and at sites of injury and inflammation. In addition to its role in thrombosis, there is abundant evidence demonstrating the role of PAI-1 as a marker of inflammation in infection. Specifically, PAI-1 has been associated with the development of acute respiratory distress syndrome (ARDS) in the context of pneumonia (14), and increased plasma levels of PAI-1 are recognized as an independent risk factor for mortality and adverse clinical outcomes in patients with acute lung injury and ARDS (15).

In addition to its role in thrombosis and ARDS, PAI-1 is part of the molecular fingerprint of aging (1,2), and there is substantial preclinical and epidemiological evidence linking PAI-1 directly with numerous chronic diseases of aging that are associated with greater disease severity of COVID-19, including hypertension and arterial stiffness, coronary artery disease, idiopathic pulmonary fibrosis (IPF), and emphysema (3-12). Conversely, a unique founder population of Old Order Amish living in northeastern Indiana harbor a loss-of-function mutation in the gene that codes for PAI-1, and heterozygous carriers of the genetic variant appear to exhibit multifaceted protection from cardiovascular aging (13).

This proposal aims to evaluate the efficacy and safety of a novel small molecule therapy targeting PAI-1 (TM5614) for patients with severe COVID-19. Preliminary Phase I data suggests that TM5614 is safe and effectively lowers circulating plasma PAI-1. While PAI-1 antagonism has not yet been studied in patients with COVID-19, the available data identifying **the contribution of PAI-1 to thrombosis, aging-related morbidity, and pulmonary fibrosis argue that PAI-1 is a pragmatic, novel and rational target for severe COVID-19 and its vascular and cardiopulmonary complications.** A randomized, double-blind, placebo-controlled trial of TM5614 (PAI-1 inhibitor) would provide critical information on the efficacy and safety for such a concept.

3. STUDY ENDPOINTS

3.1. PRIMARY OUTCOMES

Clinical improvement, defined as discharge within 7 days of randomization OR a decrease of at least 2 points on the NIAID-defined 7-point ordinal scale.

Citrated plasma PAI-1 activity at 7 days, controlling for baseline PAI-1 level.

3.2. SECONDARY OUTCOMES

The following additional outcomes will be evaluated across study arms as they will be assessed throughout hospitalization:

- PAI-1 activity at 48 hours
- Change in CRP level
- Ventilator-free days
- Chest x-ray with pulmonary involvement
- Length of Stay
- Serious adverse events (SAEs) of special interest
  - In-hospital mortality
  - Intubation
  - Mechanical ventilation
  - Arrhythmias requiring intervention
  - Rates of in-hospital venous and arterial thromboembolism
  - Renal replacement therapy/dialysis
  - Heart failure (new onset)
- 30 Day Mortality
- Adverse events (AEs)
- Sequential organ failure assessment score (SOFA) score daily, including assessment of respiratory, blood, liver, circulatory, nerve, kidney from 0 to 4 in each system
- Hepatic function as measured by AST, ALT, alkaline phosphatase, bilirubin
- Renal function measured by estimated glomerular filtration rate

4. STUDY DESIGN

This is a single-center, double-blind, placebo controlled trial that will randomize (1:1) adult patients (≥ 65 years OR <65 years with at least one major cardiometabolic comorbidity [diabetes, hypertension, obesity or cardiovascular disease]) with COVID-19 requiring supplemental oxygen to receive TM5614 or placebo on top of standard of care. Approximately 80 patients will be randomized to receive TM5614 180 mg or placebo once daily for 7 consecutive days.

Eligible patients will be randomized at any time during hospitalization and followed for 30 days after last dose of medication. Participants will take study medication, orally once daily for up to 7 days or discharge, whichever comes first. Research blood samples for PAI-1 and C-reactive protein (CRP) will be collected at time of enrollment, 48 hours after 1st dose of medication and at

day 7 or discharge, whichever comes first. The labs will evaluate inflammatory responses and impact on COVID-19. All other lab results will be collected from participants' medical records. In addition, participants will be contacted 7 days (± 3 days) and 30 days (± 5 days) after taking the last dose of study medication to assess for any adverse events or changes in health status.

The study period for participants' involvement will consist of the duration of the hospitalization. We anticipate spending 3 months for implementing study procedures, 6 months to recruit 80 participants, and 3 months to perform the study analyses and prepare the primary study report.

4.1. STUDY POPULATION

4.1.1. Inclusion criteria

Patients must meet the following criteria to be enrolled in the study:

1) Adults ≥65 years old **or** < 65 years old AND at least one major cardiometabolic comorbidity (diabetes, hypertension, obesity [BMI > 30] or cardiovascular disease)
2) Established diagnosis of COVID-19 as evidenced by a positive nasopharyngeal or bronchoalveolar lavage viral PCR for SARS-CoV2
3) Requiring supplemental oxygen

4.1.2. Exclusion criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1) Age <18 years old
2) Pregnancy or breast-feeding
3) Known contraindication to tissue plasminogen activator (tPA), including
    a) Active internal bleeding
    b) History of cerebrovascular accident
    c) Recent intracranial or intraspinal surgery or trauma
    d) Intracranial neoplasm, arteriovenous malformation or aneurysm
    e) Known bleeding diathesis
    f) Severe uncontrolled hypertension (SBP>200 persistently >12 hours)
4) Currently receiving therapeutic dose anticoagulation (specifically will exclude those with potential drug-drug interaction such as heparin, apixaban, warfarin)
5) Platelets <50,000 platelets/μL
6) Hematocrit <30%
7) Not hemodynamically stable in the preceding 4 hours (symptomatic hypotension or systolic BP <95 mmHg at 2 out of 3 measurements)
8) Concomitant illness, physical impairment or mental condition which in the opinion of the study team / primary care physician could interfere with the conduct of the study including outcome assessment
9) Other patient characteristics (not thought to be related to COVID-19) that portend a very poor prognosis (e.g., severe liver failure, metastatic malignancy)
10) Participation in a concurrent interventional medical investigation or pharmacologic clinical trial. Patients in observational, natural history or epidemiological studies not involving an intervention are eligible.

11) Participant's responsible attending physician believes it is not appropriate for participant to participate in the study.
12) Inability or unwillingness to provide written informed consent
13) Involvement in the planning and/or conduct of the study
14) Previous randomization in the present study
15) Unable to complete study procedures.
16) Patients with active venothromboembolic disease
17) Patients who are receiving other investigational agents for COVID-19.
18) Alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥ 3 X upper limit of normal (ULN).
19) Impaired renal function (GFR < 25 mL/min or on dialysis)

4.1.3. Vulnerable Populations

This study will not recruit participants from a vulnerable population, including: a) individuals who are not yet adults (minors): i.e. infants, children, or teenagers or b) prisoners or other detained individuals.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1. SCHEDULE OF EVENTS

Table 1- Schedule of Events

Study Activities	Screening & Randomization	Daily	Day 7 or Discharge	Day 14
Informed consent	X			
Demographics	X			
Inclusion and exclusion criteria	X			
Blood pressure, heart rate and weight measurements	X	X	X	
Medical history	X			
Concomitant medications	X	X	X	
D-dimer	SOC	SOC	SOC	
PAI-1	X	X*	X	
PT/PTT/INR	SOC	SOC	SOC	
CRP	X	X	X	
Comp Chem Panel	SOC	SOC	SOC	
CBC w/plat & diff	SOC	SOC	SOC	
Exploratory Blood Sample+	X	X	X	
Chest x-ray	SOC			
Sequential organ failure assessment score (SOFA)	X	X	X	
Ordinal Scale				
Randomization	X			
Study Drug dispense	X	X		

Study Drug Accountability		X	X	
Medication adherence		X	X	
Participant status		X	X	X
AEs and SAEs		X	X	X

*PAI-1 drawn at baseline, 48 hours and Day 7/discharge. X=research test. ⁺Exploratory blood samples collected at baseline, 48 hours ± 24 hours, Day 7/last day of study medication and prior to discharge.

5.2. VISIT PROCEDURES

Signed Informed Consent

No study procedures are to be carried out until participants have provided written informed consent. Participants willing to take part in the trial will be consented per the local regulatory and ethical requirements. In brief, Participants will be given an adequate explanation about the trial and will be given ample time to consider their trial participation. They will be given the opportunity to ask questions about the trial and what their participation involves and will receive full answers from the trial site staff. Before a subject participates in the trial, a written informed consent form (using translated versions where appropriate) approved by the Northwestern IRB should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion and must attest an informed consent form. A copy of the signed informed consent form will be given to the trial participant.

Demographic and Other Baseline Characteristics

Demographics including date of birth, ethnicity and sex will be collected at Screening.

Assessment of Participant Eligibility

Each potential participant will be assessed for eligibility to participate in the trial as per the protocol defined eligibility criteria. Responsible site investigator(s) will ensure that only eligible participants are enrolled.

Medical and Medication History

To be completed at the Screening Visit to ensure subjects meet the inclusion criteria for the study. Any clinically significant history should be noted in the eCRF, including the cardiometabolic comorbidity (hypertension, obesity, diabetes, CVD) that fills eligibility criteria (if applicable).

Concomitant Medications

All medications (prescription and over-the-counter) will be recorded in the appropriate section of the eCRF while on study medication.

The following are Contraindicated Therapies:

- Use of any investigational therapy during the study is not permitted, including other investigational agents for COVID-19.

- Therapeutic dose anticoagulation (specifically those with potential drug-drug interaction such as heparin, apixaban, warfarin)

Ordinal scale

The ordinal scale will be obtained daily and consists of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring low-flow supplemental oxygen; 5, hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19); 6, hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol); and 7, not hospitalized. The scale will be obtained every 24 hours until Day 7/discharge using the worst parameters measured during the prior 24 hours.

Sequential Organ Failure Assessment (SOFA) Score

SOFA is a mortality prediction score that is based on the degree of dysfunction of six organ systems: respiratory, coagulatory, liver, cardiovascular, renal, and neurologic. The score is calculated on admission and every 24 hours until discharge using the worst parameters measured during the prior 24 hours.

Chest X-ray

Abnormal findings on chest x-rays will be reported (presence of nodules, signs of congestion, pneumothorax, location, etc.).

Adverse Event Collection

Adverse events reported by the subject (or, when appropriate, by the subject's physician, a caregiver, surrogate, or the subject's legally acceptable representative) will be captured from the time of randomization until 7 days after the last dose of study drug. Specific details on adverse event reporting are provided in **Section 14.1**.

Clinical Laboratory Evaluations

Current standard of care includes daily monitoring of d-dimer in addition to renal and hepatic safety markers. This study will monitor these clinically obtained parameters for safety throughout the hospitalization. In addition to these routine labs samples for PAI-1 and CRP will be collected at baseline, 48 hours and Day 7 or discharge.

All standard laboratory testing (i.e., CBC, Chemistry, CRP, d-Dimer) for the STOP Severe COVID-19 study will be handled directly by Northwestern Memorial Hospital Lab. Northwestern Memorial Hospital Lab services meet good clinical practice (GCP) standards for high-quality and reliable testing. Blood samples collected for this study will only be used for this study and will be destroyed after testing per the NMH laboratory guidelines.

The following labs will be performed by the NMH lab:

- Hematology: hemoglobin, hematocrit, platelets, WBC, RBC, lymphocytes, neutrophils
- Coagulation: International normalized ratio (INR)/Prothrombin time (PT), Partial thromboplastin time

- Chemistry Panel: Sodium, Potassium, glucose, total bilirubin, total protein, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), BUN, bicarbonate, creatinine, albumin
- C-Reactive Protein (CRP)
- D-dimer

The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition may be, at the discretion of the Investigator, repeated until confirmed, explained, or resolved as soon as possible. Any clinically relevant changes occurring during the study should be documented in the adverse event section of the eCRF.

PAI-1 testing

Samples for PAI-1 antigen and activity levels testing will be collected at time of enrollment, 48 hours after starting medication and at Day 7 or discharge, whichever occurs first. Samples are collected in sodium citrate- or EDTA vacutainers and placed on ice during transport. The plasma samples will be stored at -80 C in Dr. Vaughan's laboratory located on the 8th floor, room 8-400, of the Simpson Querrey Biomedical Research Center (303 E. Superior St.). Time of sample collection and storage will be recorded. Samples will be stored until analysis and then discarded.

Exploratory Blood Collection/Storage

An additional 5 mL of blood will be collected at baseline (prior to 1st dose), 48 hours ($\pm$24) and Day 7/discharge for exploratory tests (i.e., ACE2 and the RAS peptides) of COVID-19 in this population. The samples will be archived at -70C until time of analysis. Records will be treated with strict confidentiality and stored in a secured, limited access area. A randomly assigned number rather than name will identify all collected samples. No protected health information will be recorded on the specimens.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. Participants will retain the right to have the sample material destroyed at any time by the following process: (1) notify the study doctor/staff, (2) study investigator provides the laboratory with the patient's assigned study code; (3) any remaining sample will be located and destroyed. Any data or analysis which was generated prior to the subject's request to have their sample destroyed will not be removed; however, no further analysis will be done. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

5.3. STUDY VISITS

Screening

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. The study site will record patient's basic personal details, including name, contact details, gender, height, weight, date of birth, age, and self-reported ethnicity. Subject screening numbers are assigned to all subjects as they consent to take part in the study. This number is assigned to subjects according to the sequence of presentation for study participation. The following will be conducted at Screening:

- Obtain consent (must be obtained prior to performance of any study-specific tests or evaluations that are not considered standard of care).

- Confirm inclusion/exclusion criteria
- Record demographic information
- Record prior/concomitant medications including all prescription and non-prescription drugs, vitamins, and dietary or herbal supplements
- Review medical history
- Record hematology, d-dimer, coagulation and clinical chemistry results
- Record vital signs: BP, PR, respiratory rate, temperature
- Review chest x-ray report and use of supplemental oxygen

Day 0/Randomization

This visit may be performed on the same day as Screening if all procedures have been completed.

- Record vital signs: BP, PR, respiratory rate
- Assess concomitant medications and/or procedures
- Obtain Sequential Organ Failure Assessment Score (SOFA)
- Collect blood sample for CRP
- Collect blood sample for PAI-1 testing
- Collect blood sample for exploratory testing
- Randomization - subjects will be assigned to 1 of 2 treatment groups (TM5614 180 mg or matching placebo) in a 1:1 ratio based on a randomization schedule developed by the Investigational Pharmacy. First dose should be administered on the day of randomization. Study drug will be administered by clinical staff on the in-patient units per order. Subjects will take 6 tablets per day, preferably in the late afternoon/evening.
- Obtain Sequential Organ Failure Assessment Score (SOFA) and Ordinal scale

Treatment Period - Daily for seven (7) days or discharge (End of Study, EOS)

The following procedures will be captured daily while on study medication:

- Record any changes in procedures, prescription and non-prescription drugs
- Record vital signs: BP, PR, respiratory rate
- Assess adverse events
- Study drug administration and accountability
- Record hematology, d-dimer, coagulation and clinical chemistry results
- Collect blood sample for CRP
- Collect blood sample for PAI-1 testing (48 hours after 1st dose of medication and Day 7/discharge only (± 24 hours))
- Collect blood sample for exploratory testing (48 hours ± 24 and Day 7/discharge only)
- Obtain Sequential Organ Failure Assessment Score (SOFA) and Ordinal scale

Post-Treatment Evaluation Period

Subjects will be contacted 30 days (±7) after the last dose of the study medication for review of any adverse events or assessment of ongoing (S) AEs. This visit can be completed by telephone.

6. RECRUITMENT METHODS

Participants with a positive viral PCR for SARS-CoV2 requiring supplemental oxygen at any time during hospitalization will be recruited from Northwestern Medicine. The study team will use the Epic-based health information technology system and the Northwestern Medicine Enterprise Data Warehouse (EDW) to identify potential participants who are eligible based on the concomitant clinical diagnoses of COVID-19. These systems allow for rapid electronic identification of eligible participants based on routinely collected clinical data as well as direct communication with their clinicians to seek their permission to contact potential participants. This methodology has been used in numerous studies by Northwestern investigators for successful trial recruitment.

After obtaining a list of potential participants, the study staff will review these potential participants' charts in the electronic health records, ensure permission from the patients' treating physicians to contact for potential participation in the study.

In the event of lagging recruitment or lack of diversity in study population to reach our targets, we plan to open recruitment and enrollment efforts to additional Northwestern Medicine site(s). If this occurs, then we will submit a protocol amendment and seek IRB approval prior to initiating study procedures at any additional sites.

7. RISKS AND BENEFITS TO PARTICIPANTS

7.1. RISKS OF STUDY MEDICATION- TM5614

If participants are randomized to the active intervention arm, then they will be taking the small molecular inhibitor, TM5614. To date, this drug has only been tested in a Phase I study.

Use of TM5614 in humans is limited. When the study drug was given to 9 healthy adult males once a day for 7 days after breakfast, a total 4 subjects and 6 reports of adverse events were observed in the TM5614 group along with a total 2 subjects and 2 reports in the placebo group. The adverse events which occurred included 1 subject and 1 report of an increase in the test for liver damage (ALT) in the 60 mg group, 3 subjects and 5 reports (1 report of oral paraesthesia - an unpleasant sensation of tingling or pricking, erythema migrans linguae-reddening of the floor of the mouth, rhinorrhea – filling of the nasal cavity with mucus, pyrexia - fever, and diarrhea) in the 120 mg group, and 2 subjects and 2 reports (1 report of ALT increase and taste abnormality) in the placebo group; however, all of these were mild.

In addition to these risks, this research may harm participants in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death, but this is not expected.

This study involves the use of participants' identifiable, personal health information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the possibility of this happening.

The study drug may also hurt a pregnancy or fetus in ways that are unknown.

There is also the possibility that the patient may worsen during therapy or after stopping therapy. Should this occur study investigators will work with the treating physicians to implement supportive care with conventional therapies to mitigate any worsening in clinical status.

The study team will continue to follow these participants and collect any AE and study-related data through the final study time point.

7.2. POTENTIAL BENEFITS TO PARTICIPANTS

During this research study, participants will have a 50-50 chance to receive medications for COVID-19, which may help improve their outcomes during this period.

8. WITHDRAWAL OF PARTICIPANTS

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a participant is withdrawn or decides to withdraw from the study, then a close-out visit will be conducted.

If a participant is incarcerated, becomes terminally ill, or experiences any other circumstance that would make continued involvement in the study unsafe or unethical, then the study physician may withdraw the participant without his / her consent. In all cases, any data already collected will not be removed from the study database and may still be used in analyses. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded on the electronic Case Report Form (eCRF) and source documents.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Investigator decision

9. DATA MANAGEMENT AND CONFIDENTIALITY

9.1. DATA MANAGEMENT

Electronic data will be stored in the electronic case report forms (eCRFs) maintained using the Northwestern University REDCap platform. Thus, only those with an appropriate Northwestern NetID and password will have ability to enter and view study data. Export rights will be restricted to the study statistician only, and data will only be exported when necessary for reporting and quality control purposes to a restricted NM or ‘fsmresfiles’ location at Northwestern. These files are routinely backed up through Northwestern’s Information Technology services. The

randomization list and any blinded material will also only be restricted to the study statistician and NM investigational pharmacy.

Paper CRFs will be housed at the study site in a locked, secure location. Only authorized study staff, monitors or auditors will have access to these files. The study team will retain all study records required by applicable regulatory bodies in a secure and safe facility for a minimum period of seven years. Access to study records will be limited to study team members, unless through written application to and approval by the study Steering Committee.

We will create a Data and Safety Monitoring Plan (DSMP) and Data Management Plan (DMP) to outline details on data and safety monitoring and quality checks. To ensure data quality, we will build in field validation(s) and branching logic within the forms, use a first / second pass data entry workflow, and we will use the field comment logs and data resolution workflow module within REDCap. Before obtaining data entry rights in production, study team members must complete a training and pilot test entry of hypothetical data. We will document these training sessions and successful completion of any study data entry practicums.

Further, we will perform centralized monitoring through Data and Status Quality Reports (DSQRs) and REDCap reporting features. The DSQRs will use the REDCap application programming interface (API) functionality to export the study data, and then restructure and summarize the data using statistical software such as R or SAS. The output for these DSQRs will be housed on Northwestern University's secure servers with restricted access to study team members only. The reports will be reviewed and discussed weekly, on average, but once the systems are in place and code generated, the reports may be updated in real-time. The contents of these reports may continually evolve throughout the course of the study, but they will focus on the following essential study data:

- Baseline information – screening and consent, enrollment, demographics
- Adherence to intervention and protocol adherence
- Primary and secondary response variables
- AEs / SAEs
- Concomitant medications
- Other pre-specified response variables and/or covariates (laboratory data, exploratory outcomes)

For the purposes of these reports, we will present data in aggregate form overall. In addition to these general data summarizations, we plan to employ statistical methods for monitoring clinical trial data. The general strategies may include:

- Exploration of:
    - Descriptive statistic summaries overall and by site for essential study data as indicated above.
    - Frequency of outlying values.
    - Process measures overall:
        - Screen failure rate
        - Outlier and inlier rates
        - Correlation coefficients of key covariates

    - Deviations and AEs
    - Timeliness of data entry
    - Proportion of dropouts / losses to follow-up
- Evaluating important response and safety data univariately and also longitudinal trajectories over time (within the same person).
- Multivariate techniques involving principal components (PC1 vs. PC2) and examining multivariate outliers. Plot PCs for p-values for all variables and identify outliers (those outside of the central cloud).
- Tests on randomness – Benford's law on the distribution of digits.

9.2. CONFIDENTIALITY

This study involves collection and use of Protected Health Information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. All participants will be identified by a unique study ID. Access to the full study database with identifying information (names, medical record numbers, dates) will be restricted to authorized study personnel. Data collection will be secure, and these data will not be used for any other purpose than to contact the study participant during their participation in the trial and to disseminate results. Data shared from this study will be completely de-identified. If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects to be identified.

9.3. SHARING RESULTS WITH PARTICIPANTS

When the study is over, research findings will be available at www.ClinicalTrials.gov as required by US law. Study staff will be available to speak with participants about the study over the telephone at any time. After all participants have completed the research study, each participant will receive a letter indicating which study drug he/she received at randomization. The research findings will also be published in the form of research articles or presented at scientific meetings.

10. STATISTICAL ANALYSIS

10.1. SAMPLE SIZE

A total of 80 participants will be randomized (1:1 allocation). This sample size is conservatively based on an analysis of covariance (ANCOVA), comparing primary outcome (PAI-1 levels at seven days post-randomization), controlling for baseline. PAI-1 distributional assumptions and estimates from the literature were used to inform sample size calculations. Specifically, we assumed a standard deviation of 2.35, an R^2 of 0.25 as a measure of the association between baseline PAI-1 and the outcome, and a two-sided type one error rate of 0.05. Sample sizes of 35 in each group will provide 80% power to detect a mean difference in PAI-1 of at least 1.48. This effect size translates to a 50% reduction of PAI-1 in the treated arm, assuming a baseline mean of 2.96. Inclusion of additional covariates believed to be prognostic of PAI-1 in secondary analyses may improve precision of the treatment effect estimate.

Analysis Population: Primary analyses will be based on an Intention-to-treat (ITT) principle. In the case of missing outcome data, a modified ITT analysis will be considered including those who are randomized and for which outcome data is available.

10.2. PRIMARY ANALYSES

The primary study outcome will be PAI-1, measured at 7 days post-randomization. In general, analyses will employ an ANCOVA, controlling for baseline PAI-1 (Y_0). As we anticipate a non-normal distribution for PAI-1, a log transformation of the outcome will be employed. Secondary analyses may also consider adjustment for relevant baseline covariates known to be associated with PAI-1: sex, race, age, and BMI, assuming model stability. These analyses will assume the following model for PAI-1 (Y) for participant *i (i=1…N)* at 7 days:

$$\log(Y_i) = \beta_0 + \beta_1 \boldsymbol{I}(active\ arm) + B_2(Y_{0i}) + e_i$$

Under the assumption that error terms $e_i \sim N(0, \sigma^2)$, and the hypothesis test of interest is:

$$H_0: \beta_1 = 0\ vs.\ H_1: \beta_1 \neq 0$$

Residual diagnostics will be examined and relevant assumptions will be assessed using graphical display and statistical testing where appropriate. In situations where assumptions are in question, nonparametric methods, transformations, or inclusion of higher order terms, may be applied.

10.3. ADDITIONAL SECONDARY ANALYSES

Similar methods as described above will also be considered for PAI-1 levels at 48 hours. Safety outcomes, including adverse event rates and other relevant outcomes previous listed, will be tabulated overall and by arm. Chi-squared tests or exact methods will evaluate the differences across arms in event rates at the participant level. For outcomes such as relevant side effects that may occur more than once in any participant, descriptive statistics or generalized linear mixed modeling GLMMs will be examined. Continuous laboratory safety assessments will also be analyzed as specified above (ANCOVA or GLMM, as appropriate).

10.4. PLANNED SUBGROUP ANALYSES

Subgroup analyses will be conducted for pre-specified baseline covariates of interest. Specifically, assessment of interaction terms between the treatment arm and each of the following: sex, race (white vs non-white), age group (<65 vs 65+), and obesity (BMI <30 vs BMI 30+) will be considered. Although we anticipate being underpowered for these specific hypothesis tests, these models will be used to identify any trends that suggest the effect of the intervention is different depending on these pre-specified covariates.

10.5. MISSING DATA

Mechanisms of missing data will be examined, and if appropriate, sensitivity analyses will be performed using multiple imputation methods. Specifically, multivariate imputation by fully conditional specification will be considered under missing at random and missing not at random assumptions. Results will be compared across approaches to assess the effect of missing data and validity of specified models.

11. STUDY DRUG

TM5614 (TM5614) is a PAI-1 inhibitor under research and development by Tohoku University. Tohoku University/ Renascience Co. LTD will supply study drug and matching placebo in sufficient quantity to conduct this investigation.

11.1. STUDY DRUG ADMINISTRATION

Subjects will be instructed to take 6 tablets per day and to take the tablets with a glass of water. Subjects will also be instructed swallow the study medication whole. Subjects will be instructed to dose at a consistent time of day, preferably in the late afternoon. For participants who have difficulty swallowing or become intubated study medication may be crushed and administered via liquid suspension or nasogastric tube (NGT).

11.2. STUDY DRUG ACCOUNTABILITY

Study Medication and matching placebo will be shipped to the Northwestern Memorial Investigational Drug Services (IDS). NM IDS will maintain accountability for each dose of medication it receives, dispenses, disposes, transfers, or returns to the manufacturer in accordance with institutional policy of Study Drug supplies.

Drug accountability at the participant level will be monitored by the Investigational Pharmacy, via study coordinator during visits and through completion of the eCRF. The investigational product will be verified for 100% of enrolled participants; any discrepancies / queries / violations at the participant level will be noted in REDCap.

Study Drug not taken by a participant will be returned daily to Northwestern Investigational Drug Services for accountability and destruction. Return will follow Northwestern Investigational Drug Services procedures.

Table 2: Study Drug Dosing Information

Study Drug	Total Dose	Volume to Administer	Frequency
TM5614	180 mg	6 tabs	Daily, Q evening
Placebo	N/A	6 tabs	Daily, Q evening
N/A = not applicable			

11.3. LABELING AND STORAGE

TM5614 tablets are packaged in blister packs each containing 6 tabs. TM5614 tablets are orange film-coated and contain 30 mg of TM5614 drug substance.

Study drug labels and cartons will contain information to meet the applicable regulatory requirements. Study drugs are stored separately from general inventory according to storage instructions in locked areas of NM investigational pharmacy. All study drug inventory will be labeled with the Protocol Number and temperatures are monitored and recorded. Study drug and matching placebo will be stored at temperatures between 68-77 ºF. Shelf life for Placebo and TM5614 is 12 months.



11.4. DOSE ADJUSTMENT

The dose of study drug may be decreased, interrupted or stopped as clinically warranted at the Investigator's discretion.

While we do not anticipate any significant adverse events related to renal or liver dysfunction laboratory parameters will be monitored and development of acute renal or liver failure will result in discontinuation of study drug.

The management of bleeding in patients receiving study medication will be supportive, as study drug does not have a specific antidote. If major bleeding occurs study drug may be discontinued and follow-up continued. Local measures should be applied if needed to control bleeding (e.g., local pressure, endoscopy and injection of a bleeding vessel, as in embolization) and intravenous fluids and blood transfusion support should be provided as indicated. In the rare case of life-threatening bleeding, the investigator may consider obtaining advice from a hematologist.

If a participant begins any drug that may adversely interact with the intervention, specifically, therapeutically dosed anticoagulation (e.g. heparin, apixaban, warfarin) we will stop Study Drug administration and continue follow-up. We will assess any additional therapies at each collection time point to ensure monitoring for drug-drug interactions.

The following will result in permanent discontinuation of study drug:

- Doubling of serum creatinine
- Increase above 4-times the upper limit of normal of liver enzymes AST or ALT
- Grade 3 hematological bleeding events
    - Platelets <50,000 platelets/μL
    - Hemoglobin <7 g/dL or 25% drop
- Requirement for therapeutically dosed anticoagulation (e.g. heparin, apixaban, warfarin)
- Need for ECMO
- Development of impaired renal function (GFR < 25 ml/min or need for dialysis)

Any changes to drug dose will be recorded including time of discontinuation or down titration. Patients should be monitored closely until clinically stable.

12. RANDOMIZATION

Patients will be randomized after all Screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in **Sections 4.11 and 4.12**. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

NM Investigational Drug Services (IDS) will develop and maintain the randomization schedule. Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study.

This will preserve the blinding of treatment allocation, since only the study statistician (or representative as a backup) will have access to the master list of drug assignment numbers and corresponding treatment codes.

12.1. UNBLINDING OF TREATMENT ASSIGNMENT

The patients, site investigators, monitors, and study personnel will be blinded to treatment assignment throughout the study. An unblinded randomization schema will be maintained securely at by the Northwestern Medicine Investigational Pharmacy.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is locked. Otherwise, the blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the subject. If a patient has suffered a Serious Adverse Event (as defined in **Section 14.1**) and when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient.

The date, time, and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes.

13. ETHICS

13.1. ETHICAL CONDUCT OF THE STUDY

The procedures set out in this protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the investigator(s) and study personnel abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from the Northwestern University IRB will be obtained before start of the study, according to GCP, local laws and regulations.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB approval. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB. Any deviations from the protocol must be explained and documented by the investigator.

13.2. SUBJECT CONSENT

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the patient in accordance with 21 CFR Part 50. Participation will require informed consent from all participants. The study coordinator will consent participants at Northwestern Memorial Hospital in their inpatient room. The subject or his/her legal representative will be given ample time and opportunity to inquire about details of the study and all questions will be answered to the satisfaction of the subject or the representative.

Prior to participation in the trial, the written informed consent form should be signed and personally dated by the subject or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). Prior to randomization, we will confirm participant consent and understanding of the trial. The subject or his/her legal representative will receive a copy of the signed and dated informed consent form.

If a legal representative (LAR) gives initial consent on behalf of a participant, consent will also be obtained from the participant when s/he is able.

Electronic Consent – COVID MyStudies App/REDCap

In order to limit face-to-face contact use of electronic platform, such as FDA COVID MyStudies or REDCap, will be used to obtain informed consent electronically. FDA COVID MyStudies data storage environment is secure and supports auditing necessary for compliance with 21 CFR Part 11 and the Federal Information Security Management Act, so it can be used for trials under Investigational New Drug oversight. The FDA had made this app available to investigators at no cost for IND trials. Participants will need to download the free app available in the Apple App and Google Play store. In addition, Northwestern is scheduled to release an updated version of REDCap in early 2021 that will be 21 CFR Part 11 compliant, upon release will be implemented for use in this project

The consent form built in the electronic platform will mirror that of the Northwestern University IRB approved consent. Through the COVID MyStudies app/REDCap, the investigator or designee can send the informed consent document electronically to the patient or his or her legally authorized representative. Once the patient or representative has signed the form, he or she will receive an electronic copy. The investigator or designee can then access the signed consent in a secure manner and print it or transfer the file electronically.

The participant can choose to review the consent form with the coordinator over the phone or review independently. If the patient decides to participate s/he will complete the consent process by typing their name, date and sign using a mouse or touch screen (depending on device). The research team will receive an email notification when participant completes the consent process and sign/date and follow-up with the participant to ensure all questions are addressed.

A copy of the signed consent form will be sent in PDF format automatically upon participant's signature, along with site contact information in case of questions. Subjects will also be informed they can request a paper copy be mailed to them.

Non-English Speaking Participants

We do not anticipate enrolling non-English speaking participants in this study. However if the situation arises the following procedure will be followed:

- If the participant's primary language is not English, the person obtaining consent is responsible for determining if the individual and/or LAR sufficiently understands English.
- If it is determined that the participant cannot be properly consented in English, the participant/ LAR should receive a consent document that has been translated into the potential participant/ LAR's primary language and the process described above should be followed for the participant/LAR's native language using a qualified interpreter.
- Use of the short form consenting process when it is not feasible (e.g., due to limited time to obtain consent) for the participant and/or LAR to read and sign a full translated consent document:
    - The following documents are included in this process and must be approved per NU IRB policies:
        - Summary of Research – this document includes adequate information to cover all of the required elements of informed consent. This summary uses terms and language that are understandable to the target population. The full English consent document is acceptable for this purpose.
        - Short Form Consent Document – a brief document that lists the required elements of informed consent, asks the participant to confirm that all of the required elements have been verbally explained, and asks whether the person voluntarily agrees to participate.
    - When using the short form process, the actual process of obtaining informed consent proceeds as for the standard consent process described above with the following exceptions:
        - The Summary of Research is read to the participant/LAR as appropriate instead of the participant/LAR reading the full consent form themselves.
        - Adequate time should still be allowed for the individuals to consider participation in the research, however:
        - It is understood that given the nature of the research setting an open-ended period of time is generally not feasible.
        - The participant/ LAR may not have the opportunity to take information about the research home or to consult with others that are not present.
        - A witness must be present throughout the entire short form consenting process.
- Translating Informed Consent Forms and Ongoing Communication with Participants Utilizing Languages Other Than English
- If the need for consenting in a language other than English is sufficient (i.e. using the same language short-form process more than once) the full NU-IRB approved informed consent form will be translated into that language.
- Future versions of the ICF requiring re-consenting will be translated into the language in question.

- All such documents will be submitted to NU IRB along with the corresponding certificate/s of translation prior to use.
- NMH interpreters or research personnel fluent in the language will conduct a GCP compliant informed consent process with the participant. Details of the consent process will be documented in the participant's study records and a copy of the informed consent form will be saved in the electronic medical record per applicable NMH policy at the time.
- NMH interpreters, study personnel fluent in the language, and/or family members fluent in the language and in English will be present at all follow-up visits to facilitate study procedures and assist with questionnaires. Any such facilitation/assistance will be documented in the participant's study record.

Compensation for Research-Related Injury

This study is investigator-initiated. If participants become ill or are injured as a result of study medications or procedures they are directed to seek medical treatment through their doctor or treatment center of choice and to promptly tell the study doctor about any illness or injury. The researchers and clinical staff will not pay for medical care required because of a bad outcome resulting from participation in this research study. This does not keep participants from seeking to be paid back for care required because of a bad outcome.

Economic Burden to Participants

We do not anticipate that patients will experience additional economic burdens related to participation in this study. Management of COVID-19 will be performed according to clinical standards of care by treating physicians. Study drugs will be provided at no cost to participants. Research lab tests will be covered by the study and not billed to the patient

Compensation for Participation in Research Activities

Study participants will not be compensated.

14. SAFETY

14.1. SAFETY DEFINITIONS

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical investigational product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All AEs should be captured in the source documents and reported in the eCRF.

Worsening of conditions, recurrent episodes, and further complications if any are to be reported as a follow-up of the original event.

Serious Adverse Event Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening
  - NOTE*:* The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is another serious or important medical event as judged by the investigator

Intensity/Severity of An Adverse Event

All AEs/SAEs will be graded as mild, moderate, or severe by the investigator based on her/his medical judgment and the following guidance:

- **Mild:** asymptomatic or mild symptoms; does not interfere with subject's usual function; clinical or diagnostic observations only; intervention not indicated.
- **Moderate:** minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone)
- **Severe:** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self).

Relationship to the Trial Medication

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes.

All AEs/SAEs will be assessed by the investigator and the symptom relatedness to the study drug according to the following:

- **Unrelated** = clearly not related to the study medication
- **Unlikely** = doubtfully related to the study medication
- **Possible** = may be related to the study medication
- **Probable** = likely related to the study medication
- **Definite** = clearly related to the study medication

14.2. SAFETY REPORTING

Reporting of AEs

During study participation, research staff will review participant records and assess participants for the occurrence of AEs from the time of randomization until 7 days after the last dose of study drug. All AEs that site staff becomes aware of after randomization until 7 days after last dose of the trial medication was taken must be recorded. The following information will be collected for each AE: event name, date of onset, severity, a possible cause of the event, relationship to trial medication, action taken regarding the trial medication, treatment given to manage the event (if applicable), outcome of AE, and date of resolution (if applicable).

For participants remaining hospitalized beyond 7 days after the last does of study drug, ongoing AEs will be assessed until resolution or until the 30th day after the last does of study drug.

An increase in the severity of a previously reported AE during the trial will be reported as a new AE with higher severity. A decrease in the severity of a previously reported AE during the trial, will not require changes to the reported severity.

Reporting of SAEs

AEs that meet the criteria of an SAE that is mentioned in the preceding section apply to the reporting of SAEs as well. All SAEs will be reported by the site staff via the eCRF within 24-hours of first becoming aware of the event. Additional information will be collected including, seriousness criteria, relatedness to study drug, action taken with study drug, hospitalization date and discharge (if applicable), and procedures performed (if applicable).

Trial Investigator Responsibilities In Reporting (S)AEs

Regardless of the suspected causality, every AE occurring after the participant is randomized and until 7 days after last dose of study medication will be reported by the site investigator as per the local regulatory and ethical requirements. All SAEs should be reported by completing the relevant form AE/SAE form. The reports should identify participants by unique identification numbers assigned to the trial subjects.

Investigators are responsible for assessing if an AE meets criteria for reporting as serious, the intensity of the event and the relationship of the event with the trial medication. SAEs should be promptly reported to the concerned parties and followed up until resolution as per the local ethical and regulatory requirements. The Investigator should supply additional information (e.g. laboratory results, specialist/hospital letters, and autopsy results, etc.) if required by the DSMB.

Reporting of Trial Medication Use Errors Or Misuse

Reports of study treatment overdose, abuse, off-label use, misuse, or any other medication error should not be reported as AEs unless they are associated with suspected adverse drug

reactions, in which case the suspected adverse drug reaction should be reported as AE or SAE depending on the seriousness of the event. Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or patients. All study treatment overdose, misuse and other medication errors associated with suspected adverse drug reactions should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, etc.).

14.3 STUDY-SPECIFIC EVENTS OF INTEREST

In-hospital mortality

Mortality will be classified as cardiovascular or non-cardiovascular death (any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide).

Intubation/Mechanical ventilation

Total duration in hours will be recorded. Counting will begin from the start of intubation; the clock stops after weaning, extubation, or patient discharge/transfer.

Arrhythmia

Any new onset cardiac arrhythmia requiring intervention (i.e., drug, cardioversion).

Renal replacement/dialysis

Indication and use of renal replacement therapy will be recorded. Techniques include intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRT) and peritoneal dialysis (PD).

New onset of heart failure

- Current (presence of ≥ 2) signs/symptoms of HF (NYHA Class II-IV) including: shortness of breath or dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, pulmonary edema, rales, peripheral edema, JVD, S3, hepatojugular reflex, elevated BNP (≥ 100 pg/mL), or altered hemodynamics consistent with HF
- Pulmonary or systemic congestion requiring initiation or increase diuretics or vasoactive drugs.

HF will further be defined as:

- Systolic heart failure- reduced EF (HFrEF) < 40%
- Diastolic heart failure- preserved EF (HFpEF) LVEF ≥ 40%

Venous and arterial thromboembolism

Venous thromboembolism (VTE) events (deep vein thrombosis, pulmonary embolism) and arterial thromboembolism (ATE) events (myocardial infarction, ischemic stroke, acute limb ischemia) will be recorded.

Stroke

Stroke will be defined as a new the rapid onset of a new neurological deficit of cerebrovascular cause that persists beyond 24 hours (non-fatal) or is interrupted by death within 24 hours (any) with evidence of new neurological lesion on imaging modalities.

Bleeding events

Bleeding events will be reported based on the following criteria.

Major: hemodynamically important, life or limb threatening, accompanied by transfusion. Clinically overt bleeding will be classified as 'Major' if it is associated with a fall in the hemoglobin level of at least 2.0 g/dl transfusion of 2 units of red blood or involvement of a critical site (e.g., intracranial, intraspinal)

Minor: Less severe clinically overt bleeding will be classified as minor and does not require action/treatment.

Major bleeding, minor bleeding, need for transfusion, and intracranial bleeding will be assessed during the study period and reported. Data on complications will be captured on the Case Report Forms in a way that enables their outcomes to be categorized according to FDA guidelines.

Clinical Laboratory Evaluations

A change in the value of a clinical laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

15. MONITORING

15.1. DATA & SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will be established to monitor the trial data and advise the Investigators on the continuing safety of trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. Information on the DSMB membership, responsibilities, periodic data review plan is described in the DSMB charter.

The Data Safety Monitoring Plan (DSMP) documents the provisions to monitor the data and ensure safety of all study participants. Briefly, (1) we will convene an independent DSMB, which will consist of three members with diverse backgrounds and fields of expertise (2) the DSMB will meet at minimum prior to trial initiation and after enrollment of the 5th participant, then every 10th participant thereafter to review safety and essential study data; (3) we will employ centralized monitoring approaches as mentioned below to monitor data quality and safety; (4) and we will adhere to regulatory requirements for expedited AE / SAE reporting.

15.2. DATA MONITORING

In addition to pre-programmed edit checks in the eCRF, regular remote data monitoring will be conducted by the Clinical Trials Unit and designated monitors for confirmation of participant eligibility, identification of missing data, data consistency and general data quality checks. Automated queries may be generated via programming in the eCRF and can also be manually generated by monitoring staff. Monitoring visits will also be conducted to review source documents and to resolve any issues at the site. Full details of monitoring activities will be described in the study Monitoring Plan. The investigator should allow the monitors, the Ethics Committee, and of the Regulatory Authorities to have direct access to source data/documents.

16. QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Sanjiv Shah, MD (Principal Investigator) is the Neil J. Stone Professor of Medicine at Northwestern University and the Director of the Heart Failure with Preserved Ejection Fraction Program at Northwestern University Feinberg School of Medicine. Dr. Shah is internationally-recognized for his expertise in heart failure with preserved ejection fraction and has experience leading and participating in multi-center clinical trials, including within the NHLBI Heart Failure Research Network. He also has experience in leveraging the electronic health record to enhance efficiency of recruitment. He has experience in clinical medicine as a practicing cardiologist and heart failure specialist.

Dr. Shah will collaborate with a multi-disciplinary team of co-investigators, which include additional experts in pulmonary critical care, infectious diseases, cardiology, as well as biostatistics. Resources through the Clinical Trials Unit of the Bluhm Cardiovascular Research Institute including study coordinators, project managers, and nursing.

The study team will hold routine meetings on a weekly basis with all operations staff. All members of the study team have previous experience in clinical trials and have current certification in Protection of Human Subjects and Good Clinical Practice.

Douglas Vaughan, MD (co-Investigator) is currently the Irving S. Cutter Professor of Medicine and Chairman of the Department of Medicine at Northwestern University Feinberg School of Medicine and Physician in Chief of Northwestern Memorial Hospital. For the last two decades, his laboratory has been involved in basic, preclinical, and clinical investigations that have helped

to define the molecular physiology of PAI-1 and its role in arterial thrombosis, fibrosis, and aging. Moreover, he has experience performing numerous physiological and mechanistic clinical trials in humans that have identified key regulators of vascular fibrinolytic function and novel therapeutic approaches to reduce plasma PAI-1. He has led and previously served as PI on the SCCOR in Hemostasis and Thrombosis at Vanderbilt. He also a led a multidisciplinary group at Vanderbilt that was selected to participate in the NHLBI-sponsored Cardiac Cell Therapy Network, which includes 5 academic cardiovascular programs organized to perform Phase 2 clinical trials in humans. From a patient safety perspective, he has served on the DSMB for the JUPITER study and currently serves as chair of the DSMB for the NHLBI-sponsored Heart Failure Network.

Sadiya S. Khan, MD, MSc (co-Investigator) is an Assistant Professor of Medicine and Preventive Medicine at Northwestern University. She has experience leading and participating in single center and multi-center clinical trials in patients with heart failure with preserved ejection fraction, including ongoing studies of sodium glucose transporter 2 inhibitors. She also has experience in clinical medicine as a practicing heart failure physician.

17. REFERENCES

1. Chang, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS and Sharma L. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA*. 2020.

2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X and Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.

3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS and China Medical Treatment Expert Group for C. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020.

4. Livingston E and Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020.

5. Liu YC, Liao CH, Chang CF, Chou CC and Lin YR. A Locally Transmitted Case of SARS-CoV-2 Infection in Taiwan. *N Engl J Med*. 2020;382:1070-1072.

6. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, Nguyen TT, Cao TM and Pham QD. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *N Engl J Med*. 2020;382:872-874.

7. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirglmaier K, Zange S, Wolfel R and Hoelscher M. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med*. 2020;382:970-971.

8. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, Lewis J, Baer A, Kawakami V, Lukoff MD, Ferro J, Brostrom-Smith C, Rea TD, Sayre MR, Riedo FX, Russell D, Hiatt B, Montgomery P, Rao AK, Chow EJ, Tobolowsky F, Hughes MJ, Bardossy AC, Oakley LP, Jacobs JR, Stone ND, Reddy SC, Jernigan JA, Honein MA, Clark TA and Duchin JS. Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. *N Engl J Med*. 2020.

9. Wu Z and McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020.

10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X and Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020.

11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J and Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.

12. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep 2020;69:343-346*.

13. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B and Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020.

14. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM and Metra M. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020.

15. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X and Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020.

16. Zheng YY, Ma YT, Zhang JY and Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020.

17. Madjid M, Safavi-Naeini P, Solomon SD and Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol*. 2020.