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Title: A Phase II Study Evaluating Fostamatinib for Hospitalized Adults with COVID-19

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Drug Name:	Fostamatinib
IND Number:	152131
Sponsor:	NHLBI OCD
Manufacturer:	Rigel Pharmaceuticals

Coordinating Center: National Heart, Lung, and Blood Institute, Office of the Clinical Director
Responsible Data Safety Monitoring Board (DSMB): NHLBI Lung DSMB

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STATEMENT OF COMPLIANCE

Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation.

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

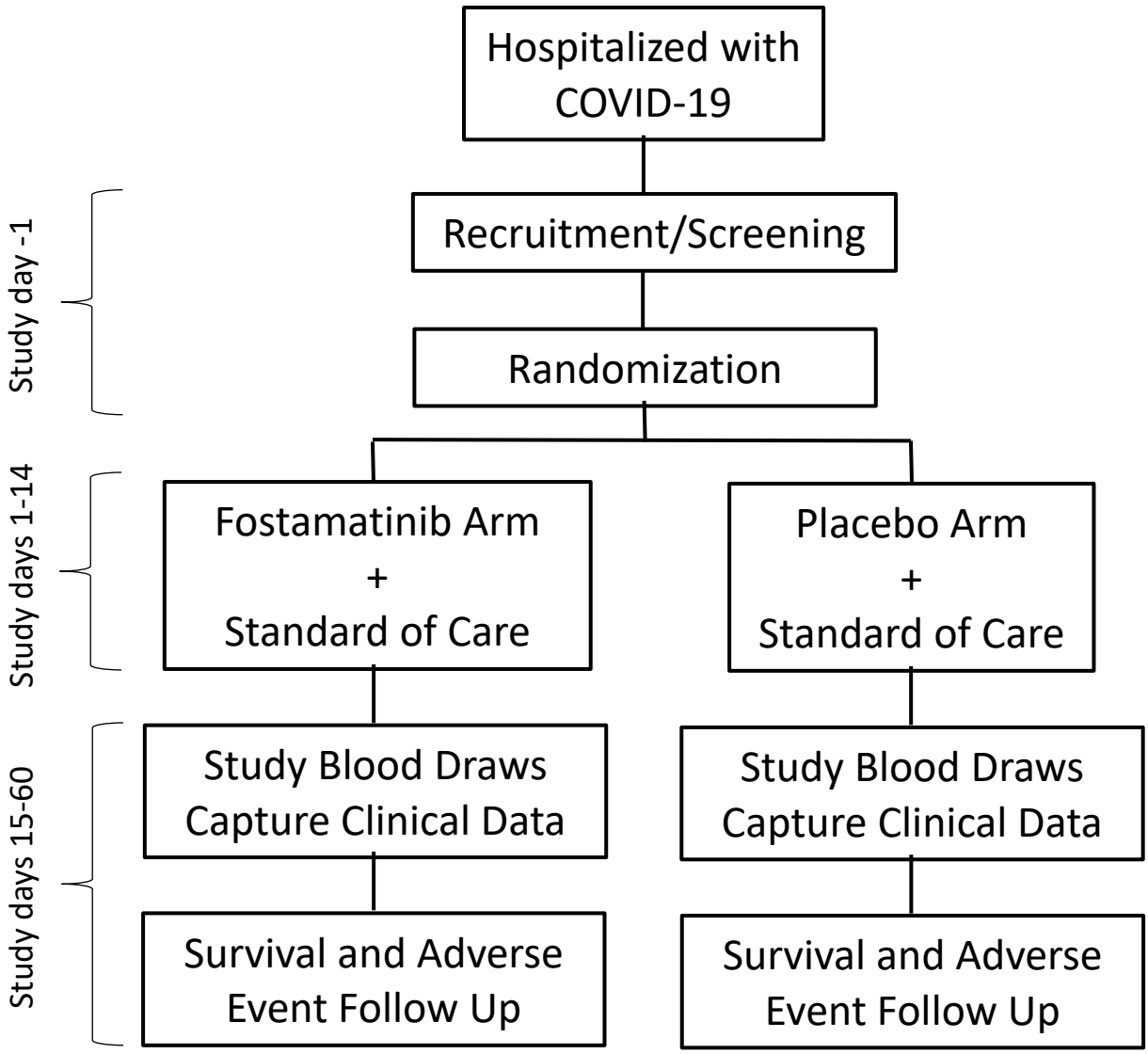
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**A Phase II Study Evaluating Fostamatinib for Hospitalized Adults with COVID-19**
Study Description:	This is a randomized, double-blind, placebo-controlled trial of fostamatinib for the treatment of hospitalized patients with COVID-19. We will randomly assign fostamatinib or matched placebo (1:1) to approximately 60 eligible COVID-19 patients who are a 5 to 7 on the 8-point scale (requiring supplemental oxygen via nasal canula or non-invasive ventilation, requiring mechanical ventilation or extracorporeal membrane oxygenation).
Objectives:	The primary objective of this study is to evaluate the safety of fostamatinib for the treatment of hospitalized patients with COVID-19. Secondary objective will be to assess the early efficacy and clinically relevant endpoints of disease course Exploratory objective will be to study the host immunological response to COVID-19 and potential mechanism of action of fostamatinib
Endpoints:	The primary endpoint is cumulative incidence of SAEs through day 29. Secondary endpoints are: 1. Time to recovery: day of recovery is defined as the first day on which the subject satisfies one of the following three categories by Day 29: Ordinal scale 3: hospitalized, not requiring supplemental oxygen-no longer requiring ongoing medical care; Ordinal scale 2: non-hospitalized, limitations on activities and/or requiring home oxygen Ordinal scale 1: non-hospitalized, no limitations on activities 2. Number of days free of mechanical ventilation [patients with baseline ordinal scale 5-6 only] 3. 14-day and 28-day mortality 4. Grade 3 and 4 AE through day 60. 5. Days of hospitalization 6. Ordinal scale at day 15 and day 29

	7. Change in CRP, IL-6, d-dimer, ferritin, fibrinogen, absolute lymphocyte count, absolute neutrophil count, and platelet count from baseline [day 3, 5, 8, 11, 15, 29] 8. Number of days in the ICU [entire hospitalization] 9. Relative change in PaO2/FiO2 or SpO2/FiO2 ratio 10. Change in SOFA score from baseline (day 1) [day 3, 5, 8, 11, 15, 29] 11. Number of days on oxygen (Including nasal canula, non-invasive, and mechanical ventilation) 12. Days free of renal failure [entire hospitalization] 13. Clinically relevant deep vein thrombosis (DVT) or pulmonary embolism (PE) [entire hospitalization]
Study Population:	This trial is intended to enroll hospitalized patients with COVID-19, who are at least 18-years old requiring supplemental oxygen via nasal canula or non-invasive mechanical ventilation (5 or 6 on the 8-point scale) or on mechanical ventilation or ECMO (7 on the 8-point scale).
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	This will be a multicenter study. Enrollment will take place at the NIH Clinical Center and Inova health system hospitals with the potential of expanding to a 3rd site. We will enroll a total of approximately 60 evaluable patients . The study will be conducted exclusively in the United States.
Description of Study Intervention:	The study intervention is fostamatinib, an inhibitor of spleen tyrosine kinase that will be administered orally at a dose of 150 mg twice daily for 14 days or 28 doses. Subjects will receive standard of care and be randomized to receive fostamatinib or matching placebo.
Study Duration:	This study will enroll over 2-3 months and it will take another 1 month for data analysis.
Participant Duration:	An individual subject will complete the study in a maximum of 60 days, from screening at Day -1 or 1 to follow-up through Day 60 ± 3 days.

1.2 SCHEMA


Hospitalized with COVID-19
Recruitment/Screening
Randomization
Fostamatinib Arm + Standard of Care
Placebo Arm + Standard of Care
Study Blood Draws Capture Clinical Data
Study Blood Draws Capture Clinical Data
Survival and Adverse Event Follow Up
Survival and Adverse Event Follow Up
Study day -1
Study days 1-14
Study days 15-60

1.3 SCHEDULE OF ACTIVITIES (SOA)[L]

Study Day	-1	1[h]	2	3	4	5[d,f]	6	7	8[d,f]	9	10	11[d,f]	12	13	14	15[c,d,f]	Daily until day 15 if discharged on study drug or daily if in hospital until day 60	22[c,d,f]	29[c,d,f]	60 [c,d,f]
Informed Consent	X[b]	X[b]																		
Inclusion/exclusion	X[b]	X[b]																		
SARS-CoV-2 Test	X[b]	X[b]																		
Pregnancy Test	X[b]	X[b]																		
Medical History	X[b]	X[b]																		
Randomization		X																		
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X	X	X
Vital signs[a]	X	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x[i]	x[i]	x[i]	x[i]	x[i]
Physical Exam/Review of symptoms	X[b]	X[b]																		
BMI Measurement	X																			
Ordinal Score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOFA Score		X		X		X			X			X				X		X	X	

Chest x-ray	X[b]	X[b]																	
Safety labs: CBC, BMP, LFTs[j]	X	x		x		x			x			x				x[i]		x[i]	x[i]	x[i]
Study drug		x	x	x	x	x	x	x	x	x	x	x	x	x	x					
Research bloods		x[e]		x[e]		x[e]			x[e]			x[e]				x[e,i]		x[e,i]	x[e,i]	x[e,i]
Oropharyngeal swab for viral RNA		x[e]		x[e]		x[e]			x[e]			x[e]				x[e,i]		x[e,i]	x[e,i]	x[e,i]

a) Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, and O2 saturation
b) Can be done on day prior or day of enrollment, except SARS-CoV-2 test which can be done up to 7 days prior.
c) If still in hospital phone visit not required. If discharged assess for adverse events, clinical status on ordinal scale, readmission, and mortalityCan be performed while in hospital, done as outpatient visit, or via telehealth if subject unable to travel for any reason.
d) Can be performed +/- 2 days from scheduled visit
e) Outpatient visit can be +/- 3 days from scheduled visit for days 5, 8, 11, 15, 22, 29, 60 as applictable
f) Following discharge patients only required to return for day 15, 22, 29, and 60 follow up visits unless they are discharged on study drug in which they will receive daily phone calls and will be required to have safety labs drawn as scheduled on days 3, 5, 8, 11 as applicable
g) Day 1 is the first day of study drug
h) Outpatient visits on day 5, 8, 11,15, 22, 29, and 60 visits are prefered as in-person visits but may be done via telehealth and there is no need for vital signs or scheduled sample collection when telehealth is utilized unless outpatient labs can be requested via outside source (example Quest)Subjects with LFTS above 3x the ULN at enrollment will have LFTs checked daily during the hosplitalization phase of the study.
i) Outpatient adverse event monitoring will be performed via phone call
j) Inpatient assesments will be done at the initial site of patient enrollment (NIH Clinical Center or Inova Health Systems.) After patient discharge, all outpatient assesments will be done at NIH Clinical Center, however laboratory can be done at non-NIH facility of patients who a having a telephone assessment.

2 INTRODUCTION

2.1 STUDY RATIONALE

Coronavirus Disaease-19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and is associated with significant mortality. Currently, two therapies have shown efficacy in large multicenter trials for the treatment of COVID-19, one of which is an antiviral (remdesivir) and the other is an immunosuppressant corticosteroid meant to dampen the immune response (dexamethasone). This study is designed to evaluate the safety and early efficacy of fostamatinib in addition to standard of care for hospitalized patients with COVID-19.

2.2 BACKGROUND

COVID-19 first described in Wuhan, China in December of 2019 and subsequently has resulted in a global pandemic with an excess of 3 million infections and over 130,000 deaths as of early July 2020 in the United States. SARS-CoV-2 primarily infects the upper and lower respiratory tract and can lead to acute respiratory distress syndrome (ARDS) in a subset of patients with a known high mortality rate. Additionally, some patients develop other organ dysfunction including myocardial injury, acute kidney injury, shock along with endothelial dysfunction and subsequently micro and macrovascular thrombosis (Berlin, Gulick & Martinez, 2020). Much of the underlying pathology of SARS-CoV-2 is thought to be secondary to a dysregulated immune response and more recently a hypercoagulable state leading to immunothrombosis (Rapkiewicz et al., 2020).

Currently, two therapies have shown efficacy in large multicenter trials for the treatment of COVID-19, one of which is an antiviral (remdesivir) (Beigel, 2020) and the other is an immunosuppressant corticosteroid meant to dampen the immune response (dexamethasone) ("Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report", 2020). Meanwhile many other immunomodulators are under investigation that may provide a much more targeted mechanism of action than broad acting steroids, which in some patients may actually worsen outcomes.

Spleen tyrosine kinase (SYK) is a cytoplasmic tyrosine kinase involved in the intracellular signaling pathways of many different immune cells. In this pilot study we propose to use fostamatinib (a SYK inhibitor) as a targeted therapy for the immunological complications of hospitalized patients with COVID-19. The biological mechanisms by which SYK inhibition may improve outcomes in patients with COVID-19 include the inhibition of pro-inflammatory cytokines by monocytes and macrophages, decreased production of neutrophil extracellular traps (NETs) by neutrophils, and inhibition of platelet aggregation; three pathways that are mediated through Fc receptors (FcR) recognition of antigen-antibody complexes or activation of c-type lectin receptors (CLEC) (Hoepel et al., 2020).

It is noted that a primary driver of SYK signaling is through the FcγRIIA which is driven by immune antigen-antibody complex. It is becoming increasing clear that there is an exuberant antibody response in patients with severe disease compared to those with less severe disease, a response that may be driven by viral load. By blocking this immune response, it is possible that fostamatinib may improve outcomes of patients with COVID-19. More specifically, in

monocytes and macrophages SYK is known to mediate the pro-inflammatory process through the production of pro-inflammatory cytokines such as IL-6. The production of pro-inflammatory cytokines has been reversed with the inhibition of SYK in MERS-CoV infected macrophages (Zhao et al., 2019). A recent study also found that anti-Spike IgG from serum of severely ill COVID-19 patients induces a hyperinflammatory response by human macrophages including elevated levels of IL-1β, IL-6, IL-8, TNF, and IL-10, a response that can be counteracted by SYK inhibition with fostamatinib. Furthermore, this study found that anti-Spike IgG is able to break down pulmonary endothelial barriers and induce microvascular thrombosis as evidenced by increase platelet adhesion and expression of von Willebrand's factor (Zhao et al., 2019).

In addition to the inhibition of the hyperinflammatory response from stimulated macrophages SYK inhibition of neutrophils and platelets may lead to decreased immunothrombosis resulting in less organ dysfunction in many patients with COVID-19 who become critically ill. In neutrophils SYK inhibition can lead to decreased production of neutrophil extracellular traps (NETs) which are known to be a driver of microthrombosis in heparin-induced thrombocytopenia, a process that is provoked by antigen-antibody complex stimulation of the Fc receptor (Zhao et al., 2019). In platelets SYK in known to inhibit multiple pathways associated with platelet aggregation including FcγRIIA activation by immune complex, GPVI activation by collagen, and CLEC-2 activation by rhodocytin, all while not affecting ADP mediated platelet aggregation. By decreasing NET production and inhibiting platelet aggregation, SYK inhibition may lead to decreased immunothrombosis potentially decreasing organ dysfunction in patients with COVID-19 and ultimately improving outcomes.

Lastly, fostamatinib was identified in a screen of 3,373 compounds in different stages of development to reduce mucin-1 (MUC1) expression, a membrane bound molecule expressed on the apical surfaces of epithelial cells and a marker associated with increased severity of ARDS. In this study fostamatinib reduced MUC1 expression in lung epithelial cells in a mouse model of acute lung injury, providing additional rational for why it may be advantageous in patients with COVID-19 ARDS (Alimova et al. 2020).

Fostamatinib is FDA approved in the US for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had insufficient response to a previous treatment and additionally, there is extensive experience with this drug in patients with rheumatoid arthritis (Weinblatt et al., 2008). Previous clinical reports support the clinical use of fostamatinib by showing it decreases interleukin-6 level in rheumatoid arthritis patient. Also, animal models using lipopolysaccharide induced inflammation have demonstrated that fostamatinib decreases acute lung injury and acute kidney injury (Al-Harbi et al., 2019) (Nadeem et al., 2019), making fostamatinib a candidate for the treatment of COVID-19. To date fostamatinib has not been used for the treatment of COVID-19. In light of overlapping toxicity between fostamatinib and other treatment modalities along with the clinical presentation of COVID-19 that can have significant overlap with the toxicities of fostamatinib we seek to perform a double blinded placebo control randomized clinical trial to test primarily safety of this drug in this hospitalized population.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 Known Potential Risks

Potential Risks of Fostamatinib:

Fostamatinib is FDA approved for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment (FDA label 2020). To date, over 4,800 patients have received fostamatinib as part of randomized controlled and open label trials across a variety of disease states including rheumatoid arthritis, ITP, autoimmune hemolytic anemia, and oncologic diseases. It has a consistent safety profile and the most common adverse reactions (≥5% and more than placebo) are diarrhea, hypertension, nausea, respiratory infection, dizziness, ALT/AST increased, rash, abdominal pain, fatigue, chest pain and neutropenia. Warnings and precautions included in the US product label include hypertension, elevated liver function tests, diarrhea, neutropenia, and embryo-fetal toxicity.

Hypertension	Hypertensive crisis occurred in 1% of patients and patients with pre-existing hypertension may be more susceptible
Hepatotoxicity	AST/ALT levels more than 3x the upper limited of normal occurs in 9% of patients
Diarrhea	Occurred in 31% of patients treated with severe diarrhea occurring in 1%
Neutropenia	Occurred in 6% of patients with febrile neutropenia occurring in 1%
Embyro-fetal toxicity	Based on findings from animal studies and mechanism of action fostamatinib can cause fetal harm.

Concomitant use with strong CYP3A4 inhibitors with fostamatinib will increase exposure to R406 that may result in increased risk of adverse reactions while concomitant use of strong CYP3A4 inducers reduces exposure to R406. Fostamatinib may increase the concertation of some CYP3A4 substrate drugs, some BCRP substrate drugs (ex. rosuvastatin), and some P-glycoprotein substrate drugs (eg. Digoxin).

It is not expected that there will be additive or synergistic adverse events with the addition of fostamatinib with standard of care except for remdesivir, which can cause increase in AST/ALT.

In addition to the fostamatinib adverse reactions listed above, the major potential risks of this study relate to the underlying disease (COVID-19) which has a high associated mortality in hospitalized patients. All subjects will be asked to provide personal identifiable information (PII). While every effort will be made to keep PII confidential, there is a chance PII may be obtained by unauthorized personnel. Electronic files will be password protected and all files will be locked in a cabinet or maintained in a locked room at the participating clinical site. Any publication will not have identifying information.

2.3.2 Known Potential Benefits

Fostamatinib may or may not improve the clinical outcome of individuals with COVID-19. However, there is benefit to society for their participation and insights may be gained about the therapeutic intervention under study. Additionally, individuals may benefit from a shortened disease course if fostamatinib is successful in this clinical trial.

2.3.3 Assessment of Potential Risks and Benefits

Fostamatinib has a consistent safety profile and adverse events are clearly documented. Currently the only immunomodulating therapy that has proven benefit in patients with COVID-19 is dexamethasone which improved mortality from 24.6% to 21.6% (RR 0.80, 95% CI 0.74-0.92, p=<0.001) when compared to usual care in patients with COVID-19. This improvement in mortality was more dramatic in patients who required mechanical ventilation where mortality improved from 40.7% to 29.0%, resulting in a need to treat 8 patients to show benefit in one. However, the high mortality rate in the control group compared to usual care in the United States, the multiple randomizations permitted, and lack of remdesivir as part of usual care make interpreting the results of this study for patients in the United States difficult. Furthermore, the mechanism of action by which dexamethasone would improve outcomes is not known as steroids have indiscriminate broad ranging effects on immunosuppression. Fostamatinib has many potential advantages over steroids including a targeted mechanism of action that inhibits multiple pathways in the pathogenesis of COVID-19 including decreasing Fc receptor signaling on neutrophils, monocytes and macrophages and CLEC receptors on neutrophils and platelets. Through these mechanisms we hypothesize that fostamatinib will decrease the immunodysregulation associated with COVID-19 along with the NETosis and inflammatory driven immunothrombosis that precedes much of the organ failure.

3 OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the safety of fostamatinib for the treatment of hospitalized patients with COVID-19.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the safey of fostamatinib in hospitalized patients with COVID-19	Cumulative incidence of SAEs through day 29.	This endpoint was chosen to evaluate the safety of fostamatinib for the treatment of hospitalized patients with COVID-19.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To assess the effect of fostamatinib on clinically relevant endpoints of disease course	1. Time to recovery by day 29: day of recovery is defined as the first day on which the subject satisfies one of the following three categories: Ordinal scale 3: hospitalized, not requiring supplemental oxygen-no longer requiring ongoing medical care; Ordinal scale 2: non-hospitalized, limitations on activities and/or requiring home oxygen; Ordinal scale 1: non-hospitalized, no limitations on activities 2. Number of days free of mechanical ventilation [patients with baseline ordinal scale 5-6 only] 3. Mortality at day 14 and 28 4. Grade 3 and 4 AE through day 60 5. Days of hospitalization 6. Ordinal scale at day 15 and day 29 7. Change in CRP, IL-6, ferritin, d-dimer, fibrinogen, absolute lymphocyte count, absolute neutrophil count, and platelet count from baseline [day 3, 5, 8, 11, 15, 29] 8. Number of days in the ICU [entire hospitalization] 9. Relative change in PaO2/FiO2 or SpO2/FiO2 ratio 10. Change in SOFA score from baseline (day 1) [day 3, 5, 8, 11, 15, 29] 11. Number of days on oxygen (Including nasal canula, HFNC, non-invasive, and mechanical ventilation) 12. Days free of renal failure [entire hospitalization]	Each of the secondary clinical endpoints were deemed to be clinically relevant indicates for improved or worsening disease course

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	a. Renal failure defined as i. Increase in serum creatinine by ≥0.3mg/dL within 48 hours or ii. Increase in serum creatinine by ≥1.5 times baseline which is known or presumed to have occurred within the prior seven days, or 13. Clinically relevant deep vein thrombosis (DVT) or pulmonary embolism (PE) [entire hospitalization]	
Tertiary/Exploratory		
1) To study the host immunological response to COVID-19 and potential mechanism of action of fostamatinib.	As an exploratory endpoint we will study the immune mechanism by which fostamatinib improves outcomes in patients with COVID-19. 1. Characterization of plasma biomarkers of immune activation 2. Measure platelet-leukocyte aggregates 3. Measure leukocyte activation assays 4. Measure plasma cytokine and chemokine levels 5. Evaluate the coagulation cascade 6. Measurement of immune antigen-antibody complexes 7. Measure thromboelastography (TEG) 8. Measure biomarkers of endothelial dysfunction 9. Characterize leukocyte extracellular traps 10. SARS-CoV-2 viability via cell culture from oropharyngeal samples	These exploratory endpoints are relevant *ex vivo* and *in vitro* analysis that will help determine disease and mechanisms of action while on fostamatinib

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	11. Detection of viral antigen blood and oropharyngeal samples	

4 STUDY DESIGN

4.1 OVERALL DESIGN

We intend to study fostamatinib for the treatment of hospitalized patients with COVID-19.

- This will be a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial with the objective to evaluate the safety of fostamatinib compared to matching placebo in COVID-19 patients who are hospitalized with a 5, 6, or 7 on the 8-point ordinal scale.
- The NHLBI will be the Coordinating Center for this multicenter study. All participating sites will enroll and treat subjects as described below. Research labs for exploratory endpoints will be processed at participating sites or shipped to the NIH Clinical Center for processing.
- All study participants will receive standard of care throught the entire study and then will be randomizd to 150 mg of fostamatinib twice a day or placebo for 14 days (total 28 doses).
- Subjects will be assessed daily while hospitalized and followed until day 60. If patients improve and are discharged prior to day 14 the study drug will be continued until day 14 as an outpatient. Patients who are discharged on study drug will receive a phone call daily to assess for adverse events and will have safety labs drawn on days 3, 5 8, 11 as applicable (outpatient third party lab aquisition may be utilized as needed). We will make every effort to bring back discharged patients for outpatient visits on days 15, 22, 29, and 60 to include laboratory draws. In patients who are unable to follow-up, they will receive a telephone visit as a follow up.
- Day 1 of study is the first day of study drug and patients will be followed until day 60.

8-point ordinal scale for secondary endpoint of efficacy and stratification (World Health Organization 2020)

Scale	Description
8	Death
7	Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

6	Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
5	Hospitalized, requiring any supplemental oxygen
4	Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions)
3	Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)
2	Not hospitalized, limitation of activities, home oxygen requirement, or both
1	Not hospitalized, no limitations of activities

Standard of Care:
For the purposes of this study standard of care is defined primarily as remdesivir as an antiviral intended to decrease viral load and dexamethasone a broad-spectrum anti-inflammatory intended to dampen the immune response to SARS-CoV-2. However, it is noted that in the middle of a pandemic evidence for and against specific therapies for the treatment of COVID-19 continue to evolve and therefore standard of care may change throughout this study. At the current time once enrolled, use of any biologic therapy outside of local standard of care are prohibited. This includes monoclonal antibodies targeting cytokines (e.g., TNF inhibitors; interleukin-1[IL-1], IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept); monoclonal antibodies targeting B-cells (e.g., rituximab in the last 6 months, and including any targeting multiple cell lines including B-cells); JAK inhibitor(s) other than baricitinib (e.g., imatibib, genfinitib); and interferon, plasma, or immunoglobulin (IgG) therapies for COVID-19 are not permitted. However, if patient has a clinical deterioration while on fostamatinib rescue therapies above including convalescent plasma may be considered. Additionally, if a specific site has a change in their standard of care outside of remdesivir and dexamethasone these medications will be permitted.

This study is randomized placebo-controlled study. All patients will receive standard of care described above.

4.2 JUSTIFICATION FOR DOSE

The dose of 150 mg twice daily is based on the safety and efficacy of fostamatinib from others trials. For chronic immune thrombocytopenia fostamatinib is initially started at a dose of 100 mg twice daily and up titrated to a maximum dose of 150 mg twice daily to achieve the goal of platelets above $50x10^9$/L while utilizing lowest possible dose to achieve that goal. Because the treatment duration of fostamatinib in this study may be only 14 days and we are interested in inhibition of the dysregulated immune response, we will start the study drug at the higher dose of 150 mg twice daily.

5 STUDY POPULATION

Subject Inclusion and Exclusion Criteria will be reviewed as appropriate by a member of the study team. If there is any uncertainty, the PI should make the decision on whether a potential subject is eligible for study enrollment. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

5.1 INCLUSION CRITERIA

1. Patient must be hospitalized, or had their inpatient stay extended, for COVID-19.
2. Age ≥18 years
3. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
4. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
5. Females of childbearing potential must agree to be abstinent or use a medical acceptable form of contraception from the time of enrollment through 30 days after last day of study drug
6. Laboratory confirmed SARS-CoV-2 RT-PCR test within 7 days of enrollment
7. Illness of any duration with SpO2 of less than 94% on room air requiring supplemental oxygen via nasal canula or non-invasive mechanical ventilation, or mechanical ventilation or ECMO (5 to 7 on the 8-point scale)

5.2 EXCLUSION CRITERIA

1. ALT or AST > 5 times the upper limit of normal (ULN) or ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN.
   Estimated glomerular filtration rate (eGFR) <30ml/min
2. Pregnancy or breast feeding
3. Anticipated discharge in the next 72 hours
4. Allergy to study medication
5. Uncontrolled hypertension (systolic blood pressure >160mmHg or diastolic blood pressure >100mmHg)
6. Shock or hypotension at the time of enrollment
7. Neutrophil count <1000/μL
8. Concern for bacterial or fungal sepsis
9. Received immunomodulatory treatment within 30 days prior to enrollment e.g., Bruton's tyrosine kinase/phosphoinositide 3 kinase/Janus kinase inhibitor or cytokine-targeting biologic therapy (anti-TNF, IL-6), or B-cell depleting antibody in the prior 6 months (rituximab, other anti-CD20 mAb)
10. Received a live vaccine the last 4 weeks
11. Those who were cognitively impaired or mentally disabled prior to COVID diagnosis

1.1 INCLUSION OF VULNERABLE PARTICIPANTS

12. Participation in another clinical trial for the treatment of COVID-19.

5.3 INCLUSION OF VULNERABLE PARTICIPANTS

Certain human subjects are categorized as vulnerable populations and require special treatment with respect to safeguards of their well-being. For this clinical trial, examples include intubated individuals who are sedated. When it is determined that a potential research subject is cognitively impaired, federal and institutional regulations permit researchers to obtain consent from a legally authorized representative (LAR). The study team will obtain consent from these vulnerable subjects using an IRB-approved protocol- specific process for consent using a LAR.

For subjects for whom a LAR gave consent, during the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

It is particularly important to include patients who may be sedated while on mechanical ventilation or extracorporeal membrane oxygenation because they are they patients who have suffered the most severe complications of this disease.

5.4 LIFESTYLE CONSIDERATIONS

Study participant should refrain from drinking alcohol while taking study drug.

Once discharged, subjects of child bearing potential should avoid pregnancy through abstinence or use of at least one contraceptive until 30 days after last day of study drug.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study because the participants did not meet the trial eligibility or withdrew consent. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once. Rescreened participants should be assigned the same participant number as for the initial screening.

5.6 STRATEGIES FOR RECRUITMENT

This is a multi-site study and subjects will be enrolled at the NIH Clinical Center, Inova Fairfax and Alexandria hospitals. Hospitalized participants will be recruited from within NIH and from the Inova hospitals.

A written strategic recruitment plan will be authored by the NHLBI Patient Recruitment Office (PRO) and ongoing regular recruitment-focused meetings will be held with the PRO and study staff and partners to ensure the study is meeting enrollment projections. If enrollment projections

are not being met, a strategy to boost enrollment will be implemented, and may include local news media coverage and live social media events.

Source of participants include inpatient hospital setting, outpatient clinics, and general public. The participants may also be recruited via self-referral, from in-patient services of regional hospitals and from outpatient settings.

Participants may be recruited through the use of:

- Flyers, documents/info cards, etc. for in-hospital use with patients and family;
- Recruitment advertisements and writeups placed in the NIH Record, NIH websites, the Clinical Center News;
- ResearchMatch.org;
- Newspaper writeups (print and digital) in local newspapers or outlets;
- NIH email listservs;
- Media interviews with investigators;
- NIH social media on Facebook and/or Twitter;
- ClinicalTrials.gov, Clinical Center "Search the Studies" website, NHLBI website, and NIH CC study recruitment page facilitated by CC communications office;
- Paid, targeted advertising, including digital social media ads, to local public population may be done led by the NHLBI digital communications specialist.
- A letter to physicians about the study may be provided to area ICUs and hospitalist groups.
- Hospital partners will be provided with written study materials, and in-service sessions by the study PI to educate and inform about the study.

There are no restrictions based on gender, race or ethnicity, or non-English speaking subjects.

All advertising/recruitment language will be IRB reviewed/approved prior to posting/using. Recruitment materials may be translated from English into other languages, including Spanish. Anticipated accrual rate is approximately 25 patients per month.

5.6.1 Costs

There are no costs associated to this study for subjects treated at the NIH.

By virtue of NHLBI sponsorship of clinical research protocols, enrolling sites qualify for Centers for Medicare and Medicaid Services (CMS) coverage of associated routine costs of medical care under the CMS Clinical Trial Policy (CTP). This policy is detailed at https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html. According to this policy, CMS is explicitly authorized to provide payment for routine patient care costs and costs due to medical complications associated with participation in clinical trials.

5.6.2 Compensation

Study subjects will be compensated for outpatient phlebotomy and follow up visits that occur at the NIH as follows:

- $50 for each blood draw;

- $20 for your first hour, and $10 for each subsequent hour spent at NIH Clinical Center during the follow up visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

All patients will be randomized to receive fostamatinib or matching placebo. All patients will receive standard of care.

6.1.1 Study Intervention Description

Patients hospitalized with COVID-19 on oxygen will receive fostamatinib at a dose of 150 mg twice daily for 14 days or placebo. Patients who are discharged prior to completing a 14 day course will continue therapy as an outpatient.

Fostamatinib is a spleen tyrosine kinase inhibitor that is currently FDA approved for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

The use of fostamatinib for the proposed indication is investigational and the study will be conducted under FDA IND #152131.

Fostamatinib is a prodrug with an active metabolite, R406, which is known to inhibit Fc-activating receptors and B-cell receptors. R406 is protein bound and has a half-life of 15 hours, with 80% of excretion occurring in feces and 20% excreted in urine.

Concomitant use with strong CYP3A4 inhibitors with fostamatinib will increase exposure to R406 that may result in increased risk of adverse reactions while concomitant use of strong CYP3A4 inducers reduces exposure to R406. Fostamatinib may increase the concertation of some CYP3A4 substrate drugs, some BCRP substrate drugs (ex. rosuvastatin), and some P-glycoprotein substrate drugs (eg. Digoxin).

6.1.2 Dosing and Administration

All patients will start fostamatinib or matched placebo at a dose of 150 mg orally twice daily for a total of 14 days (28 scheduled doses) to be swallowed as an oral tablet. If necessary, tablets can be crushed until granular with an approximate particle size <2 mm, added to approximately 10 mL of water, and stirred to mix before administration through the orogastric or nasogastric tube. Dose modifications based on adverse reactions are described in section 6.1.2.3

6.1.2.1 Dose Escalation

N/A

6.1.2.2 Dose Limiting Toxicity

N/A

6.1.2.3 Dose Modifications

Adverse Reaction	**Recommended action**
Hypertension	

Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	Initiate or increase antihypertensive medication for patients with increased risk of cardiovascular risk, and adjust as needed. No dose modification to study drug required.
Stage 2: systolic at least 140 or diastolic at least 90 mmHg	Initiate or increase antihypertensive medication and adjust as needed until BP control. No dose modification to study drug required.
Hypertensive crisis: systolic over 180 and or diastolic over 120 mmHg	Discontinue study drug until blood pressure is below systolic blood pressure of 160 and diastolic less than 100 mmHg. When restarting study drug dose should be reduced to 100 mg twice daily or matching placebo for the remainder of the study
Hepatotoxicity	
Increase in AST/ALT by x3 from level at the time of enrollment	Stop study drug and recheck liver function tests the next day. May restart when AST/ALT have returned to less than 3x baseline. When restarting study drug dose should be reduced to 100 mg twice daily or matching placebo for the remainder of the study*
Increase in AST/ALT to 3X ULN and total BL (bilirubin) greater than 2 x upper limit of normal (ULN)	Stop fostamatinib and recheck liver function tests the next day. May restart when AST/ALT have returned to less than 3x ULN and total BL has returned to less than 2x upper ULN. When restarting study drug dose should be reduced to 100 mg twice daily or matching placebo for the remainder of the study*
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	Continue study drug with frequent monitoring since isolated increase in unconjugated (indirect) bilirubin may be due to UGT1A1 inhibition
Diarrhea	
Diarrhea	Manage diarrhea using supportive measures (e.g., dietary changes, hydration and/or

	antidiarrheal medication) early after the onset until symptoms resolve. If symptoms become severe (grade 3) or above), temporarily stop study until symptoms resolve to mild (grade 1). When restarting study drug dose should be reduced to 100 mg twice daily or matching placebo for the remainder of the study
Neutropenia	
Neutropenia	If absolute neutrophil count decreases (ANC less than 1.0x10^9/L) discontinue fostamatinib. When ANC returns to above 1.0x10^9/L, restart study drug. When restarting study drug dose should be reduced to 100 mg twice daily or matching placebo for the remainder of the study

*Parameters and laboratory abnormalities must resolve within 3 days to restart the study drug.

6.1.2.4 Drug Administration

Study drug may be taken with or without food. In the case of a missed dose of study drug subjects should take their next dose at its regularly scheduled time. For patients able to swallow medication should be taken orally. For patients who are unable to swallow, on mechanical ventilation or on EMCO drug should be crushed and provided via nasogastric or orogastric access. Tablets should be crushed until granular with an approximate particle size <2 mm, added to approximately 10 mL of water, and stirred to mix before administration through the orogastric or nasogastric tube

If a subject is discharged from the hospital and then readmitted prior to Day 14, they may be given the remainder of the same study product up until day 14 that they were taking as an outpatient already. If the subject did not withdraw his/her consent to participate in the study, there is no need to reconsent upon readmission to the study hospital. The study team will need to notify the study pharmacist of the readmission. No study medication should be given past Day 14 (total 28 doses).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and Accountability

Investigational product (IP) will be shipped to the site either directly from Rigel Pharmaceuticals, or from other regional or local drug repositories. All other supplies should be provided by the site. Multiple lots of IP may be supplied.

Study products received at the sites will be open label unless specified in the protocol-specific pharmacy manual. Drug preparation will be performed by the participating site's unblinded research pharmacist on the same day of administration to the subject.

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s).

6.2.2 Formulation, Appearance, Packaging, and Labeling

Fostamatinib will be provided by Rigel Pharmaceuticals and stored in the pharmacy of each participating hospital. The drug product consists of 2 strengths of orange film-coated, plain, bioconvex tablets. The 150 mg tablet is oval and the 100 mg tablet is round. The tablets are supplied in white opaque high-density polyethylene bottles capped with white polypropylene child resistant closures with foil induction seals. Placebo tablets to match fostamatinib 100 mg and 150 mg will be provided by Rigel.

6.2.3 Product Storage and Stability

Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Do not remove desiccants.

6.2.4 Preparation

For patients who are unable to take oral medication tablets should be crushed until granular with an approximate particle size <2 mm, added to approximately 10 mL of water, and stirred to mix before administration through the orogastric or nasogastric tube

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study will randomize subjects 1:1 to placebo or fostamatinib. Once a subject has completed the screening and baseline period and evaluation for inclusion/exclusion criteria, the randomization process will begin. The site investigator or designee will obtain the randomized assignment for that subject from the data coordinating center. Randomization will be stratified by site and severity of illness at enrollment. Severity of illness will be stratified into ordinal scale 5 and 6 (supplemental oxygen via nasal canula or non-invasive ventilation), mechanical ventilation, and ECMO.

6.3.2 Blinding and Masking Procedures

As both arms are receiving standard of care, the product for standard of care is not blinded.

The fostamatinib and matched placebo is blinded. Fostamatinib and placebo tablets are identical in appearance.

Unblinding of the study will occur after all subjects enrolled have reached the end of study, and these visits are monitored and data is cleaned, or if the DSMB recommends unblinding.

If AEs occur and investigators are concerned about the treatment allocation, the treatment can be discontinued. If a Serious Adverse Event occurs, that is thought to be related to the study drug, and the treating clinician believes that knowledge of the treatment arm may change the therapy provided to the patient, the individual subject can be unblinded

6.4 STUDY INTERVENTION COMPLIANCE

During the inpatient phase of the study each dose of study product will be administered by a member of the clinical care team who is qualified and licensed to administer the study product. Administration, date, and time will be entered into the appropriate case report form (CRF).
If a patient is discharged prior to day 14, study drug supply will be given to the patient to be taken at home up until day 14, for a total of 28 doses. The participant compliance will be monitored by pill counts at the day 15 visit. If this visit takes place remotely via telehealth, the investigator will observe the research subject counting the remaining pills. The quantity of taken drug, date, and time will be entered into the appropriate case report form (CRF).

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and supplements used for the treatment of COVID-19.

For patients that are eligible for the study, other therapy received prior to enrollment with any other experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 or the SARS-CoV-2 infection not identified in the exclusion criteria are permitted but must be discontinued on enrollment.

In patients who have clinical deterioration while on fostamatinib any rescue or investigational therapy that a provider thinks may benefit a patient may be administered (e.g. tocilizumab and convalescent plasma). Administration of these drugs will be tracked via the CRF.

Venous thromboembolism (VTE) prophylaxis is recommended for all patients unless there is a major contraindication such as active bleeding events or history of heparin-induced thrombosis.

Concomitant medications will be assessed only from 7 days prior to enrollment through discharge. Report all prescription medications taken during this time period.

Do not report vitamins, herbal supplements, or topical medications. Do not report over-the-counter cold medicines and antipyretics that the subject reportedly took at home prior to hospitalization.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Study product administration for any given subject may be stopped for SAEs, clinically significant adverse events, severe laboratory abnormalities, or any other medical conditions that indicate to the Investigator that continued dosing is not in the best interest of the patient.

See section 6.1.2.3 for information on dosing modifications or discontinuation rules based on laboratory abnormalities or other adverse events.

Subjects who have the study product stopped for a safety related issues will not continue with dosing. In addition, subjects who have an allergic reaction that is temporally associated with study product administration and the PI believes it to be related to study product will not receive any more study product.

In addition, a subject in this clinical study may discontinue study drug at their request for any reason. Every effort should be made to encourage subjects to remain in the study for the duration of their planned outcome assessments. Subjects should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Unless the subject withdraws consent, those who discontinue study drug early will remain in the study. The reason for subject discontinuation of study drug should be documented in the CRF.

Discontinuation from the study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Date of last study drug administration
- Any adverse event
- Patients will be followed for clinical data required for the duration of the study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from study drug for the following reasons:

- Disease progression which requires discontinuation of the study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Positive pregnancy test
- Participant unable to receive study drug
- Lost to Follow Up

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

Subjects who withdraw from this study or are lost to follow-up after signing the informed consent form and administration of the study product, will not be replaced. The reason for subject withdrawal from the study will be recorded on the appropriate CRF.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken to maximize study subject retention and prevent missing data if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 days of the visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, the clinical team will try to ascertain vital status through vital record search; and the participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

8.1.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of SARS CoV-2 test results.

8.1.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent this study.

- Physical examination
- Pregnancy test (for female subjects of childbearing age)
- Clinical labs (CBC, liver enzymes panel, chemistry panel), if not available
- X-ray, if not available

The overall eligibility of the subject to receive the study drug will be assessed once all screening values are available and completion of an eligibility checklist.

8.2 EFFICACY ASSESSMENTS

For all baseline assessments and follow-up visits, refer to the Schedule of Assessments (SOA) for procedure to be done, and details below for each assessment.

Inpatient assesments will be done at the initial site of patient enrollment (NIH Clinical Center or Inova Health Systems.) After patient discharge, all outpatient assesments will be done at NIH Clinical Center either in person or remotely using NIH approved TeleMedicine software and approved NIH TeleMedicine guidance.

The subject's clinical status will be captured on each study day while hospitalized up until and including Day 60. If a subject is discharged prior to Day 15, clinical status is captured on Day 5,8,11, 15, 22, 29, and 60 if the subject returns for an in-person clinic visit or by phone or telehealth if an in-person visit is not possible. Clinical status will also be captured on Day 22 during a phone or telehealth visit. Clinical status is defined by secondary outcomes.

8.2.1 Clinical Evaluations

Physical examination: A baseline physical examination will be performed prior to initial study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. Post-baseline physical examinations will be done only when needed to evaluate possible adverse event(s) (i.e. any new signs or symptoms). No routine physical exam is needed for study visits after Day 1.

Radiographic or other imaging assessments. Chest x-ray are to be done at day 1 and repeated as clinically indicated.

8.2.2 Biospecimen Evaluations

Research bloods will be sent from Inova hospitals to the NIH for processing in either the clinical laboratory -or in a NHLBI research lab.

The amount of blood that may be drawn from subjects for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

Test/assay	**Volume blood (approx.)**	**Type of tube**	**Frequency******	**Location of specimen analysis**
Routine* • CBC • BMP • Hepatic	3 mL 4 mL	EDTA tube (lavender) Lithium Heparin tube (light green)	Baseline (prior to enrollment) D1-entire hospitalization, D15, D22, D29, D60 if outpatient	**Clinical Lab** **At participating sites**
Research* • PT • PTT • INR • Fibrinogen • D-dimer • Von Willebrand factor	3 ml x2	Sod Citrate (BLU) x2	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Clinical Lab**
Research* • P-selectin • Thrombomodulin	3 ml	Sod Citrate (BLU)	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Clinical Lab**
Research* • IL-6	3mL	EDTA (lavender)	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Clinical Lab**
Research* • Ferritin • CRP	4 mL	Lithium Heparin tube (light green)	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Clinical Lab**
Research (exploratory) • **Serum tube**	8 mL	Serum Separator Red top tube	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NHLBI Research lab (Childs)**

Research (exploratory) • **Plasma** • **PBMC**	2 mL 9 ml	Sod Citrate (BLU) Sodium Heparin Green top	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NHLBI Research lab (Childs)**
Research (exploratory) • **TEG****	3mL	Sodium Citrate	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Site and Clinical Lab only**
Research (exploratory) • **RNA*****	5mL	Paxgene	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NHLBI Research lab (Childs)**
Research (exploratory) • **Cell free DNA*****	5mL	Shreck tube	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NHLBI Research Lab (Agbor-Enoh)**
Research (exploratory) • **SARS-CoV-2 test********	OP swab	Oropharyngeal swab	D1, 3, 5, 8, 11, 15, 22, 29, 60	**NIH Clinical Center Lab**

*Residual bloods from clinical care can be transferred to the NHLBI research lab for storage.

**TEG (thromboelastography) to be performed at NIH site only.

***Only one of either RNA collections via Paxgene tubes or cell free DNA collection via Shreck tubes will be performed at the discretion of the principal investigator a decision that will be made for each individual patient.

****Day 1 labs should be drawn prior to first study drug administration.

***** SARS-CoV-2 testing done for research purposes. This test will not be used for diagnostic purposes..

In addition to the research blood requested above, we will request residual blood from clinical labs for research purposes, as available for research purposes.

8.2.3 Correlative Studies for Research Studies

As an exploratory endpoint, we will study the immune mechanism by which fostamatinib improves outcomes in patients with COVID-19.

1. Characterization of plasma biomarkers of immune activation
2. Measure platelet-leukocyte aggregates

3. Measure leukocyte activation assays
4. Measure plasma cytokine and chemokine levels
5. Evaluate the coagulation cascade
6. Measurement of immune antigen-antibody complexes
7. Measurement of thromboelastography (TEG)
8. Measure biomarkers of endothelial dysfunction
9. Characterize leukocyte extracellular traps
10. SARS-CoV-2 viability via cell culture from oropharyngeal samples
11. Detection of viral antigen blood and oropharyngeal samples

8.2.4 Samples for Genetic/Genomic Analysis

There are no genetic/genomic analyses planned on any of the samples. If a decision is made to perform DNA or RNA sequencing on any of the samples, the protocol will be amended with a GDSP and ICF updated to reflect this.

8.2.4.1 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

N/A

8.2.4.2 Management of Results

N/A

8.2.4.3 Genetic counseling

N/A

8.3 SAFETY AND OTHER ASSESSMENTS

Physical examination A targeted physical examination will be performed at baseline prior to initial study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. Post-baseline physical examinations will be done only when needed to evaluate possible adverse event(s) (i.e. any new signs or symptoms). No routine physical exam is needed for study visits after Day 1. Targeted physical exam constitutes assessment of vital signs, neurological, cardiac, and pulmonary exam.

Vital signs:

Vital signs will be done daily and include temperature, systolic blood pressure, heart rate, respiratory rate, and O2 saturation.

Radiographic or other imaging assessments:

Chest x-ray will be done on enrollment.

Assessment of adverse events:

Assessment of adverse events will be performed daily by the study team and as clinically indicated. Adverse events that have not resolved after completion of study drug administration will be followed until day 60.

Subjects with LFTS above 3x the ULN at enrollment will have LFTs checked daily during the hosplitalization phase of the study.

Subjects who are discharged on study drug will receive a daily phone call until day 15 to assess for adverse events and will have safety labs drawn as per the schedule safety labs schedule on days 3, 5, 8, 11, and 15 as applicable.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS.

8.4.1 Definition of Adverse Event

An advers event (AE) is any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related

(21 CFR 312.32 (a)).

8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

This study will utilize the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) for toxicity and adverse event reporting. A copy of the CTCAE v5.0 can be downloaded from the https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs will be recorded, verified, and followed until satisfactory resolution (return to baseline or, if event was not present prior to study drug initiation, grade 1 or lower).

Severity definitions found in the CTCAE v5.0 will be used for grading the severity (intensity) of AEs:

1) **Mild (Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2) **Moderate (Grade 2):** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*

3) **Severe (Grade 3):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4) **Life- threatening (Grade 4):** Life-threatening consequences; urgent intervention indicated.
5) **Death (Grade 5):** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator or designee who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or

underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.4.3.3 Expectedness

The site principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention in the package insert or investigator's brochure.

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

For this study, all grade 3 and 4 AE, clinically significant laboratory abnormalities, and all SAEs occurring from the time the informed consent is signed through the Day 60 visit will be documented, recorded, and reported in an NHLBI-approved research database. All other AEs will be collected in the subject's medical records.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All reportable AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened and until participant receives the first dose of study drug will be considered as baseline and not reported as an AE. AE occurrence will be assessed as any change from baseline in any medical condition that results in worsening in severity and/or frequency of the medical condition, whether or not considered related to study medication.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.4.5 Adverse Event Reporting

Information on AEs will be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a

clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

Disease related events are still being determined as COVID-19 is a new disease however we know that COVID-19 can lead to: (Berlin, Gulick & Martinez, 2020)

- Thromboembolism (Deep venous thrombosis, pulmonary emboli)
- Cardiac (myocarditis, cardiogenic shock, takotsubo cardiomyopathy)
- Renal (acute kidney injury, proteinuria)
- Neurological (ageusia, myalgia, anosmia, stroke, headache)
- Gastrointestinal (diarrhea, weight loss, anorexia)

Due to the overlap of expected GI symptoms in subjects receiving fostamatinib, GI symptoms are highly likely to have at least a possible attribution to the study drug.

8.4.6 Serious Adverse Event Reporting

The study investigator will report any SAE to the Data Coordinating Center (DCC)/study sponsor (NHLBI) no later than 72 hrs after the investigator becomes aware of the SAE, whether or not considered study-intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

SAEs from all sites will be reported to the IRB of record (NIH intramural IRB) in accordance with the Policy 801. The sites should report SAE locally in accordance with institutional requirements.

IND safety reports will be submitted to FDA by the IND sponsor in accordance with 21 CFR 312.

Data Coordinating Center (DCC)/study sponsor (NHLBI) will provide Rigel with copies of all IND Safety Reports concurrently with their submission to the FDA. The IND Safety Reports should be sent to the following email or fax:

Email: clinsafety@rigel.com
Fax: +1.650.745.0971

The site may contact Rigel Drug Safety at the above fax/e-mail with questions regarding reporting of SAEs.

Reports to the NHLBI Clinical Director

Data Coordinating Center (DCC)/study sponsor (NHLBI) will refer to NHLBI DIR Policy to determine Clinical Director reporting requirements and timelines.

Reports to the DSMB

The NHLBI Lung DSMB as the independent data safety monitoring commitee will review and approve the protocol before the enrollment. SAEs that meet the definition of an Unanticipated Problem will be submitted to the DSMB within 7 days of the investigator being notified of the event. DSMB will have access to safety data upon request any time. The monitoring plan will be developed and approved by the DSMB before enrollment. Additionally, the DSMB will be available for ad hoc reviews for AE/SAE, or safety concerns. The study will not stop enrollment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent stopping of enrollment based on their safety reviews.

8.4.7 Events of Special Interest

N/A

8.4.8 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the Sponsor on the appropriate CRF. Pregnancy should be followed to outcome.

8.5 UNANTICIPATED PROBLEMS

8.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

8.5.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

This study plans to enroll approximately 60 eligible subjects, randomized in a 1:1 ratio to fostamatinib or placebo.

The primary outcome of the study is cumulative incidence of SAEs through day 29. Because of data on safety of the fostamatinib in combination with standard of care is unavailable, the sample size is determined by the feasibility to assess the activity and safety of the study treatment in a diverse group of hospitalized adults. As background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety will be based on data from concurrently randomized subjects between fostamatinib and placebo arm. Randomization is essential to evaluate the safety and early efficacy of fostamatinib, which may lead to generalizable evidence of future confirmative studies.

9.2 POPULATIONS FOR ANALYSES

9.2.1 Evaluable for toxicity

All randomized patients will be evaluated for toxicity from the time of their first treatment with study drug.

9.2.2 Evaluable for primary analysis

All randomized patients who heave received any study drug or placebo will be included in the primary outcome analysis

9.3 STATISTICAL ANALYSES

9.3.1 General Approach

Descriptive statistics will be used to summarize baseline characteristics and severity of illness. For continuous measures, the mean (standard deviation) or median (interquartile range) will be presented. For categorical variables, the frequency and the percentage in each category will be presented. All randomized patients receiving any study drug or placebo on study will be included in the safety analysis.

9.3.2 Analysis of the Primary Endpoints

Primary endpoint analysis will include descriptive statistics on the incidence of serious adverse events by the study arm. The difference in the percentages of SAEs between the treatment arms will be assessed by Fisher's exact test.

9.3.3 Analysis of the Secondary Endpoint(s)

To determine a subject's clinical status using the ordinal scale: On Day 1, report their clinical status at enrollment (start of study drug). On Day 2, report the period from enrollment to midnight on Day 1. On Day 3 through Day 11, or until discharged, and on Days 15, 22 and 29, provide the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 –

23:59 (24-hr clock)). For example, on study Day 3 when completing the form, the worse clinical outcome measure of Day 2 is captured with the worst being death followed by ECMO, mechanical ventilation, etc. The Day 2 measurement is assessed as occurring anytime in that 24-hour period (00:00 to 23:59).

Secondary endpoints will be evaluated as follows:

1) The time to recovery by Day 29, it will be estimated by median and 95% confidence interval by study arm. The cumulative recovery rate will be estimated by the Kaplan-Meier method. The comparison between two treatment arms will be assessed by the log-rank test. The recovery ratio and hazard ratios will be based on the Cox model. The analysis will be stratified by disease severity at enrollment.

The time to recovery will be evaluate and censored up until Day 29. It is defined as the elapsed time in days from the day 1 to the earliest day at which a subject reaches recovery (having 1-3 of the 8-point ordinal scale). Any subjects that are lost to follow-up prior to an observed recovery will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience recovery will be censored at Day 29. All deaths within Day 29 (and prior to recovery) will be considered censored at Day 29. Analysis will be based on intention to treat including all randomized patients. Patients who have received at least four doses of study drug will be considered in a sensitivity analysis for this secondary outcome.

2) Duration of events (e.g., mechanical ventilation or days in the ICU) will be summarized with median and interquartile rage by the study arms and compared between the treatment arms by Wilcoxon's rank sum test or log-rank test.

3) Binary events (e.g., need for intubation) will be summarized as percentages and 95% confidence intervals by the study arms and compared between the treatment arms by Fisher's exact test.

4) Mortality rate and the time to event endpoints will be estimated by Kaplan-Meier method and 95% confidence intervals by study arm and compared between the treatment arms by log-rank test.

5) Longitudinal measurements of each biomarker variables will be plotted over time. The mean and percent change from baseline for each variable will be estimated and compared to study arm using appropriate parametric or nonparametric tests and regression modeling.

9.3.4 Safety Analyses

The planned analyses will also include descriptive statistics on the incidence and severity of adverse events. The proportions of serious adverse events (SAEs) will be summarized using sample proportions and confidence intervals for binomial distributions. Safety will be summarized using descriptive statistics to assess the difference between the two study arms. Summaries will be produced for all adverse events (AEs), related AEs (those considered by the Investigator as related to study treatment), SAEs, AEs leading to treatment discontinuation, and AEs Grade ≥3 in severity. Individual subject listings will be provided for any deaths, SAEs, AEs leading to interruption and AEs leading to treatment discontinuation for the fostamatinib arm compared to the placebo arm.

9.3.5 Baseline Descriptive Statistics

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

9.3.6 Planned Interim Analyses

Interim safety analysis will be performed as requested by the by the NHLBI appointed, independent DSMB. Stopping guidelines will be evaluated if excess deaths or SAEs occur in the fostamatinib arm compared to the placebo arm. The number of interim montoring looks and the stopping boundary based on the differences in the mortality rate and SAE between the two study arms will be developed and approved by the DSMB before the study enrollment. DCC will monitor the stopping boundary to alert DSMB if the stopping boundary is reached and have DSMB make further evaluation and recommendation about stopping the study due to safety reasons.

9.3.7 Sub-Group Analyses

The following subgroups analysis will be performed.

- Symptoms duration >10 and ≤10 days
- Baseline disease severity
- Race (White, Black, Asian)
- Age (18 to <40, 40 to <66, ≥65)
- Sex (male and female)
- Concomitant therapies (e.g. treatment with and without remedesivir, steroids (dexamethasone, prednisone, hydrocortisone, methylprednisolone), convalescent plasma, tocilizumab or other immunomodulators intended for the treatment of COVID-19
- Therapy with anti-coagulation by dose

9.3.8 Tabulation of individual Participant Data

Individual participant data may be listed by severity, measures received and time points in future study communications or publications.

9.3.9 Exploratory Analyses

Exploratory correlative analysis will be performed to study the longitudinal changes of biomarkers with time to recovery and treatment response, and the immune mechanism by which fostamatinib improves outcomes in patients with COVID-19.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 Consent Procedures and Documentation

Informed consent shall be documented using the current IRB-approved consent form. The investigational nature and objectives of this trial, the procedures and treatments involved, and

their attendant risks and discomforts and potential benefits will be carefully explained in person to the patient, and a signed informed consent document will be obtained by the PI or any person authorized to consent.

When consent is obtained, the consent document(s) must be signed and dated by the subject, and the person obtaining consent. Telephone or any institution-approved electronic consent process can be used.The original, signed informed consent document will be placed in the medical record, and the subject will receive a signed copy of the informed consent document. Documentation of informed consent and the signed consent form will be maintained per institution requirements.

10.1.2 Participation of Subjects who are/become Decisionally Impaired

Subjects unable to consent due to complications from COVID may be enrolled in this study at participating/enrolling sites. The process for determining capacity and obtaining legally effective consent will be determined by applicable regulations and local policies. At the NIH the PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to

participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NHLBI OCD. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NHLBI OCD.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 FUTURE USE OF STORED SPECIMENS AND DATA

We may share specimens and data with other researchers for future use.

Following analyses of biospecimens for primary research purposes as described in the protocol, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB approval. Biospecimens may be destroyed only when permitted by the clinical director and approved by the IRB. Any future research use of identifiable biospecimens not defined in the research protocol will occur only after IRB review and approval.

10.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including pulmonary and critical care medicine. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest.

The monitoring plan for interim safety and efficacy data will be developed and approved by DSMB before study enrollment. The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. If there is a pattern of unexpected AEs and safety concerns, the DSMB will be asked to review unblinded safety data in an ad hoc meeting. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input and recommendations to Dr. Richard Childs, who is the sponsor's authorized representative for the NHLBI Office of the Clinical Director

10.6 CLINICAL MONITORING

As per ICH-GCP 5.18 and FDA 21 CFR 312.5 clinical protocols are required to be adequately monitored by the study sponsor. The monitoring of this study will be conducted by Clinical Research Associates (CRAs)/Monitors employed by an independent contract organization working under an agreement with NHLBI to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent form (ICF) and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; UPs, and deviations, 3) to compare abstracted information with individual subjects' records and source documents (subject's charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol and with the appropriate regulations. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP) and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.
The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records) readily available for inspection by the local IRB, the site monitors, and the NHLBI staff for confirmation of the study data.

10.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.8 DATA HANDLING AND RECORD KEEPING

10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, or as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.9 PROTOCOL DEVIATIONS

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to Dr. Jeffrey Strich, and Dr. Richard Childs, Sponsor's authorized representative. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.10 PUBLICATION AND DATA SHARING POLICY

10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Dr. Richard Childs, who is the accountable investigator.

10.10.2 Genomic Data Sharing Plan

N/A

10.11 COLLABORATIVE AGREEMENTS

10.11.1 Agreement Type

A Clinical Research and Development Agreement (CRADA) between NHLBI and Rigel Pharmaceutics for the conduct of this study is being executed.

Transfers that are associated with correlative studies conducted under an approved protocol: Investigators in the NIH intramural program will participate in this multi-site clinical trials the coordinating center. Human materials will be transferred from external sites to the intramural program for correlative studies that are part of the approved protocol. The tests conducted under the correlative studies, and each institution participating in the clinical study are bound by the terms of their Protocol and their obligations under the statutes and regulations.

10.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be

required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

ACTT	Adaptive COVID Treatment Trials
AE	Adverse Event
ARDS	Acute respiratory distress syndrome
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRADA	Clinical Research and Development Agreement
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
NETs	Neutrophil Extracellular Traps
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NHLBI	National Heart, Lung, and Blood Institute
OCD	Office of the Clinical Director
OHRP	Office for Human Research Protections
PI	Principal Investigator
PRO	Patient Recruitment Office
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SYK	Spleen Tyrosine Kinase
UP	Unanticipated Problem

US	United States

12 REFERENCES

Al-Harbi, N., Nadeem, A., Ahmad, S., Alanazi, M., Aldossari, A., & Alasmari, F. (2019). Amelioration of sepsis-induced acute kidney injury through inhibition of inflammatory cytokines and oxidative stress in dendritic cells and neutrophils respectively in mice: Role of spleen tyrosine kinase signaling. *Biochimie*, *158*, 102-110. doi: 10.1016/j.biochi.2018.12.014

Alimova M. et al. A High Content Screen for Mucin-1-Reducing Compounds Identifies Fostamatinib as a Candidate for Rapid Repurposing for Acute Lung Injury during the COVID-19 pandemic (2020). Retrieved 22 July 2020, from https://www.biorxiv.org/content/10.1101/2020.06.30.180380v1.full.pdf

Beigel, J., Tomashek, K., Dodd, L., Mehta, A., Zingman, B., Kalil, A., et al. (2020). Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal Of Medicine*. doi: 10.1056/nejmc2022236

Berlin, D., Gulick, R., & Martinez, F. (2020). Severe Covid-19. *New England Journal Of Medicine*. doi: 10.1056/nejmcp2009575

Fostamatinib FDA label (2020). Retrieved 22 July 2020, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209299lbl.pdf

Hoepel, W., Chen, H., Allahverdiyeva, S., Manz, X., Aman, J., & Bonta, P. et al. (2020). Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. Retrieved 22 July 2020, from https://www.biorxiv.org/content/10.1101/2020.07.13.190140v1

Nadeem, A., Ahmad, S., Al-Harbi, N., Al-Harbi, M., Ibrahim, K., & Kundu, S. et al. (2019). Inhibition of spleen tyrosine kinase signaling protects against acute lung injury through blockade of NADPH oxidase and IL-17A in neutrophils and γδ T cells respectively in mice. *International Immunopharmacology*, *68*, 39-47. doi: 10.1016/j.intimp.2018.12.062

Rapkiewicz, A., Mai, X., Carsons, S., Pittaluga, S., Kleiner, D., & Berger, J. et al. (2020). Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *Eclinicalmedicine*, 100434. doi: 10.1016/j.eclinm.2020.100434

The RECOVERY Collaborative Group (2020). Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *New England Journal Of Medicine*. doi: 10.1056/nejmoa2021436

Weinblatt, M., Kavanaugh, A., Burgos-Vargas, R., Dikranian, A., Medrano-Ramirez, G., & Morales-Torres, J. et al. (2008). Treatment of rheumatoid arthritis with a syk kinase inhibitor: A twelve-week, randomized, placebo-controlled trial. *Arthritis & Rheumatism*, *58*(11), 3309-3318. doi: 10.1002/art.23992

World Health Organization 2020. WHO R&D Blueprint, novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Retrieved August 27, 2020, from https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis

Zhao, X., Chu, H., Wong, B., Chiu, M., Wang, D., & Li, C. et al. (2019). Activation of C-Type Lectin Receptor and (RIG)-I-Like Receptors Contributes to Proinflammatory Response in Middle East Respiratory Syndrome Coronavirus-Infected Macrophages. *The Journal Of Infectious Diseases*. doi: 10.1093/infdis/jiz483