Sirolimus Treatment in Hospitalized Patients With COVID-19 Pneumonia

NCT04341675

Study protocol, Statistical analysis plan and Informed consent

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MEDICAL IRB RESEARCH PROTOCOL

Protocol Synopsis

Title	Sirolimus treatment in hospitalized patients with COVID-19 pneumonia (The SCOPE Trial)
Rationale	In late 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in the city of Wuhan, China. This virus has now been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease has been named COVID-19. To date, COVID-19 has affected >1,000,000 individuals across 204 countries and led to ~50,000 deaths. United States currently has the world's highest number of affected individuals with COVID-19 in the world, with >200,000 cases and >5,000 fatalities. The disease spectrum from COVID-19 varies within individuals and can broadly be categorized into three subsets: 1) mild upper respiratory tract illness in ~80%, 2) severe pneumonia requiring hospitalization in ~15%, and 3) critical illness with multiorgan dysfunction in ~5% of the patients. The overall fatality rate from COVID-19 is estimated at ~2%. A number of different investigational agents have been prescribed to patients with COVID-19; these agents can broadly be classified into two subgroups: 1) drugs aimed at inhibiting the viral growth such as the antiviral agents remdesivir and lopinavir-ritonavir, and hydroxychloroquine (either alone or in combination with azithromycin) and 2) drugs such as the IL-6 inhibitor tocilizumab, that are aimed at dampening the cytokine storm that is prevalent in critically ill patients with COVID-19. However, there is no proven effective pharmacological therapy against COVID-19 and supportive care remains the cornerstone of management. Development of novel treatment options for COVID-19 is a critical public health need. A variety of laboratory parameters have emerged as prognostic biomarkers in patients with COVID-19 that can portend an increased propensity to progress towards acute respiratory distress syndrome (ARDS) and death. Key prognostic biomarkers reported thus far include elevated serum levels of ferritin, d-dimer, LDH, and lymphopenia. Lymphopenia has been observed in 60-80% of the hospitalized COVID-19 patients. Absolute lymphocyte count is inversely proportional to disease severity in patients with COVID-19 and patients with worse lymphopenia have increased risk of progression to ARDS and death. Lymphopenia was also seen in 50-80% of cases and predicted poor prognosis in patients with severe acute respiratory syndrome (SARS), a similar illness to COVID-19 that also assumed epidemic proportions and was caused by a related coronavirus, SARS-CoV. Analysis of blood and autopsy specimens from SARS patients revealed the presence of viral particles within circulating and tissue resident lymphocytes, thus implicating direct viral damage as the mechanism for the observed lymphopenia. T-lymphocytes have been demonstrated to play a crucial role in viral clearance in SARS, and play a key role in inhibiting the hyper-activation of innate immunity. A recent single cell transcriptome analysis performed on bronchoalveolar lavage fluid specimens obtained from six hospitalized individuals with COVID-19 revealed that patients with mild disease

	had a more robust CD8 T cell adaptive immune response compared to patients with severe disease. Sirolimus (rapamycin) is a macrolide produced by *Streptomyces hygroscopicus* that complexes with FKBP-12 and binds to and inhibits the mechanistic target of rapamycin (mTOR) pathway. Sirolimus is primarily used as an immunosuppressive agent to prevent rejection in organ transplant recipients. However, in contrast to its role as an immunosuppressive agent in the renal transplant population, sirolimus has been demonstrated to exert an immunostimulatory effect on CD8 T lymphocytes in response to viral infections. In addition, sirolimus has been shown to have an inhibitory effect on the replication of a variety of different viral pathogens, including a related coronavirus, MERS-CoV. In a single center trial, the addition of sirolimus to standard of care treatment resulted in faster viral clearance and improved oxygenation in critically ill patients with H1N1 influenza. Inhibiting the mTOR pathway has been shown to reduce mortality in a murine influenza model, upregulate antiviral gene expression, and boost the response to influenza vaccination in elderly patients. Lastly, a recently conducted pharmacology network analysis has suggested mTOR inhibition as a potentially useful strategy in patients infected with SARS-CoV-2.
Clinical Phase	II
Principal Investigator	Nishant Gupta, University of Cincinnati, Cincinnati OH
Participating Site(s)	University of Cincinnati - Cincinnati, OH
Accrual Objective	30 subjects
Study Objectives	The main objective of our study is to determine if treatment with sirolimus can improve clinical outcomes in hospitalized patients with COVID-19. Based on the results of this trial, additional phase III clinical development trials may be designed.
Study Design	Randomized, double blind, placebo-controlled study design
Dose and Duration of study drug	Sirolimus will be given as a 6mg oral loading dose on day 1 followed by 2mg daily for a maximum treatment duration of 14 days or until hospital discharge, whichever happens sooner.
Primary endpoint	Progression to respiratory failure requiring advanced support measures, either due to inadequate ventilation (non-invasive or invasive mechanical ventilation) or inadequate oxygenation (CPAP* or high flow supplemental oxygen at rates ≥ 15 liters/minute), in patients given sirolimus compared to the placebo group. * CPAP use for known obstructive sleep apnea will not be considered as disease progression.
Secondary endpoints	Key secondary endpoints: • Escalation in level of care • Increase in total lymphocyte count

	• Normalization of biomarkers (Ferritin, LDH, and d-dimer) • Survival to hospital discharge • Drug safety profile (Incidence and type of adverse and serious adverse events) Other outcomes measures: • Fever • Duration of advanced respiratory support • Duration of hospital stay (in survivors) • Time from treatment initiation to death (in non-survivors) • Need for initiation of other off-label rescue therapies such as Anti IL-6 agents, at the discretion of treating clinicians
Inclusion Criteria	Subjects enrolled in the trial must meet **all** of the following criteria. • Confirmed COVID-19 pneumonia • Hypoxia as defined by room air oxygen saturation less than 92% or supplemental oxygen requirement • Presence of at least one additional biomarker that has been shown to predict poor prognosis: a) serum ferritin ≥500ug/l, b) LDH ≥250U/L, c) d-dimer ≥1ug/L, or d) lymphopenia as defined by absolute lymphocyte count <1,000/uL • Age ≥ 18 years • Completed informed consent
Exclusion Criteria	Subjects who meet **ANY** of the following criteria are not eligible for enrollment as study participants: • Known allergy or hypersensitivity to sirolimus • Inability or refusal to provide informed consent • Advanced respiratory support (high flow oxygen ≥ 15 L/min, CPAP, non-invasive or invasive mechanical ventilation) • Active enrollment in other interventional clinical drug trials. Co-enrollment in observational studies and biorepositories is allowed. • Pregnant women • Breast feeding • On chronic immunosuppression for other medical conditions such as rheumatological disorders, inflammatory bowel disease, or in patients with organ transplants. A list of these medications is provided in Section 12.3.4 • Any clinically significant medical disease which in the opinion of the investigator precludes the patient from enrolling in the trial, including (but not limited to): o History of liver cirrhosis o End stage renal disease or need for renal replacement therapy o Decompensated heart failure o Known active tuberculosis or history of incompletely treated tuberculosis o Uncontrolled systemic bacterial or fungal infections o Active viral infection other than COVID-19

	○ Lymphoma or other systemic malignancies, either current or treated within the past 2 years. Localized non-melanoma skin cancer is not an exclusion.
Study Overview	The main objective of our study is to determine if treatment with sirolimus can improve clinical outcomes in hospitalized patients with COVID-19. We will employ a randomized, double blind, placebo-controlled study design. 30 subjects will be randomized in a 2:1 fashion to receive sirolimus or placebo. Sirolimus will be given as a 6mg oral loading dose on day 1 followed by 2mg daily for a maximum treatment duration of 14 days or until hospital discharge, whichever happens sooner. Chart reviews will be conducted daily to determine changes in clinical status, concomitant medications and laboratory parameters. Study specific biomarkers will be measured at baseline and then at days 3, 7 and 14.
Sample Size	In a study evaluating 201 hospitalized patients with COVID-19 in China, 82% (165 patients) required supplemental oxygen. Among the patients needing supplemental oxygen, 40% (67 patients) progressed to require advanced respiratory support during their hospital stay. Considering the fact that our study inclusion criteria mandates the need for supplemental oxygen and the presence of at least one additional poor prognostic biomarker, we anticipate that 50% of our control group will progress to require advanced respiratory support during their hospitalization. We expect that treatment with sirolimus will reduce the need for advanced respiratory support to 25%. The goal of this pilot study is to determine a meaningful treatment difference in order to conduct a larger confirmatory trial. Given the limited data on treatment responsiveness in COVID-19 populations, we examined various enrollment sizes commensurate with planning a pilot study. Specifically, we undertook a recommended approach for pilot studies in clinical research, which is to not perform hypothesis testing with a significance level set at the traditional value of 0.05. The confidence intervals for the treatment difference were calculated based on demonstrating a reduction in the proportion of subjects needing advanced respiratory support from 0.50 in the placebo group to 0.25 in the sirolimus group. Various levels have been proposed as optimal thresholds for the tolerance of type I error in the context of pilot studies, with the highest being p=0.25. We chose the type I error rate of 0.2 to denote significant treatment effect between the treatment and placebo arms in our study, as proposed by Stallard. A sample size of 30 patients randomized in a 2:1 fashion in favor of sirolimus will allow us to estimate the treatment differences with 80% confidence based on a binomial two-proportion test. A two-sided test will be used since we are unsure if the treatment will have a beneficial effect in this patient population.
Data Analysis	The primary endpoint of this study is progression to respiratory failure requiring advanced support measures. The difference in proportions of progression between the placebo and sirolimus groups and the 80% confidence interval will be calculated. If the confidence interval for the difference in proportions does not include zero, then we will conclude that the treatment difference is clinically meaningful. Considering the small sample size of our study, the significant impact of age and other pre-existing conditions such as diabetes mellitus on overall prognosis in patients with COVID-19 cannot be accounted for in the primary analysis. Patients will be randomized according to a computer-generated

	permuted block randomization stratified on age: <50 years, 50 - 64 years, and ≥65 years. In case recruitment lags we will add external study sites. In such a scenario, University of Cincinnati and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC will follow the same randomization scheme. In case of other external sites, randomization will be stratified based on site in addition to the above-mentioned age-based stratification. As exploratory analysis, we will conduct analyses examining differences based on other prognostic factors, and concomitant medication use, such as corticosteroids, hydroxychlororquine, azithromycin etc. An intent-to-treat analysis will be performed for the primary outcome.

Table of Contents

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2. Glossary of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CAPA	Corrective and Preventative Action
CBC	Complete blood count
CFR	Code of Federal Regulations
cGCP	Current good clinical practice
Cmax	Peak plasma concentration
COVID-19	Coronavirus disease-2019
CPAP	Continuous positive airway pressure
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IND	Investigational New Drug

IRB	Institutional Review Board
LAR	Legally authorized representative
LDH	Lactate dehydrogenase
MAR	Medication administration record
MERS	Middle East respiratory syndrome
mTOR	Mechanistic Target of Rapamycin
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protection
PPE	Personal protective equipment
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SUSAR	Suspected, Unexpected Adverse Reaction
Tmax	Median time to achieve peak plasma concentration
UC	University of Cincinnati
WBC	White blood cell

3. Background and Rationale

3.1 Background:

In late 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in the city of Wuhan, China. This virus has now been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease has been named COVID-19. To date, COVID-19 has affected >1,000,000 individuals across 204 countries and led to ~50,000 deaths. United States currently has the world's highest number of affected individuals with COVID-19 in the world, with >200,000 cases and >5,000 fatalities.[1] The disease spectrum from COVID-19 is variable and can broadly be categorized into three subsets: 1) mild illness in ~80%, 2) severe pneumonia requiring hospitalization in ~15%, and 3) critical illness with multiorgan dysfunction in ~5% of the patients. The overall fatality rate from COVID-19 is estimated at ~2%.[2] A number of different investigational agents have been prescribed to patients with COVID-19; these agents can broadly be classified into two subgroups: 1) drugs aimed at inhibiting the viral growth such as the antiviral agents remdesivir[3] and lopinavir-ritonavir[4], and hydroxychloroquine (either alone or in combination with azithromycin)[5] and 2) drugs such as the IL-6 inhibitor tocilizumab,[6] that are aimed at dampening the cytokine storm that is prevalent in critically ill patients with COVID-19. However, there is no proven effective pharmacological therapy against COVID-19 and development of novel treatment options for COVID-19 is a critical public health need.

3.2 Lymphopenia and other poor prognostic biomarkers in COVID-19

A variety of laboratory parameters have emerged as prognostic biomarkers in patients with COVID-19 that can portend an increased propensity to progress towards acute respiratory distress syndrome (ARDS) and death. Key prognostic biomarkers reported thus far include elevated serum levels of ferritin, d-dimer, LDH, and lymphopenia.[7,8] Lymphopenia has been observed in 60-80% of the hospitalized COVID-19 patients.[8-11] Absolute lymphocyte count is inversely proportional to disease severity in patients with COVID-19 and patients with worse lymphopenia have increased risk of progression to ARDS and death.[7,8]

3.3 T lymphocytes play a critical role in viral clearance in patients with SARS as well as COVID-19

Lymphopenia was also seen in 50-80% of cases and predicted poor prognosis in patients with severe acute respiratory syndrome (SARS),[12,13] a similar illness to COVID-19 that also assumed epidemic proportions and was caused by a related coronavirus, SARS-CoV. Analysis of blood and autopsy specimens from SARS patients revealed the presence of viral particles within circulating and tissue resident lymphocytes, thus implicating direct viral damage as the mechanism for the observed lymphopenia.[14] T-lymphocytes have been demonstrated to play a crucial role in viral clearance in SARS,[15] and play a key role in inhibiting the hyper-activation of innate immunity.[16] A recent single cell transcriptome analysis performed on bronchoalveolar lavage fluid specimens obtained from six hospitalized individuals with COVID-19 revealed that

patients with mild disease had a more robust CD8 T cell adaptive immune response compared to patients with severe disease.[17]

3.4 Sirolimus is effective against a variety of viral pathogens including influenza as well as related coronaviruses

Sirolimus is a macrolide produced by *Streptomyces hygroscopicus* that complexes with FKBP-12 and inhibits the mechanistic target of rapamycin (mTOR) pathway. Sirolimus is primarily used as an immunosuppressive agent to prevent rejection in organ transplant recipients.[18] However, in contrast to its role as an immunosuppressive agent in the renal transplant population, sirolimus has been demonstrated to exert an immunostimulatory effect on CD8 T lymphocytes in response to viral infections.[19] In addition, sirolimus has been shown to have an inhibitory effect on replication of a variety of viral pathogens, including a related coronavirus, MERS-CoV.[20-23] In a single center trial, the addition of sirolimus to standard of care resulted in faster viral clearance and improved oxygenation in critically ill patients with H1N1 influenza.[24] Inhibiting the mTOR pathway has been shown to reduce mortality in a murine influenza model,[25] upregulate antiviral gene expression, and boost the response to influenza vaccination in elderly patients.[26] Lastly, a recently conducted network analysis has suggested mTOR inhibition as a potentially useful strategy in patients infected with SARS-CoV-2.[27]

3.5 Rationale for the proposed study

Improved understanding of the role of host immune response to SARS-CoV-2 infection and development of novel treatment options for COVID-19 are critical unmet public health needs. By harnessing the similarities between SARS-CoV-2 and SARS-CoV, and utilizing the insights gained from SARS, we believe that the key to successful recovery from COVID-19 lies in targeted stimulation of the host adaptive immune response. The mTOR inhibitor, sirolimus, has been shown to exert an immunostimulatory effect on CD8 lymphocytes in response to a variety of different viral pathogens, including a related novel coronavirus, MERS-CoV. We postulate that impaired T cell responsiveness is a key driver in the pathogenesis of severe COVID-19 and that treatment with sirolimus can enhance the virus-specific T cell response leading to effective viral clearance and improved clinical outcomes in patients with COVID-19. Sirolimus also inhibits viral replication by limiting cellular proliferation and progression through the cell cycle. Successful completion of our aims will lead to improved understanding of the role of adaptive immune response in mitigating COVID-19 pathology, and pave the way for the development of a novel treatment option for patients with COVID-19.

4. Study Objectives and Endpoints

4.1 Main Study Objective

The main objective of our study is to determine if treatment with sirolimus can improve clinical outcomes in hospitalized patients with COVID-19.

4.2 Primary Endpoint:

Progression to respiratory failure requiring advanced support measures, either due to inadequate ventilation (non-invasive or invasive mechanical ventilation) or inadequate oxygenation (CPAP* or high flow supplemental oxygen at rates ≥ 15 liters/minute), in patients given sirolimus compared to the placebo group.

4.3 Secondary Endpoints:

Key secondary endpoints:

- Escalation in level of care
- Increase in total lymphocyte count
- Normalization of biomarkers (Ferritin, LDH, and d-dimer)
- Survival to hospital discharge
- Drug safety profile (Incidence and type of adverse and serious adverse events)

Other outcomes measures:

- Fever
- Duration of advanced respiratory support
- Duration of hospital stay (in survivors)
- Time from treatment initiation to death (in non-survivors)
- Need for initiation of other off-label rescue therapies such as Anti IL-6 agents, at the discretion of treating clinicians

* CPAP use for known obstructive sleep apnea will not be considered as disease progression.

5. Study Design

We will employ a randomized, double blind, placebo-controlled study design. 30 patients hospitalized with COVID-19 and meeting the inclusion criteria specified below will be randomized to receive sirolimus or placebo in a 2:1 manner. The treatment regimen and duration are provided in Sections 5.5 and 5.6.

5.1 Identification and Screening

Patients will be identified by the medical staff that cares for patients with COVID-19 at the University of Cincinnati Medical Center and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC. In addition, the study staff will actively screen for potential subjects by chart reviews of the patients admitted on the COVID units and based on automated alerts generated on patients under investigation for COVID-19. Identification and screening will take place until 30 evaluable patients have been enrolled, or the incidence of new cases does not permit further enrollment. Potentially eligible patients will be approached by the study investigators, and then by study staff. In order to limit staff exposure to patients with COVID-19 as well as to protect critical personal protective equipment (PPE), study investigators will communicate with potential subjects remotely via telephone rather than in-person visits, as much as possible. Potential patients will be informed about the study, and following completion of the informed consent process, a screening evaluation will be performed. The patient will provide informed consent before any study procedures are performed. Patients who learn of the study from the study listing on ClinicalTrials.gov or from any other source will also be able to be screened for enrollment.

5.2 Inclusion Criteria

Subjects enrolled in the trial must meet **all** of the following criteria.

- Confirmed COVID-19 pneumonia
- Hypoxia as defined by room air oxygen saturation less than 92% or supplemental oxygen requirement
- Presence of at least one additional biomarker that has been shown to predict poor prognosis: a) serum ferritin ≥500ug/l, b) LDH ≥250U/L, c) d-dimer ≥1ug/L, or d) lymphopenia as defined by absolute lymphocyte count <1,000/uL
- Age ≥ 18 years
- Completed informed consent

5.3 Exclusion Criteria

Subjects who meet **any** of the following criteria are not eligible for enrollment as study participants:

- Known allergy or hypersensitivity to sirolimus
- Inability or refusal to provide informed consent

- Advanced respiratory support (high flow oxygen ≥ 15 L/min, CPAP, non-invasive or invasive mechanical ventilation). CPAP use for treatment of obstructive sleep apnea is not an exclusionary criterion.
- Active enrollment in other interventional clinical drug trials. Co-enrollment in observational studies and biorepositories is allowed.
- On chronic immunosuppression for other medical conditions such as rheumatological disorders, inflammatory bowel disease, or in patients with organ transplants. A list of prohibited medications is provided in Section 12.3.4.
- Pregnant women
- Breast feeding
- Any clinically significant medical disease which in the opinion of the investigator precludes the patient from enrolling in the trial, including (but not limited to):
    - History of liver cirrhosis
    - End stage renal disease or need for renal replacement therapy
    - Decompensated heart failure
    - Known active tuberculosis or history of incompletely treated tuberculosis
    - Uncontrolled systemic bacterial or fungal infections
    - Active viral infection other than COVID-19
    - Lymphoma or other systemic malignancies, either current or treated within the past 2 years. Localized non-melanoma skin cancer is not an exclusion.

5.4 Recruitment

After IRB and DSMB approval has been obtained, the screening and identification for subjects will be performed as described in Section 5.1. Interested individuals will be provided with detailed study information and the informed consent form (ICF). After they have had a chance to review the study procedures and the ICF, and after ensuring that all questions are answered, patients can be enrolled into the study. Details of the informed consent process are provided in Section 6.3.

5.5 Study Drug Treatment

Patients who meet eligibility criteria, provide informed consent and are enrolled in the study will be randomized to receive sirolimus or placebo in a double-blind manner and a 2:1 randomization scheme in favor of sirolimus. The sirolimus dose for the study will be 6mg daily on day 1 followed by 2mg daily for a maximum treatment duration of 14 days, or until hospital discharge, whatever happens first. The study drug will be provided by the drug manufacturer, Pfizer, encapsulated and dispensed by the University of Cincinnati's Investigational Drug Services (IDS) Pharmacy, and given to the patients by their bedside nurse. Patients will be reminded about the side effects of sirolimus. Every attempt will be made to give the medication at the same time every day. Chart reviews will be conducted on a daily basis to determine changes in clinical status, concomitant medications and laboratory parameters. Study specific biomarkers will be measured at baseline and then at days 3, 7 and 14. Section 6.2 provides a detailed description of the study specific schedule of events. Patients will be instructed to

contact the study staff should they experience any side effects. Study drug may be held or reduced in the event of unacceptable side effects.

5.6 Treatment Regimen

Patients will be randomized to either a 6mg oral loading dose of sirolimus followed by 2mg daily for a maximum treatment duration of 14 days, or matching placebo. We have chosen this dosing strategy to mirror the typical regimen in patients who start sirolimus following a kidney transplant, in order to ensure rapid therapeutic mTOR inhibition in these patients. The 2mg daily dose is also consistent with the Chinese randomized clinical trial that showed a clinically useful beneficial effect of sirolimus in critically patients with H1N1 influenza.[24]

6. Study Procedures and Timelines

6.1 Study and Timeline Overview

Patients will be identified by the medical and research staff at the University of Cincinnati Medical Center and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC. Recruitment will take place until 30 evaluable patients have been enrolled, or the incidence of new cases does not permit further enrollment. Patients who meet eligibility criteria, provide informed consent and are enrolled in the study will receive instructions regarding study drug dosage, route and administration. The study drug will be given each morning along with other inpatient medications at roughly the same time every day. Patients will be on the study drug for a maximum duration of 14 days, or until hospital discharge, whatever happens first. In case a patient progresses to require advanced respiratory support, the study drug can continue as scheduled at the discretion of the treating clinician(s). If deemed clinically necessary on a case-by-case basis, in these scenarios the patient may need to be withdrawn ± unblinded.

All study procedures will take place after obtaining informed consent. Details of the informed consent process are provided in Section 6.3. Prior to starting study drug, baseline demographic and clinical variables will be collected along with vital signs, amount of supplemental oxygen required, laboratory biomarkers such as absolute lymphocyte count, ferritin, LDH, and d-dimer, renal and liver function tests, concomitant medications, past medical history, and results of the chest imaging. After study initiation, chart reviews will be conducted on a daily basis to assess vital signs, changes to concomitant medications, lab values, and oxygenation indices. Study-specific biomarkers: absolute lymphocyte count, serum ferritin, d-dimer and LDH will be measured at Day 3, 7 and 14 following study initiation, unless already checked clinically in the 24 hours prior to the testing time.

6.2 Schedule of Events

Event	Screening[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14[6]	F/u[7]
Informed consent	X															
Demographics	X															
Medical history	X															
Determine study eligibility	X															
Con meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review AEs				X				X							X	
Heart rate/pulse[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MAP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Highest daily temperature (F)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oxygen saturation[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FiO_2 (%) [2, 3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[4]	X															
LDH[5]	X			X				X							X	
Ferritin[5]	X			X				X							X	
D-dimer[5]	X			X				X							X	
Absolute lymphocytes[5]	X			X				X							X	
CBC (WBCs, Hb, Platelets)[5]	X			X				X							X	
Serum creatinine[5]	X			X				X							X	
AST, ALT[5]	X			X				X							X	
Advanced resp. support (Y/N)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening visit can be the initial visit if a patient meets all inclusion/exclusion criteria

[2] Mean recorded value for the 24-hour duration of that day

[3] FiO_2 (%) will be recorded if directly available from chart review such as in patients on ultra-high flow devices (vapotherm, optiflow etc.) or in patients on advanced respiratory support. For all other patients, FiO_2 (%) will be calculated based on the following conversion:

Supplemental O_2 (l/min)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
FiO_2 (%)	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63

[4] Only required for women of childbearing potential, if not already obtained clinically

[5] No need to recheck if already drawn clinically in the 24 hours prior to the study-specified time. If not checked clinically, these can be measured as research tests. If COVID-19 biorepository sample obtained on the day of these tests, they can be postponed to the next day.

[6] In case a patient is discharged from the hospital before the 14-day period, their last hospital day will be treated similar to Day 14 with regards to study assessments

[7] Long term outcomes following the 14-day study period will be assessed by chart reviews
Abbreviations: AE = adverse event, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, CBC = complete blood count, F = degrees Fahrenheit, FiO_2 = Fraction of inspired oxygen, Hb = Hemoglobin, LDH = Lactate dehydrogenase, MAP = Mean arterial pressure, WBCs = White blood cells

6.3 Study Visits

Screening/Initial Visit
All study procedures will begin only after the subject has completed the informed consent process.

Informed consent process for this study: Potential study patients will be contacted by the study staff to determine interest in study participation. Interested individuals will be provided with detailed study information and a copy of the ICF. Patients will be given ample time to read and discuss the ICF with the study staff. The study staff will then answer any remaining questions asked by the patients. The patients will be offered the option of signing the consent form. Those who agree to participate will undergo the remainder of study procedures. In order to prevent transmission of COVID-19 from ICFs that have been in physical contact with the patients (e.g. during the act of obtaining signatures), we will obtain consent by following either the quarantine consent process or the telephone consent process, as detailed below.

Quarantine Consent

- The subject (or their legally authorized representative (LAR)) will be provided with a copy of the ICF to keep at the bedside during the quarantine period.
- The informed consent discussion will be presented to the subject (or their LAR) by an authorized study representative (investigator/coordinator) who is sufficiently knowledgeable about the research to properly interpret and correctly answer questions.
- A witness who is not a member of the study team will be present for the informed consent discussion.
- We will identify all participants and their role in the study (e.g. study staff, patient, next of kin, LAR, impartial witness etc.).
- We will review the ICF in a comprehensive manner with the patient (or their LAR), solicit and answer all questions.
- The subject (or their LAR), study team member obtaining informed consent, and the witness will sign the subject's (or their LAR's) copy of the ICF. The subject will keep the original ICF for their records.
- Immediately after the informed consent discussion, the investigator and witness will document their signatures on a separate ICF outside of isolation/quarantined areas. We will document "Quarantine consent obtained" in the subject's (or their LAR's) signature line.

Telephone Consent

The following stepwise process will be followed in order to obtain telephone consent from interested subjects prior to study enrollment.

- A copy of the ICF will be provided to the subject (or their LAR) to review over the phone.

- The informed consent discussion will be presented to the subject (or their LAR) by an authorized study representative (investigator/coordinator) who is sufficiently knowledgeable about the research to properly interpret and correctly answer questions.
- A witness who is not a member of the study team will be present for the informed consent discussion with the investigator/study coordinator.
- We will begin the call by identifying all participants on the call and their role in the study (e.g. study staff, patient, next of kin, LAR, impartial witness etc.)
- Next, we will review the ICF in a comprehensive manner with the patient (or their LAR), solicit and answer all questions.
- We will obtain verbal confirmation from the witness that the subject's questions have been answered.
- Obtain verbal confirmation from the subject (or their LAR) regarding their agreement to participate in the study, and that they have signed the ICF in their possession while the witness is still on the telephone.
- Obtain verbal confirmation from the study staff member that the subject has agreed to participate in the study and sign the ICF while the witness is still on the telephone.
- The investigator and witness will sign the ICF and document "telephone consent obtained" in the subject's (or their LAR's) signature line.

Script for telephone consent

1. Hello, my name is _____. I am calling from the University of Cincinnati regarding a research study for COVID-19. We are conducting a study to assess if an already approved medication called sirolimus can help patients hospitalized with COVID-19. I'd like to ask your permission to tell you about the study.

If the patient and/or LAR is agreeable, proceed with the following: I would like to provide you with a copy of the informed consent form for you to keep and arrange a time that I can call you back to answer any questions you may have. It is important that you have time to read the consent form and have it with you when we talk about the study.

2. Hello, this is _____ calling back about the COVID-19 study at the University of Cincinnati. Is this a good time? Also present on this phone call is _____, who will act as a witness to our conversation and be present throughout the phone call. Do we have your permission to proceed?

If the patient agrees, we will confirm that the patient has access to a copy of the ICF with them and proceed with the steps outlined above. Prior to obtaining signatures, we will explicitly solicit any questions from the subject and ensure that all questions have been answered to their satisfaction.

After obtaining informed consent, we will review the inclusion/exclusion criteria to determine study eligibility. For patients who provide informed consent and meet all eligibility criteria, the screening visit can be their initial study visit. We anticipate that in most patients the

screening visit will be the initial study visit, and the following additional steps will be completed during the visit:

- Review medical history
- Record current medications
- Record vital signs: heart rate, blood pressure, temperature as specified in Section 6.2
- Record baseline oxygenation indices: oxygen saturation and FiO_2 as specified in Section 6.2
- For women of childbearing potential, obtain a urine pregnancy test, if not already obtained during the hospitalization
- If not already obtained clinically in the previous 24 hours, then obtain measurements for study specific biomarkers: LDH, ferritin, d-dimer, and absolute lymphocyte count
- If not already obtained clinically in the previous 24 hours, then obtain other laboratory parameters: CBC (total WBCs, Hb, Platelets), serum creatinine, AST, and ALT

Subsequent visits

Subjects' medical chart will be reviewed on a daily basis after study enrollment. The following parameters will be obtained on a daily basis from chart review:

- Vital signs: heart rate, blood pressure, temperature as specified in Section 6.2
- Oxygenation indices: oxygen saturation and FiO_2 as specified in Section 6.2
- Concomitant medications
- Advanced respiratory support use status
- Vital status

In addition, the following activities will be performed on days 3, 7 and 14 of the study

- If not already obtained clinically in the previous 24 hours, then obtain measurements for study specific biomarkers: LDH, ferritin, d-dimer, and absolute lymphocyte count. If COVID-19 biorepository sample obtained on the day of these tests, they can be postponed to the next day.
- If not already obtained clinically in the previous 24 hours, then obtain other laboratory parameters: CBC (total WBCs, Hb, Platelets), serum creatinine, AST, and ALT
- Query the patient with regards to any adverse effects from the study medication. This can be done remotely via telephone interview rather than in-person visit in order to minimize study staff exposure as well as preserve PPE

In case a subject is discharged from the hospital before Day 14, every effort will be made to complete the day 14 activities on the day of hospital discharge. In case the duration of hospitalization extends beyond the study duration of 14 days, we will periodically monitor the electronic medical record and record key variables such as the need for advanced respiratory support, duration of hospitalization, duration of ICU status, time spent on mechanical ventilation, and vital status.

6.4 Enrollment

Enrollment in the study will continue until the enrollment target of 30 patients is reached. This research study will be explained in lay terms to each potential research participant. The potential participant will sign an ICF before undergoing any screening study procedures. Participants who are deemed eligible for the study (see Section 6.3) will be enrolled and assigned a unique participant ID number.

6.5 Consent for future contact

During the consent process, patients will have the option to provide permission for future contact. This permission allows for patient contact information, including their full name, address and telephone number, to be retained. The permission for future contact allows for possible patient re-contact regarding future IRB-approved studies. If the patient denies permission, no future contact will be made.

6.6 Consent for continuing data review of medical records

During the consent process, patients will have the option to provide permission for future data review of their medical records. This permission allows for study staff to contact the patient (or the patient's caregiver(s)) to obtain medical records and other information for a period of up to two years after the patient has withdrawn from or completed the study. The purpose of this data review is to capture information including but not limited to clinical, radiographic, pathologic, laboratory and pulmonary function data, after the patient has exited the study. The rationale for future data review is that there may be long term effects of COVID-19 or the study drug, that are unknown to the investigators at this time.

7. Stopping rules

7.1 Participant withdrawal criteria

Participants may be terminated early from the study for the following reasons:

a. The participant elects to withdraw consent from study activities.

b. The participant dies.

c. The participant has a serious allergic or anaphylactic reaction to the study drug

c. The participant's condition deteriorates significantly necessitating either a transfer to the intensive care unit (ICU) or the need for advanced respiratory support (high flow oxygen ≥ 15 L/minute, CPAP, non-invasive or invasive mechanical ventilation), and the treating clinician thinks it is in the best interest of the patient to be withdrawn ± unblinded. If the patient is unblinded, any open label use of sirolimus after that will be based on clinical grounds at the discretion of the treating clinician(s). The study drug (sirolimus or placebo) will continue for the maximum stipulated duration of 14 days regardless of escalation in care, unless the patient is withdrawn from the study.

d. The participant develops a medical condition or is started on new medication(s) not previously mentioned in the list of prohibited medications that, in the opinion of the investigator, may pose additional risks from participation in the study, or that may impact the quality of the data obtained from the study.

e. In the opinion of the investigator, it is not in the participant's best medical interest to continue to participate in the study.

7.2 Criteria for terminating the study

Up to 30 patients will be enrolled in this study. The maximum duration of patient participation is 14 days. In the event of any death or Grade IV Serious adverse event (SAE) that is unexpected and attributable to the study agent, enrollment will be suspended, pending Data Safety Monitoring Board (DSMB) review.

8. Study variables and measuring methods

8.1 Vital signs

We will abstract the following vital signs from electronic health record review of study subjects daily throughout the study duration: heart rate, blood pressure, and temperature.

Heart rate: The average (mean) heart rate in the 24-hour time frame corresponding to a calendar date will be recorded as that day's heart rate.

Blood pressure: The average (mean) Mean arterial blood pressure (MAP) in the 24-hour time frame corresponding to a calendar date will be recorded as that day's blood pressure. We anticipate MAP to be available in all subjects' medical charts. However, in case MAP is not recorded then we will calculate it based on this formula:

MAP = [2 x (diastolic blood pressure) + 1 x (systolic blood pressure)]/3

Temperature: The highest temperature (in degrees Fahrenheit) in the 24-hour time frame corresponding to a calendar date will be recorded as that day's temperature.

8.2 Oxygenation indices

We will abstract the following oxygenation indices from electronic health record review of study subjects daily throughout the study duration: peripheral blood oxygen saturation and fraction of inspired oxygen (FiO_2).

Oxygen saturation: The average (mean) oxygen saturation in the 24-hour time frame corresponding to a calendar date will be recorded as that day's oxygen saturation.

FiO_2: FiO_2 (%) will be recorded if directly available from chart review such as in patients on ultra-high flow devices (e.g. vapotherm, optiflow etc.) or in patients on advanced respiratory support. For all other patients, FiO_2 (%) will be calculated based on the following conversion table provided below and also in Section 6.2. The average (mean) FiO_2 in the 24-hour time frame corresponding to a calendar date will be recorded as that day's FiO_2.

Supplemental O_2 (l/min)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
FiO_2 (%)	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63

Table: FiO_2 conversion based on supplemental oxygen needs

8.3 Laboratory parameters

The following laboratory parameters will be obtained for our study: CBC (total WBCs, Hb, Platelets), absolute lymphocyte count, AST, ALT, serum creatinine, LDH, ferritin and d-dimer. These labs will be obtained at baseline (within 24 hours of study drug initiation) and at days 3, 7 and 14. In case these labs were drawn in the 24 hours prior to the study stipulated time on

clinical grounds, then we will use those values for the study. If not drawn clinically in the preceding 24 hours, then we will obtain these values as research tests. If COVID-19 biorepository sample obtained on the day of these tests, they can be postponed to the next day. In case a subject is discharged from the hospital prior to the 14-day period or is withdrawn from the study, we will make all efforts to father the Day 14 assessments on that day.

8.4 Urine pregnancy test

For women of childbearing potential, we will obtain a urine pregnancy test, if not already obtained during the hospitalization prior to study enrollment.

8.5 Other study parameters

Daily chart reviews will be performed to record other variables of interest:

Need for advanced respiratory support: Recorded as Yes/No and type, whether high flow oxygen ≥ 15 liters/minute, CPAP, non-invasive, or invasive mechanical ventilation. If a patient receives more than one form of advanced respiratory support in the same day, (e.g. started on non-invasive and worsens to require invasive ventilation, or extubated from invasive to non-invasive ventilation), we will designate the most advanced form of ventilation (in the above scenarios – mechanical ventilation) for that day. The ranking order for the above modes of respiratory support are (from most advanced to least advanced means): 1. Mechanical ventilation, 2. Non-invasive ventilation (e.g. bilevel), 3. CPAP, 4. High flow supplemental oxygen ≥ 15 L/minute. Of note, the use of CPAP employed to treat pre-existing obstructive sleep apnea will not count as advanced respiratory support.

Duration of advanced respiratory support: For patients who progress to require advanced respiratory support, the type(s) of support and the time spent on the support (individual modes as well as cumulative, days) will be recorded.

Vital status: The vital status (alive/deceased) will be recorded at study termination as well as at the time of hospital discharge (in case that happens after the 14-day study period). For non-survivors, the time from study initiation to death will also be recorded.

Duration of hospital stay (days): will be recorded starting from the day of admission to the day of hospital discharge. This parameter will only be used for analysis in patients who survive the hospital stay.

9. Risks

9.1 Risks of the investigational product

In general, sirolimus is a well-tolerated drug. The most common side effects attributable to sirolimus in clinical trials include stomatitis, diarrhea, abdominal pain, peripheral edema, hypertriglyceridemia, hypercholesterolemia, acneiform rash, headaches and myalgias.[28,29] Other less common but reported AEs from sirolimus include allergic reactions to the drug including angioedema, proteinuria, increased serum creatinine, impaired would healing, interstitial pneumonitis, and increased risk of secondary infections and malignancies such as skin cancer and lymphomas.[28] Key AEs attributable to sirolimus are summarized in the table below. It is worth mentioning that a large proportion of these AEs are derived from studies in renal transplant patients where patients are taking multiple immunosuppressive medications at the same time, and it is not clear if these AEs can be attributable to the use of sirolimus as a single agent.

Adverse reaction	**Approximate Incidence (%)**
Gastrointestinal disorders	
Nausea	25 - 35
Vomiting	20 - 25
Diarrhea	25 – 40
Constipation	25 – 35
Dyspepsia	15 - 25
Nervous system disorders	
Headache	20 - 30
Cardiovascular disorders	
Peripheral edema	50
Hypertension	40
Deep venous thrombosis	10
Pericarditis	2
Musculoskeletal disorders	
Myalgias and arthralgias	10 - 15
Skin and subcutaneous tissue disorders	
Skin rash	10 - 20
Acne	20 - 25
Mucositis/stomatitis	40 - 50
Hematologic disorders	
Anemia	20 - 30
Thrombocytopenia	15 - 30
Lipid abnormalities	
Hypertriglyceridemia	40 - 50
Hypercholesterolemia	40 - 50
Pulmonary disorders	
Pneumonitis	1 - 2
Malignant complications	
Lymphoma	1 - 3
Renal disorders	
Increased serum creatinine	30
Proteinuria	5

Infectious complications	
Herpes simplex and other viral infections	8 - 10
Urinary tract infection	20 – 30
Other AEs	
Delayed wound healing	20 - 25

Table: Key adverse reactions associated with the use of sirolimus. This is not an exhaustive list. Percentages for the incidence of a particular adverse event are derived from the FDA label and from a review of multiple clinical trials evaluating adverse effects from sirolimus.[18,28-32]

The vast majority of the common side effects (e.g. hyperlipidemia, increased risk of malignancies) are of concern with prolonged/long-term use of sirolimus. Since our study duration is limited to 14 days, these measurements may not be of significant concern. Side effects of particular interest given the nature of this study will be incidence of secondary infections and other organ system toxicities (pneumonitis, increased serum creatinine, decreased blood counts). We will carefully monitor for all laboratory abnormalities at baseline and on days 3, 7, and 14. We will also enquire about any possible AEs from the patients at days 1, 3, 7, and 14.

9.2 Risks of study procedures

Blood draws: The risks of blood draws include bleeding, bruising, discomfort, fainting and lightheadedness infection or pain at the needle site. All research personnel and hospital staff drawing blood are trained in the procedure and are familiar with proper infection control protocol. We anticipate that most of the assessments needed as part of the study will already be obtained on clinical grounds and that the need for additional blood draws specific for this research study will be minimal.

9.3 Adequacy of protection against risks

Each participant in this study will be informed of the intent of the study and asked to sign an IRB approved informed consent form. The consent form will fully describe the procedures, risks, alternatives, and potential benefits of the study. Consent will be obtained from eligible participants by a physician investigator or by the study research coordinator. The participants will be given the opportunity to refuse to participate in the study, under the assurance that such refusal will in no way affect their regular treatment. All questions asked by study subject will be answered to the best of the knowledge of the investigator and the study staff. Time will be given for the patient to read the consent form and ask questions prior to performing any study procedures. A copy of the signed and dated consent form will be given to subject. Details of the informed consent process for this study are provided in Section 6.3. There are no alternatives in this study other than not to participate. Potential risks and benefits will be thoroughly explained to the subjects participating and they are free to withdraw from this study at any point in time prior to or during the course of these investigations.

All information, data, etc., collected as a result of these studies is considered confidential and

will be released only as required by law. Information published as a result of this study will be protected completely preserving the anonymity of the participants. Per the Health Insurance Portability and Accountability Act (HIPAA) guidelines, research records will be stored in a locked room identified specifically as a patient record room. All transmitting of data is done by coded names and does not identify any types of names (first or last). Results of any procedures or tests will also be de-identified so as to hide the true identity of patient's names or any other identifiers. On occasion, it may be necessary, for legal reasons, or for good clinical practice, for third parties such as the IRB or DSMB members to review medical records that are identified by name. This however would be on special occasions and would not be a common occurrence. Every effort in all areas of care will be made to keep the patient's information as confidential as possible. As noted above, we will minimize risks to human subjects by creating and maintaining a standard of excellence such as we had with our previous clinical trials at our site. Such standard includes active interactions between faculty and staff on a weekly formal basis, and as needed otherwise, careful attention to training of staff in procedures and their possible complications, and a philosophy of ‘patient first’ in all of our dealings. Specifically, we use only trained personnel to perform procedures. The plan to handle adverse events is described in detail in the section of data and safety monitoring plan.

9.4 Plans for assuring compliance with safety guidelines and regulations

All clinical staff will be required to participate in training offered through their respective Institutional Review Boards. Training is also required in HIPAA in order to have access to study subject records. International Conference of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines are utilized daily in the clinical research practice and are reviewed periodically. The clinical research teams will have weekly conference calls to provide an opportunity for staff to review and discuss the activities of the study. All clinical and laboratory staff are required to take courses handling blood borne pathogens on a yearly basis as well as training in laboratory safety, handling of biohazards, storage and shipping of clinical and laboratory specimens including dangerous goods.

10. Benefits

10.1 Benefits of the investigational agent

As with other randomized, placebo-controlled studies, there may or may not be any benefits for the subject participating in the study. However, participation in this study will provide additional data on the safety and effectiveness of sirolimus for the treatment of hospitalized patients with COVID-19. The information learned from this research study may benefit other subjects with COVID-19, or other similar viral illnesses, in the future. Subjects who participate in the study will receive all study medications at no charge. The laboratory parameters that are obtained strictly for research purposes will not be billed to the patient or their insurance carrier(s).

10.2 Importance of the knowledge to be gained

The knowledge gained from this study may benefit many subjects with COVID-19, and other similar viral illnesses. The information obtained may improve the scientific community's understanding of the management of COVID-19. Specifically, the study will identify the safety and efficacy of sirolimus in hospitalized patients with COVID-19 and thus may alter the clinical approach to patients with this and other similar viral diseases.

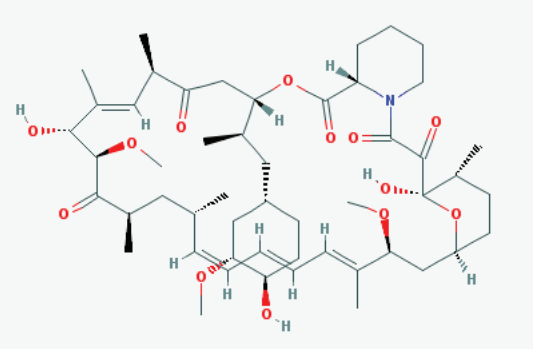
10.3 Benefits of Study Procedures

None.

11. Study Drug

11.1 Sirolimus or Placebo

Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name of sirolimus (also known as rapamycin) is (3S,6R ,7E,9R ,10R,12R ,14S,15E ,17E,19E ,21S,23S ,26R,27R ,34aS)- 9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3- [(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy- 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H ,31H)-pentone. Its molecular formula is C51H79NO13 and its molecular weight is 914.2. The structural formula of sirolimus is:



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. Sirolimus is available for administration as an oral solution containing 1 mg/mL sirolimus. Sirolimus is also available as a white, triangular-shaped tablet containing 1 mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2 mg sirolimus. The inactive ingredients in sirolimus Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol. The inactive ingredients in sirolimus tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients. The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

The placebo for the tablet is lactose powder contained in a gel capsule. All tablet medication will be over-encapsulated to maintain the blind. The placebo for the Rapamune Oral Solution is 0.9% normal saline solution.

11.2 Pharmacokinetics of sirolimus in humans

Absorption: Following administration of sirolimus oral solution, the mean times to peak concentration (t_{max}) of sirolimus are approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively. The systemic availability of sirolimus is low, and was estimated to be approximately 14% after the administration of the oral solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately

27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2mg dose level.[28]

Distribution: The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 18 in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution of sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%), α1-acid glycoprotein, and lipoproteins.[28]

Metabolism: Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease sirolimus concentrations. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the drug's activity.[28]

Elimination: After a single dose of [14C] sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean ± SD terminal elimination half-life (t1⁄2) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.[28]

11.3 Accountability of Investigational Product

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational product(s)/intervention material(s), including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any investigational product(s)/intervention material(s) accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition will be maintained by the University of Cincinnati's IDS Pharmacy located at the study site. A dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of investigational product(s)/intervention material(s) dispensed. All records regarding the disposition of the investigational product will be available for inspection by the DSMB, IRB or other appropriate monitoring bodies.

11.4 Assessment of compliance with the investigational product

Assessment of compliance will be done by daily review of the medication administration record (MAR) in the study subject's medical chart. In case of lack of absolute clarity regarding study drug administration based on MAR review, contact will be made with one or all of the following: patient's bedside nurse, investigational pharmacy, and the study subject, in order to determine if the daily dose of the study drug was administered.

12. Modification or discontinuation of the investigational product

12.1 Modification of investigational product

The tablet form of the investigational product will be overencapsulated to maintain the blind. The liquid solution will be matched with a liquid placebo solution that has an identical appearance. Placebo capsules are prepared by filling the capsule body with lactose powder.

For majority of the subjects, sirolimus will be administered in the tablet formulation. However, in some subjects this may be substituted to the oral solution while maintaining blinded randomization as clinically indicated, e.g. in patients who have progressed to require advanced respiratory support and cannot take oral pills, the liquid solution may be administered via a feeding tube.

12.2 Premature discontinuation of investigational product

Refer to Sections 7.1, 12.3 and 13.1.

12.3 Medication adjustments

12.3.1 Dose Delays

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of sirolimus must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Section 12.3.2. Given the short trial duration, this will likely result in participant withdrawal from the study. Sirolimus therapy may also be interrupted to accommodate surgical procedures or other invasive therapies at the discretion of treating clinicians. Major Events are non-treatment-related grade 3 and 4 pulmonary and non-pulmonary toxicities. Treatment should be delayed for major events if sirolimus may further complicate the non-treatment related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ Grade 1 or ≤ Baseline). For treatment-related toxicities and major events, if toxicity is not resolved in ≤ 4 weeks, patient will be taken off the treatment that is most likely to be related to the toxicity.

12.3.2 Dose Reduction

Any AE of ≥ Grade 3 and attributed as possibly, probably or definitely related to sirolimus will result in the dose being held until the AE has resolved to ≤ grade 1 or baseline. If the AE resolves, reinstitution of treatment can occur but at a reduced dose of 1mg daily. If the AE recurs at the reduced dose, treatment will be held and the subject will be withdrawn from the study. Of note, an escalation in patient's level of care (e.g. floor to ICU) or the need for advanced respiratory support will not automatically result in dose reduction of the study drug, unless deemed necessary for patient safety by the PI or the treating clinicians feel it is in the patient's best interest to be withdrawn ± unblinded. In case the dose of study drug is altered in a subject, in order to maintain blind, a corresponding change will also be made in a placebo subject. Toxicities that may be attributable to sirolimus are listed in Sections 9.1 and 14.3.6. If

any of these AEs occur at grade ≤ 2, sirolimus may be continued and the AE managed with supportive care. For any AE with a grade ≥ 3, the rules outlined in Sections 14.2 – 14.10 apply for holding of dose, dose reduction, removal from study and reporting requirements.

12.3.3 Concomitant medications

All concomitant medications including taken during the course of the study will be documented on a CRF on a daily basis. This record will include start and stop dates, dose, and indication for use for each concomitant medication.

12.3.4 Prohibited medications

Metabolism of sirolimus occurs in the liver and the small intestine by the CYP3A4 family of enzymes. Thus, concomitant administration of sirolimus with other CYP3A substrates or inducers can alter the oral bioavailability of sirolimus.[33] Because of the potential interaction with other drugs involving CYP3A4 metabolic pathways, strong inhibitors and strong inducers of CYP3A4 will not be allowed to be used concomitantly with the study medication. Similarly, patients on chronic immunosuppressive medications may be at higher risk of adverse effects from sirolimus and will be excluded from study participation. A list of the prohibited medications is provided below. While this list covers the majority of medications, the PI will carefully review the concomitant medications in each potential subject prior to enrollment to ensure the study drug can be given safely. In case, a subject is not enrolled due to a concomitant medciation not listed in this table, we will note medication and the rationale on our screening log.

List of prohibited medications for this study
Strong CYP inducers
Barbiturates
Carbamazepine
Phenytoin
Rifampin, Rifabutin
St. John's Wort
Strong CYP inhibitors
Ketoconazole
Voriconazole
Itraconazole
Nefazodone
Clarithromycin
Erythromycin
Telithromycin
Gemfibrozil
Grapefruit juice
Chronic immunosuppressive medications
TNF inhibitors such as infliximab, adalimumab, and etanercept
Methotrexate
Azathioprine
Leflunomide
Cyclosporine
Cyclophosphamide
Rituximab
Chronic prednisone ≥20 mg daily
Mycophenolate mofetil

13. Procedures

13.1 Stopping rules

13.1.1 Study discontinuation

The DSMB and the IRB have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- Early stopping rules have been met
- The study objectives have been met
- The study chair/investigators believe it is not safe for the study to continue
- The DSMB suspends or closes the trial

13.1.2 Subject discontinuation

An intent-to-treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all AEs attributable to study drug resolve. Please refer to Section 7.1 for a list of the reasons that may lead to participant withdrawal from the study.

13.1.3 Study early stopping rules

Study enrollment will be suspended pending expedited review of all pertinent data by the IRB and the DSMB if any one of the following occurs:

- Death from any cause in any subject judged related to study drug
- Multiple medically similar serious adverse events related to study medication
- Events that, in the opinion of the Principal Investigator contraindicate further dosing of additional subjects

If one of the above-listed stopping rules are met, a prompt cumulative review of safety data and of the circumstances of the event(s) in question will be conducted to determine whether study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the DSMB is required for resumption of the study in the event the study is interrupted because of one of the above-listed events.

13.1.4 Individual early stopping rules

A study participant will be terminated from the study if any of the following occurs during the study:

- Recurrent or persistent sirolimus-related toxicity unresponsive to treatment in spite of dose adjustments.
- Pregnancy
- The participant refuses to continue in the study
- The investigator determines that the participant should be withdrawn from the study for reasons not listed above

A subject will be considered evaluable if they took one dose of the study drug. Subjects who are withdrawn before initiating treatment will be considered as premature discontinuation, and will be replaced by another participant.

Every effort will be made to obtain endpoint evaluations for subjects who withdraw or who discontinue prematurely from the study. The same evaluations performed at final visit will be completed at the time of termination. If withdrawal is due to inability to tolerate investigational drug or other untoward event related to investigational drug, the withdrawal will be noted in data analysis as treatment failure.

13.2 Follow-up after early study termination

Participants who are prematurely withdrawn from study drug exposure due to adverse events will be followed to monitor safety until hospital discharge or until resolution or stabilization of the disqualifying event or until the PI determines that further follow-up is not needed.

13.3 Participant replacement

Participants with early termination from this study will be replaced if they are deemed non-evaluable.

14. Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the Data and Safety Monitoring Board (DSMB) and the University of Cincinnati IRB prior to study initiation. Participant enrollment may only begin with IRB approved consent forms. This is an interventional exploratory phase II study.

14.1 Study Oversight

The Principal Investigator (PI) has primary oversight responsibility of this clinical trial. The DSMB has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The DSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance on a periodic basis. For this study the DSMB will meet once prior to study activation, and at the following subsequent times: once the study has reached 25% (7 subjects), 50% (15 subjects), 75% (22 subjects) and 100% (30 subjects) of its target enrollment. The DSMB will review the patient safety data at these meetings in an unblinded fashion to assess for participant safety. No interim analysis for efficacy will be performed. The DSMB makes recommendations to the PI regarding the continuation status of the protocol.

The site PI and their research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying AEs. Aggregate report - detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available for site review.

14.2 Adverse Events

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and ICH E6: Guideline for Good Clinical Practice, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. These criteria have been reviewed by the study investigators and have been determined appropriate for this study population.

14.3 Definitions

14.3.1 Adverse events

An AE is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that is experienced during participation in the trial. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) Study Agent(s) or a study procedure, whether or not related to the medicinal (investigational) Study Agent(s) or study procedure. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not recorded as an AE. However, if the condition deteriorates or changes in severity at any time during the study it will be recorded and reported as an AE.

14.3.2 Suspected adverse reaction and adverse reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction (AR), which means any adverse event caused by a drug.

An AR means any AE caused by a drug. ARs are a subset of all SARs for which there are reasons to conclude that the drug caused the event.

14.3.3 Adverse events associated with study procedures

The following clinical situations and laboratory parameters will be considered to be outside of the normal range of findings and will be recorded as AEs. These situations do not limit the PI from reporting any other events, associated or not with these procedures, from being recorded and reported as AEs.

Blood draws

- Fainting/vasovagal events
- Bruising at puncture site greater than 2 cm in diameter
- Bleeding from puncture site lasting more than 5 minutes
- Swelling at puncture site larger than 2 cm

14.3.4 Adverse events associated with laboratory testing

The following table highlights the laboratory values that are being obtained as part of the study along with the reference range for normal values. While any value outside the reference range will be classified as abnormal, the clinical significance of those abnormal values will be determined based on the criteria set forth in the table. All lab values identified as clinically significant will be marked as an AE. The causality and attribution of the lab value to the study drug, as well as action items with regards to follow-up and management of laboratory values that are listed as clinically significant, will be adjudicated on an individual basis by the study PI.

Laboratory parameter	Reference Range	Reported as clinically significant if
Serum Creatinine	0.50 – 0.99 mg/dl	≥1.5 times baseline
AST	10 – 35 U/L	≥ 105 U/L (3 times ULN)
ALT	6 – 29 U/L	≥ 87 U/L (3 times ULN)
Hemoglobin	11.7 – 15.5 gm/dl	Decrease of ≥2gm/dL from baseline
Total white blood cells	3.8 – 10.8 x $10^3/\mu L$	$\leq$ 3 or ≥ 11.5 x $10^3/\mu L$
Absolute neutrophils	1500 – 7800 cells/μL	< 1,000 or > 9,500 cells/μL
Absolute lymphocytes	850 – 3900 cells/μL	< 500 or > 4500 cells/μL
Absolute monocytes	200 – 950 cells/μL	< 150 or > 1,500 cells/μL
Absolute eosinophils	15 – 500 cells/μL	< 5 or > 1,000 cells/μL
Absolute basophils	0 – 200 cells/μL	> 500 cells/μL
Platelet count	140 – 400 x $10^3/\mu L$	< 120 or > 450 x $10^3/\mu L$

Abbreviations: AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, MCV = Mean corpuscular volume, RDW = Red blood cell distribution width.
While the guidance above is meant to cover all laboratory values obtained during the study, we realize that it may not be able to cover all the unique circumstances that can arise during the conduct of a clinical trial. As such, in rare situations, the study PI may change the clinical significance of a lab value outside of the above guidance. We do not anticipate this situation to arise commonly, however, and if deviating from the above range while assigning clinical significance, the reason for this diversion will be clearly outlined in the subject's study binder.
Adverse events related to study medication will be tabulated by body system and by severity using the NCI CTCAE v 5.0.

14.3.5 Serious Adverse Event (SAE)
An AE or SAR is considered "serious" if it results in any of the following outcomes (21 CFR 312.32(a):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the opinion of the investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- An inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, in the opinion of the investigator, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Congenital anomaly or birth defect.

Regardless of the relationship of the AE to the study, the event will be reported per Section 14.3.5 as an SAE if it meets any of the above definitions.

14.3.6 Expected adverse events
Detailed information regarding adverse effects of sirolimus is provided in Section 9.1. This section lists the AEs regarded as expected for sirolimus (in alphabetical order of systems):

Cardiovascular: Peripheral edema, hypertension
Cutaneous: Acne, skin rash, mucositis
Gastrointestinal: Nausea, vomiting, diarrhea, constipation, dyspepsia
General: Fatigue, myalgias, arthralgias
Hematological: Anemia, thrombocytopenia
Infectious: Increased risk of infections
Liver: Increased serum bilirubin

Nervous system: headache
Pulmonary: pneumonitis
Renal: Increased serum creatinine

14.3.7 Unexpected adverse event

An AE or SAR is considered “unexpected” when its nature, severity or frequency is not consistent with the information that is provided with the information in the protocol.

14.4 Collecting, recording and managing adverse events

14.4.1 Identifying adverse events

Any AE that occurs from the moment the subject has signed the consent form will be recorded and is reportable. Collection time for AEs and SAEs will begin after the screening visit when the consent form is signed and will continue until the end of the treatment.

Adverse events may be discovered through any of these methods:

- Electronic medical record review
- Observing the participant
- Questioning the participant, with standardized questions/procedures.
- Receiving an unsolicited complaint from the participant.
- An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE when determined to be clinically significant by the PI. Pre-specified criteria for abnormal lab values are provided in Section 14.3.4.

14.4.2 Recording AEs

Throughout the study all identified AEs (serious and non-serious) will be recorded on all appropriate source document and AE case report forms (CRFs) regardless of their severity or relation to the study. A complete description of all AEs will include event description, time of onset, investigator assessment of severity, relationship to study agent or procedures, time of resolution/stabilization of the event, expectedness, determination of whether the AE qualifies as a SAE, and action taken. A change in the severity of the AE will also be documented. Assessment of severity and relationship will be documented on the source documents or on the CRFs.

14.4.3 Recording SAEs

SAEs will be recorded on the SAE CRF and will include a narrative of the event signed and dated by the PI.

14.5 Managing adverse events

The study investigator must apply his or her clinical judgment as to whether an AE is of sufficient severity to require that the participant immediately be removed from further receiving

the study agent under the protocol. The investigator must institute any necessary medical therapy to protect a participant from any immediate dangers.

An AE will be followed until any of the following takes place: a) it is resolved, b) participant is stable, c) participant is discharged from the hospital and the PI determines that follow-up is no longer needed.

If an abnormal value or result from a clinical or laboratory evaluation is determined to be an AE, then the evaluation that produced the value or result can be repeated until the value or result returns to normal, or the result can be explained, or the usual standard of care does not require further follow-up, and the participant's safety is not at risk.

Non-serious expected AEs will be submitted to the DSMB in a timely fashion. The events will be presented in tabular form and given to the DSMB at every scheduled meeting. Study investigators are also required to fulfill all reporting requirements of their local institutions.

14.6 Grading and Attribution

14.6.1 Grading Criteria

In addition to determining whether an AE fulfills criteria for a SAE or not, the severity of AEs experienced by study participants will be graded according to the criteria set forth in the NCI CTCAE v 5.0. This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. All AEs whether or not listed in the NCI CTCAE manual will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (A semi-colon indicates 'or' within the description of the grade):

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4 = Life-threatening consequences; or urgent intervention indicated.

Grade 5 = Death related to AE.

14.7 Definition of Attribution

The attribution of an AE to the study drug will be determined by the PI or designated physician co/sub-investigator. The PI or designee will record the determination of attribution on the

appropriate AE or SAE form. The attribution of an AE to the investigational drug or to a study procedure will be determined using the descriptors in the following table. For the purpose of this study, in addition to all study medications, the following procedures will be considered when determining attribution:

Code	Descriptor	Definition (guidelines)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related to study. The event is completely related to an etiology other than the study product or study intervention (the alternative etiology must be documented in the study subject's medical record)
2	Unlikely	The adverse event is doubtfully related to study and likely to be related to factors other than study product or study intervention.
RELATED CATEGORIES		
3	Possible	The adverse event may be related to study. There is an association between the event and the administration of study product and there is a plausible mechanism for the event to be related to the study product; there may be also an alternative etiology, such as characteristics of the subject's clinical status and/or underlying disease
4	Probable	The adverse event is likely related to study. There is (1) an association between the event and the administration of study product or study intervention, (2) a plausible mechanism for the event to be related to the study product, and (3) the event could not be reasonably explained by known characteristics of the subject's clinical status and or an alternative etiology is not apparent
5	Definite	The adverse event is clearly related to study. There is (1) an association between the event and the administration of the study product or study intervention, (2) a plausible mechanism for the event to be related to the related to the study product, and (3) causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product

For additional information and a printable version of the NCI-CTCAE manual, the NCI-CTCAE website: http://ctep.cancer.gov/reporting/ctc.html will be consulted. In a clinical trial, the study product\intervention will always be suspect when attributing an AE and the "unrelated" attribution will be used only when there is an undisputable or likely alternative explanation for the AE.

14.8 SAE Reporting Criteria and Procedures

The PI will be notified by the study staff as soon as a study staff member becomes aware of the SAE. In the absence of the PI, a physician sub-investigator will be notified. An unexpected, non-serious AE that is of Grade 3 severity or higher and study related will be recorded and reported

under the SAE reporting procedure.

14.8.1 Notifying the IRB and DSMB

The PI will submit all safety reports on an ongoing basis to the DSMB. Individual or clusters of SAEs may be reported expeditiously to the DSMB upon determination. The PI determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the AE. The DSMB Chair may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the AE. A back-up notification system will be instituted so that any delays in review by the Chair beyond a specified period of time are forwarded to a secondary reviewer.

SAE's that are **life-threatening/disabling or result in death of research participant; AND unexpected; AND related to the research** must be reported to the sponsor within 24 hours of learning of the event. The sponsor/investigator will report the event to the IRB and DSMB promptly. Investigators must report all other SAEs to the DSMB within **5 working days** (of learning of the event).

The PI will ensure the timely dissemination of SAE information, including expedited reports, to the IRB in accordance with IRB regulations and guidelines. Events that will be reported to the IRB but **do not require prompt reporting**

1. Reasonably anticipated ("expected") potential risks and adverse events *described in the Informed Consent Process and listed on the Informed Consent Form.*
2. Deaths not attributed to the research and deemed *not related to the research* (no connection between the study procedures and the death) do not require prompt reporting.
3. Protocol deviations or violations *not involving risks* to participants or *unlikely to recur*
4. Data Safety Monitoring Board reports, interim analyses, or other reports, findings, or new information *not altering the risk/benefit profile*
5. Investigator Brochure updates not involving safety information
6. Problems or findings not involving risk (unless the information could affect participants' willingness to continue in the research)

Events that require **prompt reporting** to the IRB

1. Unanticipated problems involving risks to participants and others
2. Adverse events that are unexpected, related to the research, and involve new or increased risk to participant or others
3. Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur
4. Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff
5. Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant

6. Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risks/benefit profile
7. New information indicating an unexpected change in risks or potential benefits
8. Investigator's Brochure (IB or IDB) updates or revisions to safety information
9. Other unanticipated problems such as breach of confidentiality, loss of study data or forms, etc. that could influence the safe conduct of the research

14.8.2 Notifying the FDA

The Investigational New Drug (IND) sponsor (PI) is responsible for the Food and Drug Administration (FDA) safety submissions as follows: The IND Sponsor for this study will handle all regulatory communications with the FDA and will be responsible to update the IND to include this trial, file all regulatory related issues including any MEDWATCH reports which will be reviewed and approved by the PI and Steering Committee. The IND sponsor will be responsible for submission of yearly reports and final report for this study. All DSMB recommendations will be communicated to the IND sponsor in a timely fashion.

The following process for reporting a serious adverse event ensures compliance with the ICH guidelines, 21CFR §312.32.

- Expedited safety report to the FDA applies if the adverse event is classified as one of the following:
    - Serious and unexpected suspected adverse reaction (SUSAR) (Sections 14.3.4, 14.3.6, and 14.7) (i.e. serious, unexpected, and related)
      Or
    - Aggregate analysis of adverse events that suggest a causal relationship to the study medications
      Or
    - Any findings from clinical, epidemiological, pooled analysis of data pooled across multiple studies, published or unpublished scientific papers or any findings from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, investigator brochure or other aspects of the overall conduct of the trial will be reported.

Expedited Safety Reports must be reported by the IND Sponsor to the FDA within 15 calendar days; fatal or immediately life-threatening serious, unexpected, suspected adverse reactions must be reported within 7 calendar days. SAEs that do not strictly fit the above criteria may be reported to the FDA in an expedited manner if the IND Sponsor chose to do so. Each 7-day report must be followed up by a 15-day report.

The following types of SAEs will be reported in the IND Annual Report:

- Serious, expected, suspected adverse reactions
- Serious but not a suspected adverse reaction

For standard reporting, the IND Sponsor or designee will file the IND Annual Report. All AEs (not just those requiring 24 hour reporting) will be reported in the Annual IND Report.

14.9 Reporting Pregnancy

A research subject will be terminated from the study due to pregnancy. The PI will be informed immediately of any pregnancy and will report all pregnancies within 24 hours of becoming aware of the event to DSMB utilizing the SAE report form. This report is for tracking purposes only. All pregnancies that are identified during the study will be followed to conclusion and the outcome of each will be reported. The PI will discuss with the participant and/or the treating physician the known possible risks of the investigational product(s) on the fetus. Monitoring of the participant will continue until the conclusion of the pregnancy, and a follow-up SAE report form detailing the outcome of the pregnancy will be submitted to the DSMB. Due to the short study time (maximum of 14 days), and the exclusion of pregnant women from study participation, we do not anticipate having to report pregnancy as part of this study.

14.10 Non-serious adverse events reporting

14.10.1 Notifying the data and safety monitoring board

The DSMB will be notified of non-serious AEs during their regularly scheduled meetings. The events will be presented to the Board in tabular format.

14.10.2 Notifying the Institutional Review Board

The PI will ensure the timely dissemination of AE information to the IRB in accordance with applicable regulations and guidelines.

14.10.3 Notifying the FDA

The IND sponsor (the Study Chair) will file all adverse events per 21 CFR 312.32, whether expedited or part of the IND Annual Report. The IND sponsor will be responsible for compiling the IND Annual Report.

14.10.4 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported to the DSMB and IRB, in the following time frames:

1. Unanticipated problems that are SAEs should be reported to the IRB within 1 week of the investigator becoming aware of the event.

2. Any other unanticipated problem should be reported to the IRB according to the IRB's reporting policies.

14.11 Data Management

All study data will be collected via systems created by using Research Electronic Data Capture (REDCap, an online data management software) and will comply with all applicable guidelines regarding patient confidentiality and data integrity. Data access in REDCap is password protected and limited to authorized study personnel. All paper records will be kept in secure files in locked cabinets inside locked offices with access limited to authorized study personnel. All other study specific documents and logs will be stored on computer drives hosted and protected by the University of Cincinnati policies with regular back-ups.

14.11.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site (University of Cincinnati) will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be obtained before accrual can occur from the clinical site.

Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject.

14.11.2 Data Entry

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

14.11.3 Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether

independent range and/or format limitations or ‘relative’ referential integrity limitations, can be enforced by all methods employed for data input. Quality assurance reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

The DSMB will review data quality on an ongoing basis. A risk-based monitoring plan will be developed to support the study. The purposes of study monitoring are to ensure the safety and welfare of study participants and to confirm the accuracy of study data.

An onsite monitoring visit will occur once during the conduct of the trial, with the option of making a second visit if deemed necessary by the PI, to address enrollment, or protocol deviation issues. The Monitoring Plan will detail the frequency and level of intensity of on-site monitoring visits. In general, the study will be monitored for all participants at a level of 100% of study data gathered for inclusion and exclusion criteria, informed consent procedures, AEs and unanticipated problems. The study monitor(s) will collaborate with the PI to conduct remedial site training to ensure compliance with GCP and all regulations.

During scheduled interim remote monitoring visits, the clinical monitors will verify that the protocol is being followed and that data are being collected according to protocol requirements. The clinical monitor(s) will review the Study Regulatory File to determine that all required documentation is being collected and that the IRB approval for the site is current. The monitor will then verify that each participant has signed the correct version of the ICF, and that this document is filed in the participant’s source documents. At each visit, the monitor will perform an audit of the source documents in the subject’s binder by checking them against the database. AE documentation will be checked for completeness and accuracy. At the study closeout, the monitor(s) will confirm that all data have been reviewed, all source documents have been verified, and all required documents are present in the Study Regulatory File.

Protocol deviations and unanticipated problems will be reviewed by the PI, and the regulatory and monitoring staff to determine the need for corrective and preventative action (CAPA). In the event that corrective and/or preventative action is warranted, a root cause analysis will be performed and a CAPA will be completed as per institutional policy. The PI is responsible for communicating the CAPA plan to appropriate staff (i.e. Site Investigator, study team) and obtaining appropriate signatures to address the issues at hand. The PI will work with regulatory and monitoring staff to ensure that the CAPA is followed and is effective in resolving the issue(s). Protocol deviations and unanticipated problems will be reported to the IRB as per institutional policy.

The table below describes the variables to be reviewed during monitoring visits.

Variable	**% of Records Reviewed**
Informed consents	100%
Eligibility criteria for all screened subjects	100%

Adverse events	100%
Protocol adherence	20% of active subjects
Verification of REDCap with source documents	20% of active subjects
Central study files-inclusion of all applicable documents	100%
Protocol deviations/violations	100%

14.12 Protocol Deviations
The practices below are consistent with Good Clinical Practice (GCP ICH E6) Sections:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, section 5.1.1
- Noncompliance sections 5.20.1, and 5.20.2

14.12.1 Protocol deviation Definition
14.12.1.1 Protocol Deviation - Any change, divergence, or departure from the study design or procedures of a research protocol that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a protocol violation. Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered non-major protocol deviations. Site Principal Investigator is responsible for reporting protocol deviations to the IRB using the standard reporting form. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

14.12.1.2 Major Protocol Deviation (Protocol Violation) - A protocol violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

If the deviation meets any of the following criteria, it is considered a major protocol deviation. However, the lists of deviation examples that follow are not exhaustive.

- The deviation has harmed or posed a significant or substantive risk of harm to the research subject.

Examples:

1. A research subject received the wrong treatment or incorrect dose.
2. A research subject met withdrawal criteria during the study but was not withdrawn
3. A research subject received an excluded concomitant medication.

- The deviation compromises the scientific integrity of the data collected for the study.

Examples:

1. A research subject was enrolled but does not meet the protocol's eligibility criteria.
2. Changing the protocol without prior IRB approval, except for modification to ensure the

safety of study participants.
3. Inadvertent loss of samples or data.

- The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s).

Examples:

1. Working under an expired professional license or certification.
2. Failure to follow federal and/or local regulations.
3. Repeated minor deviations.

- The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles.

Examples:

1. A breach of confidentiality.
2. Inadequate or improper informed consent procedure.

14.12.1.3 Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

14.12.2 Reporting Protocol Deviations

Deviations from the protocol are not allowed. It is the responsibility of the study site to use continuous vigilance to identify and report any protocol deviations. Upon determination that a protocol deviation has occurred, the study staff will notify the PI and complete the Protocol Deviation form. The PI will complete and sign the Protocol Deviation form and submit it to the IRB, per IRB regulations. Major protocol deviations will be reported to the DSMB at the regular DSMB reporting interval.

15. Statistical considerations

Sample size determination: In a study evaluating 201 hospitalized patients with COVID-19 in China, 82% (165 patients) required supplemental oxygen. Among the patients needing supplemental oxygen, 40% (67 patients) progressed to require advanced respiratory support during their hospital stay.[8] Considering the fact that our study inclusion criteria mandates the need for supplemental oxygen and the presence of at least one additional poor prognostic biomarker, we anticipate that 50% of our control group will progress to require advanced respiratory support during their hospitalization. We expect that treatment with sirolimus will reduce the need for advanced respiratory support to 25%.

The goal of this pilot study is to determine a meaningful treatment difference in order to conduct a larger confirmatory trial. Given the limited data on treatment responsiveness in COVID-19 populations, we examined various enrollment sizes commensurate with planning a pilot study. Specifically, we undertook a recommended approach for pilot studies in clinical research, which is to not perform hypothesis testing with a significance level set at the traditional value of 0.05.[34-37] The confidence intervals for the treatment difference were calculated based on demonstrating a reduction in the proportion of subjects needing advanced respiratory support from 0.50 in the placebo group to 0.25 in the sirolimus group. Various levels have been proposed as optimal thresholds for the tolerance of type I error in the context of pilot studies, with the highest being p=0.25.[34] We chose the type I error rate of 0.2 to denote significant treatment effect between the treatment and placebo arms in our study, as proposed by Stallard.[37] A sample size of 30 patients randomized in a 2:1 fashion in favor of sirolimus will allow us to estimate the treatment differences with 80% confidence based on a binomial two-proportion test. A two-sided test will be used since we are unsure if the treatment will have a beneficial effect in this patient population.

Data Analysis Plan: The primary endpoint of this study is progression to respiratory failure requiring advanced support measures. The difference in proportions of progression between the placebo and sirolimus groups and the 80% confidence interval will be calculated. If the confidence interval for the difference in proportions does not include zero, then we will conclude that the treatment difference is clinically meaningful. Considering the small sample size of our study, the significant impact of age and other pre-existing conditions such as diabetes mellitus on overall prognosis in patients with COVID-19 cannot be accounted for in the primary analysis. Patients will be randomized according to a computer-generated permuted block randomization stratified on age: <50 years, 50 – 64 years, and ≥65 years. In case recruitment lags we will add external study sites. In such a scenario, University of Cincinnati and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC will follow the same randomization scheme. In case of other external sites, randomization will be stratified based on site in addition to the above-mentioned age-based stratification. As exploratory analysis, we will conduct analyses examining differences based on other prognostic factors and concomitant medications such as corticosteroids, hydroxychloroquine, azithromycin etc. An intent-to-treat analysis will be performed for the primary outcome.

16. Identification and access to source data

16.1 Identifying source data

The site PI will keep accurate records to ensure that the conduct of the study is fully documented. Data derived from source documents will be transferred to protocol-specific CRFs. The results of all clinical and clinical laboratory evaluations will be maintained in the participant's medical records or hospital database and the data will be transferred to clinical CRFs, as applicable.

16.2 Updating source documentation

Documents describing the safety profile of an investigational product will be amended as needed to ensure that the description of safety information adequately reflects any new clinical findings. The site PI will provide the IRB with the most up-to-date versions of the above documents as soon as the PI becomes aware of any changes.

16.3 Permitting access to source data

The investigational site participating in this study (University of Cincinnati) will maintain the highest degree of confidentiality for the clinical and research information obtained from the participants in this clinical trial. Medical and research records will be maintained at the study site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigator, the investigational site will permit the study monitor, authorized representatives of the IRB, the FDA, and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information will be removed). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identify individuals.

16.4 Quality control and quality assurance

The PI will keep accurate records to ensure that the conduct of the study is fully documented. The investigator will ensure that all CRFs and participant study files are legible and complete for every participant.

The PI, through the use of the DSMB, will be responsible for the regular review of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data and accuracy of source documentation verification.

When the CRFs are complete, they will be reviewed and signed by the PI. All discrepancies identified by the site monitor will be reviewed, and any resulting queries will be resolved with the site PIs and the CRFs will be amended as needed.

17. Ethical considerations and compliance with good clinical practice

17.1 Statement of Compliance

This study was designed to ensure the protection of subjects according to the ethical principles of the Declaration of Helsinki and amendments concerning medical research in human subjects. This clinical study will be conducted using current good clinical practice (cGCP), as delineated in ICH, Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the DSMB, the IRB, as well as any other appropriate health authorities. Any amendments to the protocol or to the consent materials will also be approved by the appropriate bodies listed above prior to implementation.

17.2 Informed Consent

Each subject will be provided with oral and written information describing the nature and duration of the study. Written consent must be obtained prior to screening while following the informed consent procedures as detailed in Section 6.3. Prospective participant must be given ample opportunity to review the informed consent and inquire about the results of the study. All participants must read, sign, and date a consent form prior to study participation. Subject will enter the date of the consent. The original, signed consent form will be retained with the study center's records, and each subject will receive a copy. The ICF will provide information about the study to a prospective participant to allow for an informed decision about participation in the study. Consent materials for participants who do not speak or read English will be translated into the participants' appropriate language.

The ICF will be revised and receive IRB approval whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the ICF will be given to a prospective participant for review. The PI or an approved designee will discuss the consent with the prospective participant and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. The site will document details of the informed consent process within the study records.

18. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number and these numbers rather than names will be used during collection, storage, and reporting of participant information.

Data for this study will be received in electronic format from EPIC. Data will come from EPIC notes written as part of the research encounters, as well as field data collected using specific case report forms designed for this study. Field data will be collected on a stationary desktop computer using RedCap and will comply with all applicable guidelines regarding patient confidentiality and data integrity. Data access in REDCap is password protected and limited to authorized study personnel. Electronic data collected in the field will be protected from theft using whole disk encryption. During the study, data will be hosted at University of Cincinnati's secure Data Center with regular back-ups. All paper records will be kept in secure files in locked cabinets inside locked offices with access limited to authorized study personnel. Upon completion of the study, private data will be destroyed by certified system administrators per UC policy.

19. Publications

Publication of any data from this study must be carried out in accordance with the clinical study agreements. The results of the study will be reported in clinicaltrials.gov per current NIH regulations.

20. References

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SCOPE Statistical Analysis Plan

Statistical considerations

Sample size determination: In a study evaluating 201 hospitalized patients with COVID-19 in China, 82% (165 patients) required supplemental oxygen. Among the patients needing supplemental oxygen, 40% (67 patients) progressed to require advanced respiratory support during their hospital stay.8 Considering the fact that our study inclusion criteria mandates the need for supplemental oxygen and the presence of at least one additional poor prognostic biomarker, we anticipate that 50% of our control group will progress to require advanced respiratory support during their hospitalization. We expect that treatment with sirolimus will reduce the need for advanced respiratory support to 25%.

The goal of this pilot study is to determine a meaningful treatment difference in order to conduct a larger confirmatory trial. Given the limited data on treatment responsiveness in COVID-19 populations, we examined various enrollment sizes commensurate with planning a pilot study. Specifically, we undertook a recommended approach for pilot studies in clinical research, which is to not perform hypothesis testing with a significance level set at the traditional value of 0.05.34- 37 The confidence intervals for the treatment difference were calculated based on demonstrating a reduction in the proportion of subjects needing advanced respiratory support from 0.50 in the placebo group to 0.25 in the sirolimus group. Various levels have been proposed as optimal thresholds for the tolerance of type I error in the context of pilot studies, with the highest being p=0.25.34 We chose the type I error rate of 0.2 to denote significant treatment effect between the treatment and placebo arms in our study, as proposed by Stallard.37 A sample size of 30 patients randomized in a 2:1 fashion in favor of sirolimus will allow us to estimate the treatment differences with 80% confidence based on a binomial two-proportion test. A two-sided test will be used since we are unsure if the treatment will have a beneficial effect in this patient population.

Data Analysis Plan: The primary endpoint of this study is progression to respiratory failure requiring advanced support measures. The difference in proportions of progression between the placebo and sirolimus groups and the 80% confidence interval will be calculated. If the confidence interval for the difference in proportions does not include zero, then we will conclude that the treatment difference is clinically meaningful. Considering the small sample size of our study, the significant impact of age and other pre-existing conditions such as diabetes mellitus on overall prognosis in patients with COVID-19 cannot be accounted for in the primary analysis. Patients will be randomized according to a computer-generated permuted block randomization stratified on age: <50 years, 50 – 64 years, and ≥65 years. In case recruitment lags we will add external study sites. In such a scenario, University of Cincinnati and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC will follow the same randomization scheme. In case of other external sites, randomization will be stratified based on site in addition to the above-mentioned age-based stratification. As exploratory analysis, we will conduct analyses examining differences based on other prognostic factors and concomitant medications such as corticosteroids, hydroxychloroquine, azithromycin etc. An intent-to-treat analysis will be performed for the primary outcome.

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Sirolimus Treatment in Hospitalized patients with COVID-19 Pneumonia (SCOPE trial)

UC IRB Study #: 2020-0337 **Sponsor Name:** Investigator-Initiated

Investigator Information:

Nishant Gupta, MD	513-475-8523
Principal Investigator Name	Telephone Number (24-hour Emergency Contact)

Subject Name: _____ Date of Birth: _____/_____/____

KEY INFORMATION

Purpose of the Study:	The purpose of this research study is to test the safety and efficacy of sirolimus in patients admitted to the hospital with the novel Coronavirus pneumonia (COVID-19).
Length of the Study:	You will be in the research study for 14 days, or until hospital discharge, whatever happens first.
Risks:	The most common side effects related to sirolimus include nausea, vomiting, diarrhea, mouth ulcers, swelling of the legs, high blood pressure, muscle aches, high cholesterol, and increased risk of infections. Sirolimus may increase the risk that you will develop an infection or cancer, especially lymphoma (cancer of a part of the immune system) or skin cancer.
Benefits of the Study:	If you agree to take part in this research study, there may not be a direct medical benefit to you. We hope the information learned from this research study will benefit other patients with COVID-19 and similar viral illnesses in the future.
Alternative procedures:	If you do not want to participate in this study, you will continue with your regular medical care.

INTRODUCTION

You have been asked to participate in a research study. Before you agree to participate in this research study, it is important that you understand the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study. The informed consent document is a written summary of this information. Be sure to ask questions while you read this consent document. Please ask questions if there is anything that you do not understand.

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Your participation in this research study is entirely **voluntary**. You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. You will not suffer any penalty or loss of benefits if you leave the study. The researcher and sponsor of this study do not promise that you will receive any benefits from this study.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to test the safety and efficacy of sirolimus in patients admitted to the hospital with the novel Coronavirus pneumonia (COVID-19). Sirolimus is FDA approved to prevent rejection in patients who receive kidney transplants and to treat a rare lung disease named Lymphangioleiomyomatosis (LAM). Sirolimus is not FDA-approved to treat COVID-19. COVID-19 is a life-threatening illness that can lead to hospitalization in about 20% of the patients. One-fourth of the hospitalized patients are sick enough to require intensive care unit (ICU) admission. COVID-19 is fatal in about 2% of the patients.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you have been diagnosed with either confirmed COVID-19 pneumonia or your doctors feel that you have a very high likelihood of having COVID-19 pneumonia. You are eligible because you are admitted to the hospital with COVID-19 pneumonia, have low oxygen levels, and have at least one other marker that suggests that you may be at a higher risk of complications from COVID-19. You must also be over 18 years old to be eligible for this study. The results from this study will help us determine the safety and efficacy of sirolimus in treating hospitalized patients with COVID-19.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for 14 days, or until hospital discharge, whatever happens first. This consent shall remain in effect until the end of the research study, unless you choose to withdraw it.

Your doctor may remove you from the study if your disease becomes worse or if side effects become very severe. Your doctor may also remove you from the study if new scientific developments occur that indicate the treatment is no longer optimal. You may also be withdrawn from the study if you fail to follow instructions provided by the investigators.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

If you withdraw, the data collected to the point of withdrawal will remain part of the study data and may not be removed. You may be asked whether you wish to provide further data collection from your routine medical care.

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You may be contacted in the future by representatives of the University of Cincinnati to ask you survey questions about your participation in this research study. If you choose to participate in the survey, your responses will be used for quality assurance purposes only.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is being directed and carried out by Nishant Gupta MD, a researcher at the University of Cincinnati. Dr. Gupta is the lead investigator for this study. The study drug, sirolimus, is being provided by the drug manufacturer, Pfizer, at no charge.

Research will take place at University of Cincinnati and the facilities of the affiliated health systems UC Health, LLC and University of Cincinnati Physicians Company, LLC.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 30 people will take part in this study.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

You cannot participate in this study if any of the following apply to you:

- If you are not able or willing to give consent
- If you are enrolled in other clinical trials
- If you are under the age of 18 years
- If you are pregnant or breast feeding
- If you are on ventilatory support for your breathing
- If you have serious co-existing medical conditions like liver cirrhosis, kidney failure, heart failure or untreated infections other than COVID-19
- If you have active cancers such as lymphoma
- If you are on a medication that can suppress your immune system such as cyclosporine, adalimumab, methotrexate, infliximab, mycophenolate, azathioprine, or on medications that have known interactions with sirolimus such as rifampin, phenytoin, clarithromycin, ketoconazole, St. John's wort, erythromycin.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

At the first visit, we will give you this consent form to read and sign. We will explain the study to you. We will answer any questions you might have about this study. After all of your questions are answered and you have had a chance to read and sign the consent form, you will be allowed to participate in this research study.

If you take part in this study, you will be asked to provide your medical history including any available medical records. We will review your medical history to make sure that you are eligible to participate.

You will be randomly selected to receive either sirolimus or a placebo that contains no active medication. You will have a 2 out of 3 chance of receiving sirolimus and a 1 out of 3 chance of receiving the placebo. Neither you nor the researchers will know if you are getting sirolimus or placebo. This is essential in order to not bias the study results. You will receive

either sirolimus or placebo for a maximum period of 14 days. The treatment duration may be less than 14 days if you get discharged from the hospital before the 14 day time frame.

You will be given the study medication at roughly the same time by your nurse. We will collect data from your medical records on a daily basis. In addition, we will contact you on days 1, 3, 7 and 14 to check on your status and determine if you are having any side effects from the study medication. We will also collect blood to measure lab tests that can help determine if the treatment has had a beneficial effect. These tests will be performed on days 3, 7, and 14. The trial may end before all of your study procedures are completed if trial continuation is determined to be unsafe.

If you take part in this study, you will have the following tests and procedures:

1. **Blood Draw:** Blood tests to measure laboratory parameters that can help assess treatment benefit will be drawn at baseline and then at days 3, 7 and 14. Up to four tubes of blood are withdrawn from one of the large veins of the forearm. The total volume of blood drawn is approximately two to three tablespoons (30-45 mL). The following tests will be performed on the blood samples: blood counts, d-dimer, ferritin, kidney and liver function tests, and LDH.

2. **Urine Pregnancy Test:** Taking sirolimus while pregnant might cause birth deformities or threaten the life of a fetus. If you have the ability to become pregnant, you will have a urine pregnancy test before enrolling in the study. The result of the pregnancy test must be received before you take any study medicine.

3. **Study Medication:** You will be given study medication to take at the same time each day. It is very important that you take this medication as instructed and do not skip doses or take extra doses. The medication will be given once a day for a maximum of 14 days. If you experience significant side effects, the researchers may ask you to decrease the dose or stop the medication.

In addition to the above tests and procedures, we will collect information regarding your demographics and medical history at baseline. We will monitor your medical record on a daily basis to note the following:

1) Your clinical condition
2) Vital signs (heart rate, blood pressure, temperature)
3) Oxygenation indices (blood oxygen level and the amount of oxygen you need)
4) Other medications that you are receiving in the hospital

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

Risks of Sirolimus:
Sirolimus is in a class of medications called immunosuppressants. It works by suppressing the body's immune system. Sirolimus may increase the risk that you will develop an infection or cancer, especially lymphoma (cancer of a part of the immune system) or skin cancer.

Most of the serious side effects of sirolimus are a concern in patients who use the drug on a long-term basis. Because you will only be receiving the study drug for a maximum of 14 days, the risks associated with the study drug may be less likely to occur. Sirolimus may affect your liver and kidney function tests, as well as lead to anemia. We will monitor your blood tests closely to monitor these side effects.

Common side effects associated with the use of sirolimus

Side Effects	**The approximate number of people that may experience a side effect out of 100 people**
Increased risk of infections	10 - 30
Delayed wound healing	20 - 25
Lymphoma	1 - 3
Headache	20 - 30
Gastrointestinal disorders	
Nausea	25 - 35
Vomiting	20 - 25
Diarrhea	25 – 40
Constipation	25 – 35
Cardiovascular disorders	
Swelling of the legs	50
High blood pressure	40
Musculoskeletal disorders	
Muscle and joint aches	10 - 15
Skin and tissue disorders	
Skin rash	10 - 20
Acne	20 - 25
Mouth ulcers	40 - 50
Blood disorders	
Low blood counts	20 - 30
High cholesterol	40 - 50
Kidney disorders	
Kidney function worsening	30

Risks of Blood Collection: Laboratory tests involve removing blood from a vein with a needle. Risks associated with blood draws include soreness, bruising, and in rare instances, an

infection at the site of the blood draws. Laboratory tests will be performed to look for any side effects from sirolimus and to assess the efficacy of treatment. If any side effects should be noted, the medication may need to be adjusted or stopped.

Information that you share with any of your physicians may become part of your personal medical record. It may be available to persons who have legal access to your medical records. Questions about access to your personal medical record should be directed to your personal physician.

There may be unknown or unforeseen risks associated with study participation. If you wish to discuss the information above or any other discomforts you may experience, you may ask questions now or call the study doctor listed on the front of this form.

URINE PREGNANCY TEST

If you have the ability to become pregnant, you will have a urine pregnancy test before enrolling in the research study. The result of the pregnancy test must be received before you take any medicine.

WHAT ARE THE REPRODUCTION RISKS?

We will confirm that you are not pregnant with a urine pregnancy test before enrolling you into the study.

Because the drug in this research study can affect an unborn baby, you should not become pregnant while on this research study. This includes the 4 weeks following the last day you take study medication. This is very important because there is the possibility that sirolimus could affect the development of a fetus for up to 4 weeks following the last day that you receive the medication. Therefore, even if you are withdrawn or decide not to continue to participate in the study, you will be strongly encouraged to use birth control for 4 weeks following the last time you take the study medication. Acceptable forms of birth control include prior surgical sterilization. Qualifying surgeries include hysterectomy, removal of both ovaries, tubal ligation, and vasectomy in partner(s). You may also use complete abstinence or double barrier methods. Double barrier methods include condom with spermicide, diaphragm with spermicide, or cervical cap with spermicide. Intrauterine devices (IUD), and progestin-based contraceptives are also acceptable.

You should not nurse your baby while on this research study and for 4 weeks following the last day you receive the study medication.

You should notify your study doctor immediately if you become pregnant. We will ask to follow the outcome of the pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may not be a direct medical benefit to you. We hope the information learned from this research study will benefit other patients with COVID-19 and similar viral illnesses in the future.

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WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have the option of not participating. You may continue to receive your usual medical care or participate in other research studies.

WHAT IS THE CLINICAL TRIALS REGISTRY?

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed and dated consent form. You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Your identifying information will be retained at the University of Cincinnati in a locked file with access limited to the study team. You will be assigned a unique code by the site study team. All of your information will be identified only by this unique code. Your information will be maintained for at least 2 years following completion of the study.

The results of this research study may be published in the medical literature and announced to the media. You will not be identified in any publications. The publication or announcement will not contain information about you that would enable someone to determine your identity as a research participant. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by United States Law. This website will not include information that can identify you. At most, the website will include a summary of results. You can search this website at any time.

Results of tests that require medical follow-up or intervention outside of the study will be shared with your personal physician. Future research tests could reveal new information about COVID-19 or other medical disorders. The results of these research studies will not be disclosed to you or your doctor.

Identifiers might be removed from the identifiable private information or identifiable bio specimens and that, after such removal, the information or bio specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

You or your insurance company will be charged for continuing standard medical care. This includes hospitalization, tests and treatments of any side effects of sirolimus. This also includes any referrals to other specialists that are made during the course of this study. You may want to check with your insurance company to determine whether costs associated with these drugs are covered. In the event that your insurance does not cover, you may incur

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additional costs because of treatment for side effects. The study drug will be provided free of charge by the drug manufacturer, Pfizer. Any tests that are done for the purposes of this research study, such as some blood tests and urine pregnancy test will be provided at no cost to you.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not receive any financial compensation for your participation in the research study. Tissues or body fluids obtained in this research may result in the development of a product that could be patented or licensed. There are no plans to provide financial compensation to you should this occur.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

If you believe that you have been injured as a result of this research you should contact Nishant Gupta, M.D. at 513-558-4831 as soon as possible to discuss the concerns. Treatment for injuries is available at University of Cincinnati. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form. University of Cincinnati follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you. The standard medical care for your condition will remain available to you. If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you. If you choose to leave the study, please contact the Project Manager, Tammy Roads, at (513) 558-2148. She or another study team member will discuss your options with you.

The researcher may remove you from this study for any reason. You may be taken off of the study if:

- You fail to follow instructions
- Your condition worsens and either your treating physician or the researcher feel that it is in your best interest to not be in this study
- You need a new medication that is prohibited under this research protocol
- The study is cancelled

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If you have questions about the study, you will have a chance to talk to one of the study staff or your doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have. This consent does not release the investigator, the sponsor, the institution, or its agents from liability for negligence.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI"). PHI is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), which identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.
This information includes your name, address, date of birth, date(s) of treatment, phone/fax/e-mail addresses, medical record numbers, social security numbers, health plan beneficiary numbers, account numbers, and any other unique characteristic or code.

The monitor, the auditor, the Institutional Review Board (IRB), and other regulatory authority(ies) will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you or your legally authorized representative are authorizing such access.

Your identity will remain confidential unless disclosure is required by law. The information from the research study may be published. You will not be identified in any publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant. In order to help protect the confidentiality of your records, you will be identified only by a unique identifier for this study. All study records will be kept in a locked file in a secure location.

A copy of this consent form will be included in your research record. You will be registered in the University of Cincinnati Medical Center's computer system as a research subject. This may be beneficial for future clinical care.

Authorization to Use and Disclose Health Information

A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you. You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know, and a copy will be given to you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form. However, if you do not sign this form, you will not be able to participate in the study.

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Who Will Use and Disclose My Health Information? The study doctor and research staff (the study team) may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication without your permission.

What Health Information will be Used and Disclosed? The study team will record your medical history, the treatment you receive, and the results of examinations and tests done during the study on study forms. The study team will send the completed study forms to the study sponsor. Representatives from the groups identified below may need to look at your medical records to make sure that the information on the study forms is correct or that the study was conducted properly. Your medical records may include other health information about you. This may include documents that directly identify you. Reviews can take place at the study center or where the medical records are stored. Reviews can also take place after the study is over.

Who Will Receive My Health Information? Your study information or medical records (as described above) or both may be shared with the following people or groups:

- The study sponsor or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other study centers
- UC Institutional Review Board and any other committees responsible for overseeing the research
- Staff of the UC Human Research Protection Program
- UC health employees providing service or care to you
- Federal and State agencies, such as the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and other US and non-US government bodies that oversee or review research

Will My Information be Protected by the Privacy Rule after it is Disclosed to Others? UC Health is required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form. They could disclose it to others. The sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the sponsor may reanalyze the study data at a later date. The sponsor may combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs, devices or diseases or to help design better studies in the future. When using your information in these ways, the sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services.

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What Happens if I Leave the Study Early? If you stop participating in the study early for any reason, the study team will tell the sponsor why. If the study team asks you to come to any more study visits and you agree, the study team will send the sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire? This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over. A review of your medical records may also take place after the study is over.

May I Take Back My Authorization? You have the right to take back (revoke) your Authorization at any time. You can do this by writing to the person in charge of this research study. This person's contact information is listed on the front of this form. If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already-collected information if that is necessary for the reliability of the study. The sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look at My Study Information? You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns, complaints and/or suggestions about this research study or to report a research-related injury, please contact the researcher Nishant Gupta, M.D. at 513-558-4831.

Please call the University of Cincinnati Institutional Review Board at 513-558-5259 (Monday – Friday 8 am to 5 pm) if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, complaints and/or suggestions about the research.
- Cannot reach the research team or you want to talk to someone else.

To report complaints or concerns to an independent agency in an anonymous and confidential manner, please call the Research Compliance Hotline at 1-800-889-1547.

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UNIVERSITY OF CINCINNATI - Medical
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Sirolimus Treatment in Hospitalized patients with COVID-19 Pneumonia (SCOPE trial)

UC IRB Study #: 2020-0337

Sponsor Name: Investigator-Initiated

Investigator Information:

Nishant Gupta, MD	513-558-4831
Principal Investigator Name	Telephone Number 24 hr Emergency Contact

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. If I do not participate or if I discontinue my participation, I will not lose any benefits or any legal rights. My participation in this research is completely voluntary. I have received (or will receive) a copy of this signed and dated form for my records and future reference. I have been given the information about the use and disclosure of my health information for this research study.

I give my consent to participate.

Participant	Date

PERSON OBTAINING CONSENT
I have read this form to the participant and/or the participant has read this form. An explanation of the research was given and questions from the participant were solicited and answered to the participant's satisfaction. In my judgment, the participant has demonstrated comprehension of the information.

Signature and Title of Person Obtaining Consent and Identification of Role in the Study	Date

WITNESS
I was present throughout the discussion process for this informed consent document and verify that the subject received explanation of the research, all questions posed by the subject were answered to their satisfaction, and that the subject agreed to participate in the research project.

Signature of witness	Date

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Optional Consent for Future Contact

I agree to be contacted in the future to ask me to consider taking part in other research studies related to COVID-19. To accomplish this, I agree to allow my name, full address, and telephone number to be stored. If I do not agree my contact information will not be stored.

☐ Yes ☐ No _____Initials

Optional Consent for Future Medical Record Review

I agree to allow my complete medical records to be reviewed by the SCOPE trial investigators and study team, for up to two years after I have withdrawn from or completed the study. My caregivers or I may be contacted for copies of my medical records. The purpose of this medical record review is to capture information after the trial ends. This may include clinical, radiographic, pathologic, laboratory and pulmonary function data. Other data may be collected if needed. If I do not agree, my caregivers will not be contacted.

☐ Yes ☐ No _____Initials

_____

Signature of the Participant Date

_____

_____

Signature and Title of Person Obtaining Consent and Identification of Role in the Study Date

_____

_____

Signature of the witness Date