HAWAII CENTER FOR AIDS (HICFA)

CLINICAL STUDY PROTOCOL: **H051**

Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial of the Safety and Efficacy of Telmisartan for the Mitigation of Pulmonary and Cardiac Complications in COVID-19 Patients

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Funding: **HICFA Discretionary Funds; grant application to NIH pending**

Version Number**:** **3.0 (March 25, 2021)**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
CBC	Complete Blood Count
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HICFA	Hawaii Center for AIDS
HIPAA	Health Insurance Portability and Accountability Act
IATA	International Air Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
NP	Naso-Pharyngeal
NSAID	Non-steroidal Anti-inflammatory Drug
OHRP	Office for Human Research Protections
OP	Oro-Pharyngeal
PBMC	Peripheral blood mononuclear cell(s)
PD-1	Programmed death receptor-1
PI	Principal Investigator
PID	Patient identifier number
QA	Quality Assurance
QC	Quality Control
qd	Daily
SAE	Serious Adverse Event
SID	Subject identifier number
SOP	Standard Operating Procedures
Sub-I	Sub-Investigator(s)
UP	Unanticipated Problem
US	United States
WBC	White Blood Cell count
WHO	World Health Organization

STATEMENT OF COMPLIANCE

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

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

The principal investigator, co-investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.

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

Principal Investigator: Cecilia M. Shikuma MD

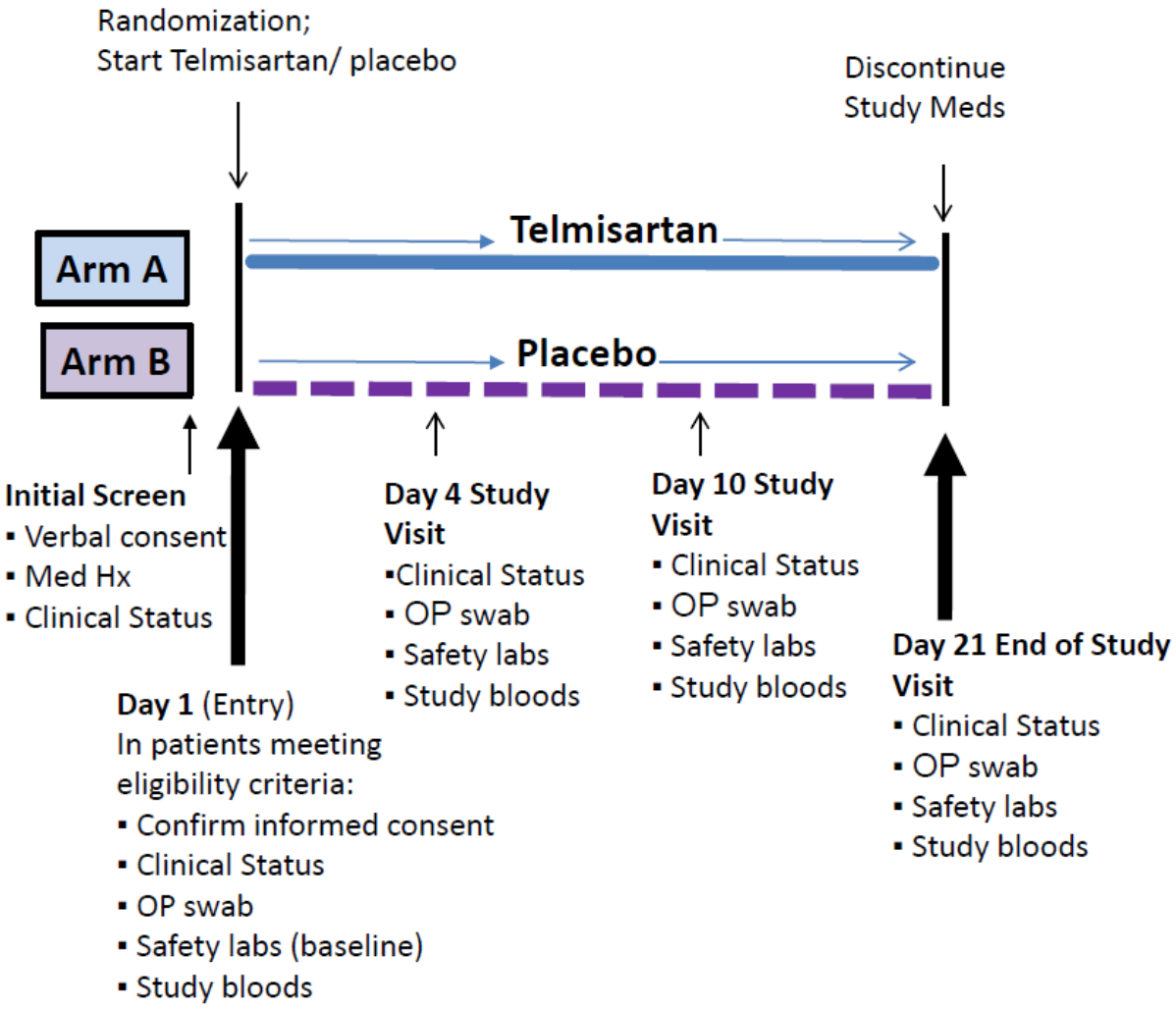
Signed: _____ *Date:* _____

PROTOCOL SUMMARY

Title:	**Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial of the Safety and Efficacy of Telmisartan for the Mitigation of Pulmonary and Cardiac Complications in COVID-19 Patients**
Study Description:	This study will enroll 40 symptomatic outpatients tested positive for COVID-19. Participants to be randomized 1:1 to Telmisartan (40 mg) vs placebo to be administered orally once daily x 21 days. Daily, the study participants will be asked to keep a record of the severity of their fever, dyspnea, and fatigue and to take their blood pressure (BP) and temperature. Study visits will occur on day 1 (entry), day 4, day 10 and day 21. Oro-pharyngeal swabs, and approximately 25 cc of blood will be collected at each study visit for safety labs and for the evaluation of the renin-angiotensin system (RAS) system and for various blood biomarkers of organ function/coagulation, inflammation, leukocyte chemotaxis, tissue remodeling/fibrosis and immune exhaustion.
Objectives:	Primary Objective: Compare the maximum clinical severity of disease between the telmisartan and the placebo arms utilizing a modified WHO COVID-19 7-point ordinal scale *Hypothesis:* Overall severity of disease will be less on the telmisartan arm compared to the placebo arm Secondary Objectives: ▪ Evaluate the safety and tolerability of Telmisartan when given over 21 days to patients with COVID-19 disease ▪ Compare the circulating RAS metabolites between the 2 arms; assess the ability of RAS metabolites to predict clinical status ▪ Compare plasma biomarkers between the 2 arms; assess the ability of plasma biomarkers to predict clinical status Exploratory Objective: ▪ Longitudinally assess the detectability of SARS-CoV-2 virus
Endpoints:	Primary Endpoint: Maximal clinical severity of disease utilizing a modified WHO 7-point ordinal scale Secondary Endpoints: ▪ Number of grade II or higher adverse events (AE) through day 21 of study ▪ Levels of various components of the RAS system including Ang(1-12), AngI, AngII and Ang(1-7) ▪ Levels of various blood biomarkers Exploratory Endpoint: ▪ SARS-CoV-2 detectability in OP samples
Study Population:	Forty (40) symptomatic participants diagnosed positive for COVID-19.

Phase:	Phase II trial
Description of Sites/Facilities Enrolling	Single site study at the John A. Burns School of Medicine – Kakaako campus, University of Hawaii
Description of Study Intervention:	Telmisartan is a member of a family of angiotensin receptor blockers (ARB) anti-hypertensive medications.
Study Duration:	One year total duration of study
Participant Duration:	21 day participation for each patient

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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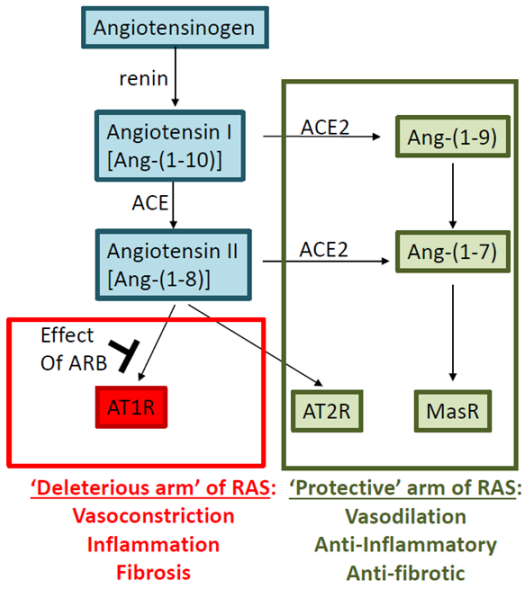
2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

COVID-19 Pandemic As of the writing of this protocol, there 2,394,278 cases of Covid-19 in 185 countries and regions throughout the world and approximately 83,764 new cases occur daily. In the largest cohort of >44,000 persons with COVID-19 from China, while disease severity was mild to moderate in 81%, pulmonary and multi-organ system dysfunction complications account for the majority of the morbidity and mortality of this disease. Severe disease (dyspnea, hypoxia, or >50% lung involvement on imaging) occurred in 14%, and critical disease (respiratory failure, shock, or multiorgan system dysfunction) occurred in 5%. Among U.S. COVID-19 cases with known disposition, the proportion of persons who were hospitalized was 19%[1]. Among patients who developed severe disease, the medium time to dyspnea ranged from 5 to 8 days, the median time to acute respiratory distress syndrome (ARDS) ranged from 8 to 12 days, and the median time to ICU admission ranged from 10 to 12 days[2-5]. Age is a strong risk factor for severe illness, complication and death[1], and the case fatality is higher for patients with co-morbidities: 10.5% for those with cardiovascular disease, 7.3% for diabetes, and approximately 6% each for chronic respiratory disease, hypertension and cancer[6].

Figure 1. 'Deleterious' and 'Protective' Aspects of the Renin-Angiotensin System (RAS)



Compared to other states, Hawaii has had relatively few cases (574 confirmed COVID-19 cases as of April 19, 2020). Early institution of public health measures including the mandatory 14-day quarantine for all individuals flying into Hawaii have been credited for these low number. However, without an effective vaccine, as normalization of the economy and re-opening of our state to visitors are attempted, more cases of COVID-19 may be inevitable.

Renin-Angiotensin System (RAS) RAS is a hormonal system best known for its ability to regulate blood pressure, fluid and electrolyte balance and systemic vascular resistance. As shown in very simplistic form in Figure 1, angiotensinogen, released by the liver, is converted by the action of renin into angiotensin I [AngI; also known as Ang-(1–10)]. AngI is subsequently converted to angiotensin II [AngII; Ang-(1–8)] by the angiotensin-converting enzyme (ACE1) found on the surface of vascular endothelial cells, predominantly in the lung.

The effect of AngII is receptor-specific with 2 predominant receptors: angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). AngII/ AT1R binding leads to the classic 'deleterious'

effects of AngII, including hypertension, arterial wall thickening, impaired lung function and fibrosis. It has increasingly been demonstrated that AngII/AT1R binding also plays an important role in lung inflammation, impaired function and fibrosis. In mouse models of ARDS, AngII/AT1R binding leads to impaired lung function and fibrosis[7]. Elevated circulating AngII concentrations in influenza A (H7N9) pneumonia were associated with higher mortality rates[8]. Angiotensin receptor blockers (ARB) medications such as telmisartan used for the treatment of hypertension and cardiovascular risk reduction exerts its known anti-hypertensive, cardio -protective effect by blocking the binding of AngII to AT1R. There is evidence that ARB may also have lung-protective effects[9].

Accumulating evidence suggests that, in contrast, an alternative, counter-regulatory 'protective' arm of the RAS system exists and that it is mediated by 2 alternative pathways as shown in Figure 1 which may be inter-related: (1) an alternative interaction of angiotensin II with AT2R; and (2) the activity of the enzyme angiotensin-converting enzyme 2 (ACE2) to cleave AngI and AngII ultimately to angiotensin (1-7) [Ang(1-7)]. Both the angiotensin II/AT2R and the angiotensin (1-7) /Mas receptor (MasR) interactions promote the counter-regulatory 'protective' effects of RAS that includes vasodilation, anti-inflammatory and anti-fibrotic responses. Our collaborator for this project (S Louie PharmD) and his colleagues have published that increased activity of this counter-regulatory RAS system as measured circulating angiotensin peptide levels correlate with survival of Acute Respiratory Distress Syndrome (ARDS) patients[10].

SARS-CoV2 and ACE2 Severe Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) responsible for the SARS epidemic in 2002 to 2004, and the SARS-CoV-2 virus responsible for the current COVID-19 pandemic, both utilize ACE2 as the receptor to enter the cells it infects[11,12]. ACE2 is found attached to the cell membrane of lung alveolar epithelial cells, enterocytes of the small intestines, arterial and venous endothelial cells and arterial smooth muscle cells in most organs[13]. **It has been postulated that the lack of ACE2 may lead to unopposed AngII accumulation and local unfavorable RAS activation, and therefore may be responsible for much of the organ injury in COVID-19 disease[14].** Several data support this view. Down-regulation of ACE2 abundance on cell surfaces has been demonstrated in mouse studies after the initial engagement of SARS-CoV-2 spike protein[15]. Down-regulation of ACE2 activity in the lung in response to bacterial endotoxin in a murine model has been shown to promote the release of proinflammatory chemokines, increase neutrophil infiltration, and exaggerate lung injury[16]. Elevated levels of plasma AngII have been demonstrated in a small study of patients with COVID-19 which in turn correlated with total viral load and degree of lung injury[17]. In autopsies of patients who died from SARS, 35% of heart samples showed the presence of viral RNA, which in turn was associated with reduced ACE2 protein expression[18].

Telmisartan an ARB approved in 1998 for the treatment of hypertension and for cardiovascular risk reduction. It is marketed by Boehringer Ingelheim Pharmaceuticals, Inc as Micardis but is also available in generic form. The dosage of 40 mg once daily is the recommended starting dose. The drug has been evaluated for safety in more than 3700 patients in clinical trials. Adverse events are generally mild with overall rates similar to that in placebo and rarely require discontinuation of therapy. The adverse events most commonly seen were upper respiration infection, back pain, sinusitis, diarrhea and pharyngitis. There are only a few contraindications to its use in the package insert. It is contraindicated in individuals with diabetes who are also receiving concomitant aliskiren, has a black box warning to discontinue telmisartan when pregnancy is detected because of fetal toxicity and should not be used while breast feeding. Telmisartan may also increase digoxin and lithium levels upon co-administration. Nonsteroidal

anti-inflammatory agents and COX2 inhibitors could reduce the antihypertensive effects of telmisartan and can decrease renal function. **Evidence for potential antiviral activity of Telmisartan** Computational methods for screening and identifying candidate therapeutic compounds are a reliable and productive approach in drug discovery. Our group implemented a structure based virtual screening method to identify compounds that may have activity against SARS-CoV-2. Of the over 1900 compounds screened, we identify an angiotensin receptor blocker with binding affinity for the viral 3 Chymotrypsin-like protease (3CLPro) (Souza, unpublished data. comparable to the N3 inhibitor of the crystal structure (PDB 6LU7). Its lowest energy conformer places the benzoic acid moiety of telmisartan over the active site of 3CLpro defined by Cys 145 and His 41[19]. By amino acid sequence alignment of SARS CoV pp1ab with SARS-CoV-2 pp1ab, 3CLpro is thought to be responsible for cleaving the SARS-CoV-2 pp1ab at 11 sites that result in the formation of 11 non-structural proteins (Nsp)[20]. Among these proteins are Nsp12, the RNA dependent RNA polymerase (RdRp), a key enzyme responsible for replication of SARS-CoV-2 RNA, Nsp7 and Nsp8 (cofactors for RdRp) and Nsp 13 (Helicase).

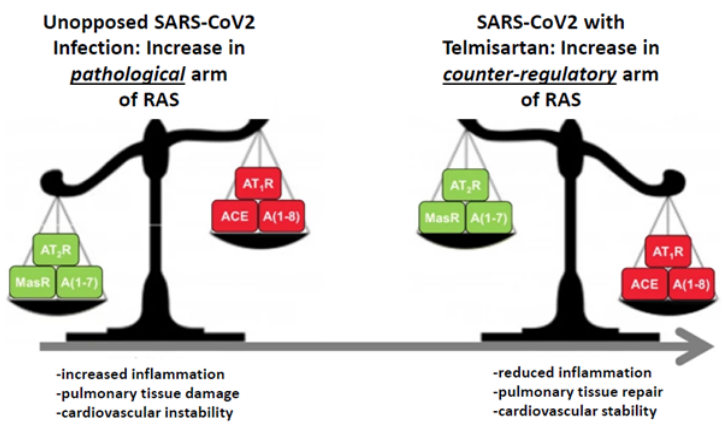
We further characterized the interaction between telmisartan and 3CLpro using an atomistic molecular dynamics simulation. The N3 ligand associated with the crystal structure was used to locate the substrate binding cleft of 3CLpro and study the interaction with telmisartan. One monomer (the 3CL protease exists as a dimer, but the binding site is far from the monomer-monomer interaction area and one telmisartan molecule were solvated in water and were allowed to interact in unbiased simulations over a timeframe of microseconds. Preliminary data suggest that telmisartan forms a favored interaction with the 3CLpro binding site. It is important to note that further inside from the initial binding site, there is a hollow area that includes hydrophilic residues, making further tight binding possible. Our results support the bioinformatics study which suggests telmisartan shows a promising binding propensity for 3CLpro.

RATIONAL FOR THE STUDY:

There is a need for a therapeutic modality to minimize the severity of COVID-19 disease Currently there are no FDA-approved drugs demonstrated safety and efficacy in randomized controlled trials in patients with COVID-19. *A*s of April 10, 2020, there were over 440 clinical trials of COVID-19 registered on ClinicalTrials.gov. While there were a few trials proposing to utilize another ARB losartan singly or in combination, to the best of our knowledge this is the only trial to propose telmisartan.

Telmisartan is an FDA-approved drug. **Repurposing FDA approved drugs can expedite the treatment of diseases particularly for conditions of unmet needs.** The safety of these drugs has already been evaluated by the FDA and the risk associated with their use is well documented. Repurposed drugs can lower development costs and shorten the time it takes to treat patients.

Figure 2. (Left) Unopposed SARS-CoV2 viral influence on the RAS and (Right) SARS-CoV2 viral influence on RAS with the addition of Telmisartan (Adapted from Stone, RE et al Journal of Neuroimmune Pharmacology 2019)



Our central hypothesis is that the use of telmisartan will mitigate the symptomatic severity of COVID-19 disease by influencing the balance between the pathologic and counter-regulatory aspects of RAS. As shown in Figure 2A (left), the binding of the SARS-CoV2 virus to ACE2 results in an imbalance in the

RAS with an increase in the pathologic effects mediated by a decrease in ACE2, i.e. an increase in AngII with excessive binding to AT1R and a decrease in the counter-regulatory protective effects of angII/AT2R and A(1-7)/MasR binding. *We hypothesize that telmisartan (Figure 2 right) will block the AT1R receptor, and correct this imbalance, i.e. resulting in a decrease in AngII/AT1R binding and an increase in AngII/AT2R and A(1-7)/MasR binding.*

In addition, *we hypothesize that telmisartan may have an anti-viral effect against SARS-CoV-2.* By computer simulation, telmisartan appears to have the ability to bind to the 3CL protease and may effectively prevent the creation of discrete viral proteins necessary for the development of infectious SARS-CoV-2 virions.

This pilot study will provide **important preliminary data on the pathogenesis of COVID-19 disease.** We propose assays of RAS peptides performed by a laboratory with demonstrated expertise in this area Assays of circulating angiotensin peptides levels conducted in Dr. S Louie's laboratory have been used to correlated clinical outcomes in patients with Acute Respiratory Distress Syndrome[10]. We also propose to assay various plasma biomarkers of organ function/coagulation, inflammation, leukocyte chemotaxis, tissue remodeling/fibrosis and immune exhaustion.

2.2 POTENTIAL RISKS AND BENEFITS

2.2.1 KNOWN POTENTIAL RISKS

According to the FDA- approved package insert, telmisartan is contraindicated in individuals with a history of known hypersensitivity to the drug or its components and in individuals with diabetes who are also receiving concomitant aliskiren. It is not recommended in pregnant or breast feeding female because it can reduce fetal renal function and increase fetal and neonatal morbidity and death. NSAIDs is believed to increase risk of renal impairment and loss of anti-hypertensive effect. Co-administration with digoxin increases the digoxin peak plasma concentration (49%) and in trough concentrations (20%). Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium.

The drug has been evaluated for safety in more than 3700 subjects in clinical trials, including 1900 for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy. In placebo-controlled trials, the overall incidence of adverse events was similar to that in patients treated with placebo. Adverse events occurring at an incidence of $\geq$ 1% in in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their casual association, were as below:

	Telmisartan n=1455 %	**Placebo n=380 %**
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. Warning and precautionary measures recommended in the package insert include the need to correct or follow closely patients who are volume- or salt-depleted; and to monitor for risk of hyperkalemia particularly in those with advanced renal impairment, heart failure or on renal replacement therapy.

2.2.2 KNOWN POTENTIAL BENEFITS

Telmisartan is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. According to the package insert, the antihypertensive effects of Telmisartan have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20 to 160 mg; one of these examined the antihypertensive effects of Telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95 to 114 mmHg), 1031 of whom were treated with Telmisartan. Following once daily administration of Telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6 to 8/6 mmHg for 20 mg, 9 to 13/6 to 8 mmHg for 40 mg, and 12 to 13/7 to 8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Some beneficial effects not related to its anti-hypertensive effects have also been reported at least for ARB medications in general. ARB medications have been reported to suppress mediators of inflammation, including ROS and C-reactive protein, and they increase expression of inhibitory κB (an inhibitor of nuclear factor-κB)[21,22]. It has also been reported that the use of ARBS lower progression of emphysema and lower incidence of inflammatory complications including rates of pneumonia and influenza[9]. In animal models, inhibition of AT_1 signaling has been shown to attenuate experimental pulmonary fibrosis induced by bleomycin, radiation, and hyperoxia. In a pilot clinical study, Couluris et al. evaluated the effect losartan, an AT_1 antagonist, on idiopathic pulmonary fibrosis progression over 12 months[23]. The study demonstrated stable or improved pulmonary function testing in 12 of the 17 patients treated with losartan. The authors concluded that losartan is a promising low-toxicity agent for treatment of idiopathic pulmonary fibrosis that requires more extensive evaluation in a placebo-controlled multicenter trial.

3 OBJECTIVES AND PURPOSE

Primary Objective: Compare the maximum clinical severity of disease between the telmisartan and the placebo arms utilizing a modified WHO COVID-19 7-point ordinal scale

Secondary Objectives:

- Evaluate the safety and tolerability of Telmisartan when given over 21 days to participants with COVID-19 disease
- Compare the circulating RAS metabolites between the 2 arms; assess the ability of RAS metabolites to predict clinical status
- Compare plasma biomarkers between the 2 arms; assess the ability of plasma biomarkers to predict clinical status

Exploratory Objective:

- Longitudinally assess the detectability of SARS-CoV-2 virus

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

A 21 day, randomized, double-blind, placebo-controlled pilot study of Telmisartan in patients with symptomatic COVID-19 disease. The study is structured as a pilot study to assess whether telmisartan may be effective in mitigating the pulmonary and cardiac complications of COVID-19 disease. Forty study participants will be randomized 1:1 to receive Telmisartan 40 mg or Placebo once daily for 21 days. Study specific procedures include daily log of fever, dyspnea and fatigue symptomology and daily blood pressure and temperature monitoring to be performed by the participant. Oro-pharyngeal swab, and blood draw for safety labs and research assays will be obtained at day 1 (entry), day 4 (72 hours post entry), day 10 and day 21 (end of study).

4.1.1 PRIMARY ENDPOINT

The primary endpoint is the maximum clinical severity of disease for each participant as assessed on a 7-point **Clinical Status** ordinal scale adapted from the WHO MASTER PROTOCOL for the Treatment of COVID-19 in Hospitalized Patients. The WHO 7-point scale was modified by adding sub-categories for the categories of 'Not hospitalized, limitation on activities' (based on scoring on a **Symptom Scale** to be filled out by participants daily, as explained below), as well as for the 'Hospitalized, requiring supplemental oxygen' and 'Hospitalized, on non-invasive ventilation or high flow oxygen devices' categories. For non-hospitalized participants, the maximum clinical severity recorded for any day $\geq$ day 3 of study will be used. For participants who become hospitalized, the maximum clinical severity prior to discharge will be used.

Clinical Status Classification	Score
Not hospitalized, no limitations on activities	1.0
Not hospitalized, limitation on activities as assessed by the **Symptom Scale** below	
(a) $\leq$ 3 points	2.0
(b) 4-6 points	2.25
(c) 7-9 points	2.5
(d) 10-12 points	2.75
Hospitalized, not requiring supplemental oxygen;	3.0
Hospitalized, requiring supplemental oxygen:	
(a) Requiring supplemental oxygen at < 6 L/min	4.0
(b) Requiring supplemental oxygen at $\geq$ 6 L/min	4.5
Hospitalized, on non-invasive ventilation or high flow oxygen devices	
(a) Non rebreather mask	5.0
(b) Noninvasive ventilation (NIV), high flow O_2 devices	5.5
Hospitalized, on invasive mechanical ventilation or ECMO	6.0
Death	7.0

'Symptom Scale' to be used for sub-classification of the 'Not hospitalized, limitation on activities' category on the modified WHO 7-point ordinal scale is as shown below. The participant will be asked to daily grade each symptom by severity to obtain a total score. For example, the assessment of grade 2 fever (2 points), grade 1 breathing (1 point) and grade 3 fatigue (3 points) will result in a total score on the symptom scale of 6 for that day. Referring back to the **Clinical Status** classification above, the clinical status on the 7 point ordinal scale would be 'not hospitalized, limitation on activities (b) 4-6 points' for a clinical status score for the participant on that day of 2.25.

SYMPTOM SCALE For each symptom below, please circle and grade how bad the symptoms were from Grade 0 (None, 0 point) to Grade 4 (Severe, 4 points):	**Grade 0** **(No symptom)** **(0 point)**	**Grade 1** **(Mild symptom)** **(1 point)**	**Grade 2** **(Moderate symptom)** **(2 point)**	**Grade 3** **(Moderately severe symptom)** **(3 points)**	**Grade 4** **(Severe symptom)** **(4 points)**
FEVER In the previous 24 hours, my highest temperature was	**Less than 100.4°** (=No fever)	**100.4° to 101.4°**	**101.5° to 102.6°**	**102.7° to 103.9°**	**104° or above**
BREATHING I am short of breath -	**None of the time**	**A little of the time** (only when doing things that require extra effort like cleaning the house or walking rapidly or uphill)	**Some of the time** (I have to stop for breath when walking at my own pace)	**Most of the time** (I have to stop for breath when speaking)	**All the time** (even at rest when doing nothing)
FATIGUE I have -	**No fatigue**	**A little bit of fatigue** but it does not prevent me from doing the things I usually do	**Some fatigue** which is preventing me from doing some of the things I usually do	**Moderate fatigue** which is preventing me from doing most of the things I usually do	**Severe fatigue** I cannot take care of myself (dressing, taking a shower, brushing my teeth)

4.1.2 SECONDARY ENDPOINT

- Number of grade II or higher adverse events (AE) through day 21 of study
- Levels of various components of the RAS system including Ang(1-12), AngI, AngII and Ang(1-7)
- Levels of various blood biomarkers

4.1.3 EXPLORATORY ENDPOINTS

- SARS-CoV-2 detectability in OP samples

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

- Able to provide written informed consent prior to initiation of any study procedures.
- Understands and agrees to comply with planned study procedures including self testing of blood pressure daily
- Male or non-pregnant female adult ≥18 years of age at time of enrolment.
- Subject reported positive SARS-CoV-2 test by a commercial laboratory or public health assay in any specimen collected ideally < 72 hours prior to randomization. Exceptions to the <72 hr inclusion criteria may be made at the discretion of the investigator.
- Positive for COVID-19 symptoms: **fever** defined as a temperature of ≥100.4 on study screening or self-report of daily fever at home OR **shortness of breath** of any degree OR **fatigue** causing greater than minimal interference with usual social & functional activities
- Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study
- Able to easily swallow pills

5.2 PARTICIPANT EXCLUSION CRITERIA

- Immediate need for hospitalization on screening
- Systolic blood pressure less than 100 mmHg
- Self-reported presence of chronic kidney disease or requiring dialysis
- Self-reported history of liver failure or untreated hepatitis B or C
- Pregnancy or breast feeding
- Allergy to the study medication
- Current use of ARB or ACE Inhibitor medications. Other blood pressure medications will be permitted in the systolic BP is higher than 90 mmHg
- Prior reaction or intolerance to ARB or ACE Inhibitor
- Use of aliskiren participant
- Current use of and on-going need for lithium, digoxin, potassium sparing diuretics such as spironolactone
- Current use of and need for potassium supplements
- Current or past participation in a research study within 12 weeks prior to the Screening Visit unless cleared by Study Team
- Inability to arrange a safe environment for study visits
- Subjects, who, in the opinion of the investigator, are unable to comply with the protocol evaluation, or for whom study participation may not be advisable

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Information about the study will be circulated widely to community physicians and medical establishments. Information about the availability of the study may be distributed at SARS-CoV-2 test sites or made known by public advertisement including by web. All advertisement materials will be approved by the UH Human Subjects Committee prior to its use.

To compensate participants for time and effort, participants will be given $60 at each study visit, for a maximum of $240 total ($60 x 4 visits) for participation in the study.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Each participant may discontinue study drug and/or withdraw completely from the study for any reason. The date and reason for termination or withdrawal will be documented.

Premature Termination of Study Drug for a study participant may occur for the following reasons:

- Possible drug-related AE or toxicity which, in the judgment of the PI or Sub-I, is considered to not be in the subject's best interest
- Request by the subject to terminate study drugs
- Subject cannot make scheduled visit(s)
- Subject does not provide OP or blood sample(s)

Withdrawal completely from the study may occur for the following reasons:

- Failure to comply with the provisions of the protocol
- Request by the subject to withdraw.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participants may withdraw or terminate involvement at any time for any reason, and that request will be honored.

No discontinuation visit is necessary. However, participants who terminate or withdraw for toxicity reasons will be followed for that toxicity until the toxicity is resolved.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated at the discretion of the study team. Study participants will be informed of study suspension or termination and whether the circumstances that led to this decision confers possible added risk to study participants.

Regulatory authorities including the IRB, the Food and Drug Administration (FDA), and ClinicalTrials.gov will be notified as warranted.

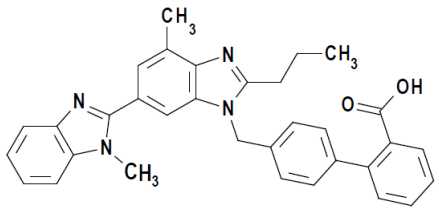
6 STUDY AGENT

6.1 STUDY AGENT AND CONTROL DESCRIPTION

6.1.1 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist.

It is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is C33H30N4O2, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base

Telmisartan is available as a patented drug originally FDA approved in 1998 and marketed under the trade name Micardis. Multiple different generics are also available with tablets varying in size, color, and shape. The appearance, packaging and labeling also differs by the generics on the market. This study will select and utilize one specific formulation for all its needs.

6.1.2 PRODUCT STORAGE AND STABILITY

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)

6.1.3 PREPARATION

Study medication to be dispensed to participants will be prepared by the research pharmacist. Telmisartan and matching placebo will be prepared using over-encapsulation.

6.1.4 DOSING AND ADMINISTRATION

Telmisartan will be dosed in this study as one tablet of 40 mg to be taken by mouth daily. All study medication will be dispensed to the study participant by the research pharmacist provided to the participant by the research nurse.

6.1.5 ROUTE OF ADMINISTRATION

Study drug will be taken orally with or without food.

6.1.6 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Participants will be randomized to one 40 mg tablet of Telmisartan daily or one placebo tablet daily. There is no dose reduction or escalation for this study.

6.1.7 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

The toxicity grading system that will be used is the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, located at:

https://rsc.tech-res.com/docs/default-source/safety/daids-aegrading-table-v2-nov2014.pdf

6.1.8 DURATION OF THERAPY

The study medication will be given for a duration of 21 days.

6.1.9 TRACKING OF DOSE

Subjects will be asked to bring back any medication not taken.

6.1.10 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Drug Accountability
The pharmacist will be responsible for ensuring adequate accountability of all used and unused study drug. This includes ordering and acknowledgment of receipt of study product (quantity and condition), subject dispensing records and returned or destroyed study product. Accountability records will document quantities including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication. Study drug will not be supplied to any person who has not consented to participate in the study. Persons authorized to distribute and control the study medication include the PI or Co-I listed on the FDA 1572 and designated staff.

Unused Study Drug
Upon study completion, unused study drug will be destroyed at the research unit (verified by witness). Original drug accountability records must be maintained in the site's records.

Placebo
Tentative plans for placebo call for the use of gelatin capsules filled with an inactive ingredient. To provide a similar appearance, telmisartan tables will be over-encapsulated with the gelatin capsules.

6.3 STUDY PROCEDURES/EVALUATIONS

6.3.1 STUDY SPECIFIC PROCEDURES

Study specific procedures include obtaining oropharyngeal swabs and research blood specimens.

6.3.2 STANDARD OF CARE STUDY PROCEDURES

Other than monitoring safety labs to assess lack of adverse events on study medication, this protocol is not meant to provide clinical care of patients with COVID-19 disease.

6.4 LABORATORY PROCEDURES/EVALUATIONS

6.4.1 CLINICAL LABORATORY EVALUATIONS

Hematology: Complete blood count (CBC)

Chemistries: Chemistry to include sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), aminotransferase (AST), alkaline phosphatase (ALK-P), total bilirubin, albumin, and glucose. In addition, LDH and hs-CRP will be assessed serially.

6.4.2 OTHER ASSAYS OR PROCEDURES

Research bloods will be drawn, processed to separate into viably preserved PBMC and plasma, and banked for batch analyses of the following:

RAS assessments: Assessments of various components of the RAS system will be performed in Dr. Stan Louie's lab. This is anticipated to include RAS peptides to be drawn in protease inhibitor containing tubes to include AngI, AngII, Ang(1-9) and Ang(1-7); ACE1 and ACE2 in plasma; and ACE1, ACE2, AT1R, AT2R and MasR in PBMC. In addition, one cc of plasma will be forwarded to Dr. Louie's lab for ACE1 and ACE2 enzymatic evaluation. A vial of 5 million cells will be forwarded for RT-PCR for AT1R, AT2R, MasR, ACE1 and ACE2 as well as neprilysin (NEP) and aminopeptidase A (APA).

Plasma Biomarkers: Blood plasma will be assessed for plasma biomarkers of organ function/coagulation, inflammation, leukocyte chemotaxis, tissue remodeling/fibrosis and immune exhaustion by Luminex multiplexing assays. While subject to change the following analytes are planned:

Organ Function/Coagulation	Inflammation		Leukocyte Chemotaxis	Tissue Remodeling/Fibrosis	Immune Exhaustion
CKMB	CRP	TNF-α	Fractalkine/CX3CL1	MMP-1	TIM-3
LDH-B	Ferritin	TNF-RI	MCP-1/CCL2	MMP-7	Galectin-9
NTproBNP	IL-1β	TNF-RII	MCP-3/CCL7	PDGF-BB	PD-1
Troponin I	IL-1ra	M-CSF	MIP-1α/CCL3	CHI3L1/YKL-40	PD-L1
Myoglobin	IL-2	G-CSF/CSF-3	MIP-1β/CCL4	LAP	CD152/CTLA-4
KL-6	IL-2R	IDO	MIP-2α/CXCL2	TIMP-1	PVR
SP-A	IL-4	TWEAK	IP-10/CXCL10	PAI-1/Serpin	VISTA/B7-H5
SP-D	IL-6	TREM-1	IL-8/CXCL8		GITR
D-dimer	gp130/IL-6RB	PTX-3	ICAM-1		BTLA
tPA	IL-7	TSLP	VCAM-1		
	IL-9	Siglec-9	E-selectin/CD62E		
	IL-10	NGAL	MIG/CXCL9		
	IL-17A/CTLA-8	Galectin-3	CCL18/PARC		
	IL-33R/ST2	MPO			
	IFN-γ	PRDX4			

Oro-pharyngeal Swab: Oro-pharyngeal swabs will be obtained at each study timepoint. These will be collected using a foam swab and placed in a multi microbe media (M4, M4RT, M5, M6), VCM (UTM) medium (green-top) tube, Amies liquid elution swab (ESwab), or equivalent Viral Transport Media (VTM). Once placed in the appropriate viral media, the specimens will be frozen at -70C and sent out for batch analysis at a later date. While it is currently anticipated that the study will utilize oro-pharyngeal swabs for determination of viral persistence, it is possible that naso-pharyngeal swabs or saliva testing or other means of viral detection may be substituted depending on sensitivity/specificity, availability, and cost.

6.4.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

6.4.3.1 Blood Draw

Collection of blood will occur at the specified time points for clinical laboratory assessments and for research blood for assays to be conducted on cryopreserved blood. The quantity of blood to be drawn at each setting is defined in the Schedule of Events.

Whole blood will be obtained by venous puncture and processed by the Processing Laboratory ideally within 1 hour of collection. If processing will be delayed (2-3 hours), the collection tube should be placed on a slow rocking table until processed.

6.4.3.2 Blood for RAS assessments

Blood will be drawn in specific tubes pre-filled with protease solution to enable to determine of various RAS components. These pre-filled tubes will be obtained from Dr. Stan Louie's laboratory and will be forwarded to his lab in Los Angeles for RAS analyses.

6.4.3.3 Plasma (EDTA tube) for banking

Plasma is separated from whole blood collected in EDTA vacutainers.

1. Spin vacutainer at 900xg for 10 minutes at room temperature (RT) to separate plasma from blood cells.
2. Remove plasma and save tube to process white blood cell separation.
3. Transfer plasma to a labelled 15mL conical Falcon tube and centrifuge at 820xg for 10 minutes at 4°C.
4. Aliquot plasma into 1mL labelled cryovials (3 to 4 aliquots).
5. Cryovials are stored at -20°C for 24 hours before being transferred to long-term cryobox storage at -80°C or placed in liquid nitrogen Dewar to snap freeze.

6.4.3.4 Peripheral Blood Mononuclear Cells (PBMC)(EDTA tube)

1. Resuspend EDTA blood pellet after plasma separation with 2x DMSO freezing medium in 1:1 ratio and freeze in 1 mL aliquots at -80°C after counting total WBCs for use in chloramine analysis assay.
2. Follow standard Ficoll Hypaque procedure to separate PBMC from 10 mL of heparinized blood.
3. Perform a cell count of the isolated PBMC.
4. Add appropriate DMSO/FBS solution for a final concentration of $5x10^6$ cells/mL.
5. Transfer 1mL aliquots ($5x10^6$ cells) to 1.25 mL cryovials. Store in Mr. Frosty at -80°C for at least 24 hours before transferring samples to long-term -140°C storage.

6.4.4 SPECIMEN SHIPMENT

Blood tubes for RAS assessment will be shipped to Dr. Stan Louie's lab at a minimum of q monthly intervals. Plasma and viably preserved PBMC will also be forwarded to Dr. Louie's lab for the planned extended analysis of the RAS components.

6.4.5 SCREENING

6.4.5.1 Initial Medical History by Phone Interview

Verbal informed consent and medical history will be obtained by phone or video-conference (selected at caller preference) interview with the potential participant. The interview will record:

- Current Illness: Obtain date of onset of current illness, date of SARS-CoV2 testing and date the positive test was reported back to the participant. Review participant's signs and symptoms associated with the illness with a focus on presence, course, and severity of fever, dyspnea and fatigue. Record grade of fever, dyspnea and fatigue on symptoms scale.
- History of co-morbidities including history of cardiovascular disease including history of hypertension, history of pulmonary diseases; history of pre-diabetes or diabetes, history liver, kidney disease or auto-immune/ immune deficiency diseases and history of alcohol, tobacco, or illicit substance abuse
- Current prescription and over-the-counter medications and medication allergies
- Self-reported weight and height

The potential participant will be asked to bring his or her COVID-19 test result to the person-to-person screening/entry visit. If documentation of the COVID-19 test result is unavailable, the potential participant will be given the option of obtaining it or providing the researchers permission to obtain the test result (this will be done at the Entry visit).

6.4.6 FOLLOW-UP SCREEN AND ENROLLMENT/BASELINE [ENTRY VISIT (VISIT 1, DAY 1)]

Potential participants who have verbally consented to the study will be given an appointment for a follow-up person-to-person screening/entry visit as soon as possible – preferably the same day. The screen/entry visit should occur within 24 hrs of the telephone screening visit.

This screen/entry in-person visit will preferably be conducted outside with the participant in his/her car or sitting comfortably in a portable tent set up in the clinic parking area of the UH Clinics at Kakaako. Study visits in other venues will be considered on a case-by-case basis. It is envisioned that such visits in other venues may occur if the participant is not able to come to the UH Clinics at Kakaako parking area in a safe manner. Study visits in other venues will occur only if the participant is willing and the setting can a) ensure participant safety; b) will not increase risk of infection or pose any other safety issues for our clinical research staff; c) will ensure adequate privacy for the participant; d) the location will allow satisfactory performance of all study mandated procedures; and e) will not break any state or county law or ordinance. A 'safe' study visit location away from the UH Clinics at Kakaako premises may include, for example, an outside patio open to outside air flow attached to the participant's home located within the immediate Honolulu area (i.e. not a distance which may make blood transport back within a reasonable time frame difficult) that could be assessed without entering the home and would ensure adequate privacy and acceptability for the participant. We will mandate that the PI (C. Shikuma), clinical Sub-Investigator (D Chow), unit coordinator (D Ogata-Arakaki), research nurse and all staff physically planning to conduct this study visit in a different venue must ALL be in agreeable that the venue is safe BEFORE a different venue is permitted. If all members of the research team are fully vaccinated (are at least 14 days beyond completion of his/her COVID-19 vaccine series), it may be decided that completing most of the interview by phone but entering the home in full PPE briefly to complete certain research needs (such as a blood draw) may be acceptable.

- Informed consent document will be reviewed. The participant will be provided with the informed consent document, asked to sign and a photo taken of the informed consent signature page.

- The current signs and symptoms will be reviewed and the presence of symptoms sufficient to meet entry requirements will be confirmed. Entry Symptom Scale and Clinical Status to be recorded.
- A photo of the person's COVID-19 test result will be taken. If unavailable and the person opts to have the researchers request it, the person will provide signed permission Consent to Release Information and a photo will be taken of the document. This will permit researchers to obtain the test result document. Also, the person will be asked to sign the Consent to Release in case of hospitalization.

With confirmation of study eligibility:

- Vitals signs will be taken to include temperature, pulse, blood pressure, respiratory rate, and O_2 sat.
- Oro-pharyngeal swab will be obtained
- Blood draw for clinical safety labs and for research assays in quantity as specified in the Schedule of Events.
- The participant will be given a Symptoms log and instructed to daily take and record his/her own blood pressure and temperature. Temperature should also be taken whenever there is tactile fever. The participant will be provided with a digital thermometer and BP monitor as needed and instructed in their use. The participant will be asked to call *immediately* if systolic blood pressure falls below 90 mmHg and to NOT take further study medications unless advised by the study team that it is safe to do so.
- The pharmacist will randomize study participant to telmisartan or placebo; then the study medication will be dispensed to the participant. Participant will be instructed to take first dose as soon as he or she is home.
- Provide the following instructions to participants:
    - Take BP daily at generally the same time of the day and record on Symptoms log. Call research team if SBP is <90 and do not take further study medication unless instructed to do so by the research team.
    - Take temperature whenever a fever is suspected but at least once daily and record
    - Record appropriate fever, dyspnea and fatigue symptoms daily
    - Record the time study medication is taken daily
    - Participants will be advised to take particular effort to remain hydrated, and to be judicious with the use of aspirin or other NSAIDS for fever/symptomatic treatment because it may increase risk for renal problems if excessive amounts are taken with study medication.

6.4.7 FOLLOW-UP STUDY VISITS

The participant will be asked to daily:

- take BP generally at the same time of day and record

- measure temperature prn tactile fever but at least daily and record
- record fever, dyspnea and fatigue

The research nurse will phone or video-conference the participant daily or at least 3x/week during the first week to monitor how the participant is doing especially if there are concerns regarding the participant's status and to reinforce the need to take daily study medications and to record BP, temperature and symptom status.

The participant will also be instructed to call the research nurse (or Physician-on-call on weekends or after-hours via the Physician Exchange Service) if side effects, problems or concerns arise.

Day 4 (+/- 1 day) and Day 10 (+/- 1 day) Study Visit At this visit, nurse will:

- Take photo of participant's log for temperature, BP and symptoms; assess current signs and symptoms and clinical status
- Update medication list
- Record adherence with study medication
- Record AEs as reported by participant or observed by investigator
- Record vital signs (temperature, pulse, blood pressure, respiratory rate and O_2 sat) and conduct targeted PE if warranted
- Collect OP swab
- Draw blood for clinical safety labs and for research assays in quantity as specified in the Schedule of Events.

6.4.8 FINAL STUDY VISIT

Day 21 Study Visit (+/- 2 days) At this visit:

- Take photo of participant's log for temperature, BP and symptoms; assess current signs and symptoms and clinical status
- Update medication list
- Record adherence with study medication
- Collect unused medication
- Record AEs as reported by participant or observed by investigator
- Record vital signs (temperature, pulse, blood pressure, respiratory rate and O_2 sat) and conduct targeted PE if warranted
- Collect OP swab
- Draw blood for clinical safety labs and for research assays in quantity as specified in the Schedule of Events.

6.4.9 FOLLOW UP PHONE CALLS

Post Day 21

- Research nurse may contact the participant after the last study visit if further follow-up information on participant status is needed

6.4.10 DISCONTINUATION OF STUDY TREATMENT

The study treatment will be prematurely discontinued for the following reasons:

- Participant becomes pregnant or starts breast-feeding
- Participant is admitted to the hospital
- Participant requires a prohibited medication

The participant will be asked to continue to be followed and attend the study visits after discontinuation of study treatment. No study procedures will be performed on the participant during hospitalization.

6.4.11 SCHEDULE OF EVENTS TABLE

Schedule of Events					
	Phone Screen	Entry (Day 1)	Day 4	Day 10	Day 21
Review COVID-19 symptoms and date of COVID-19 testing; Obtain Demographics, verbal Ht and Wt and Co-Morbid Medical History; Obtain Verbal Informed Consent	x				
Update current illness and confirm eligibility for study; verify signing of Informed Consent		x			
Complete Symptom Scale and Clinical Status		x	x	x	x
Vital Signs (Temp, Pulse, BP, Resp Rate, O_2sat)		x	x	x	x
Pregnancy test (except in post-menopausal state)		x	x*	x*	x*
Oro-pharyngeal Swab		x	x	x	x
Safety Labs (CBC with diff, chem, hsCRP, LDH) [10 ml]		x	x	x	x
RESEARCH Bloods including for RAS assessment (volume to be drawn) [25 ml]		x	x	x	x
TOTAL BLOOD VOLUME (ml)		35	35	35	35

*If possibility of pregnancy is solicited from participant

6.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

The participant's 'usual medications' may be continued unless specifically contra-indicated in this study. Antipyretics and other symptomatic medications and treatments will be allowed although participants will be asked to use judiciously and in moderation. The participant will be asked to call the Study Team if/when antibiotics or other medications are prescribed by the participant's own physician. In general these will be allowed except if drug-drug interaction with Telmisartan or if increased toxicity is of concern.

6.6 PROHIBITED OR PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Use of ARBs (other than Telmisartan/Placebo being provided by the Study), ACE Inhibitors, Aliskiren, eplerenone, triamterene, amiloride, spironolactone and potassium supplements are prohibited.

6.7 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Telmisartan will not be provided to any person outside the context of the study or following the closure of the study.

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

7.1.1 DEFINITION OF ADVERSE EVENTS(AE)

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related [21 CFR 312.32 (a)].

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug. Collection of AEs will begin at the start of the study drug infusion and continue until the Final Visit.

AEs may be volunteered spontaneously by the subject or discovered as a result of general questioning by the study staff, by physical examination, or through procedures or laboratory testing. At each evaluation, the subject will be asked, “Have you experienced any problems or changes in your health since the last evaluation?” In addition, open-ended queries will help elicit information about possible AEs. All AEs will be recorded on the source documents and subsequently the CRF. For all AEs, the PI or Sub-I must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE is required until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the CRF and on the medical record rather than in the subject’s own words. Each AE will also be described in terms of duration, frequency, severity, association with the study drug, assessment of possible causes, actions taken, and outcome, using choices given on the CRF. Specific guidelines for PI or Sub-I classification of AEs by severity and relationship to study drug are given below.

The toxicity grading system that will be used to grade the AE is the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, located at: https://rsc.tech-res.com/docs/default-source/safety/daids-aegrading-table-v2-nov2014.pdf

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

OHRP considers unanticipated problems (UP) involving risks to participants 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 participant 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

7.2 CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe AE severity.

- **Mild (Grade 1)** – An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- **Moderate (Grade 2)** – An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe (Grade 3)** – An event that prevents normal everyday activities.
- **Life-Threatening (Grade 4)** - An event that causes extreme limitation in activity or an event where significant medical intervention/therapy is required.
- **Death Related to AE (Grade 5)**- An event that results in a fatal outcome.

7.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the PI or Sub-I who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related**– There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However,

other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.2.3 EXPECTEDNESS

Dr. Shikuma and Sub-Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care. During each study visit or phone call, research nurse coordinator, PI, or Sub-I will query the participant for unsolicited and solicited AEs. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the CRF throughout the study.

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

The PI or Sub-I will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days for non-serious AEs and 30 days for SAEs after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.4 REPORTING PROCEDURES

7.4.1 ADVERSE EVENT REPORTING

All AEs will be recorded on the source documents and subsequently the CRF. For all AEs, the PI or Sub-I must pursue and obtain information adequate to determine the outcome of the AE and to assess

whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE is required until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the CRF and on the medical record rather than in the subject's own words. Each AE will also be described in terms of duration, frequency, severity, association with the study drug, assessment of possible causes, actions taken, and outcome, using choices given on the CRF. Specific guidelines for Investigator classification of AEs by severity and relationship to study drug outlined in Sections 7.2.1, 7.2.2, 7.2.3 and 7.3.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes will be recorded separately (with distinct onset dates).

AE will be reported to the IRB. The PI or designee is responsible for assessing each event and signing off on the AE report.

7.4.2 SERIOUS ADVERSE EVENT REPORTING

The PI, Sub-I, or research nurse coordinator is responsible for recording and reporting SAEs. The following procedure will be followed for reporting and handling SAEs:

The research nurse coordinator will notify the PI or Sub-I immediately on becoming aware of a potential SAE. After business hours, PI or Sub-I can be reached via pager system at 808-522-4000 or 808-566-5036. PI or Sub-I is responsible for assessing each event and will determine if the event meets the criteria for an SAE, the SAE severity, its relationship to the study intervention, and if the event was expected. PI or Sub-I assessment will be communicated to the research nurse coordinator who will record the event on the SAE form. Because each federal and local have their own reporting requirements, SAE reports will be filed in accordance with their respective time requirements.
The SAE will be followed until satisfactory resolution or the PI or Sub-I believe the situation is stable or chronic. Any other supporting documents or follow-up reports will be completed and submitted if warranted. The IRB will be notified of any unexpected fatal or life-threatening SAE within 7 calendar days of receipt notification.

7.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. PI or designee will be responsible for reporting UPs to the IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- All UPs, whether they are SAEs or not, will be reported to the IRB within the institution's specific time frame of the PI or Sub-I becoming aware of the event.

7.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

7.4.5 REPORTING OF PREGNANCY

Pregnant females are excluded from the study. Women of child bearing age will undergo pregnancy testing on entry and will be asked to be on at least one form of contraception. Pregnancy testing will be done at each study visit if there is any suspicion of possible pregnancy. Study medications will be terminated immediately upon the discovery of pregnancy.

7.5 STUDY HALTING RULES

A halt to the study will be considered by the study team if new information becomes available or adverse events connected with the study suggest that continuation of the study is not in the best interest of the participants. Should this happen, the PI or Sub-I will inform the IRB within 24 hours of the decision and will provide the IRB with written documentation detailing the circumstances leading to this decision. The PI or Sub-I will notify all regulatory bodies, ClinicalTrials.gov, and the FDA of the disposition of the study.

7.6 SAFETY OVERSIGHT

7.6.1 ROUTINE SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI from first participant screening through study completion. Safety labs are done at entry (to establish baseline) and at each subsequent study visit at day 4, 10 and 21. The results of these safety labs are reviewed by the research nurse within 24 hrs of the blood draw and any concerning abnormality reviewed with the research physician. The status of all participants on study are reviewed at weekly staff meetings.

7.6.2 DATA SAFETY MONITORING BOARD (DSMB)

As this is a small single-site pilot study and not a phase III study, a DSMB will not be convened for this study. It is anticipated that safety of the participants can be ensured by close monitoring and review of all participants on study at weekly staff meetings.

8 CLINICAL MONITORING

Quality assurance monitoring will be performed by the Unit Coordinator of the Hawaii Center for AIDS to ensure the safety of the participants, to ensure that the rights and well-being of human subjects are being protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Careful attention will be paid to GCP, applicable regulatory requirements, and the need to ensure the safety of the participants. All efforts will be expended to make sure that procedures are followed and that appropriate documentation is in place should site monitoring be requested by the IRB or other regulatory bodies.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary hypothesis: Maximum severity of disease, as assessed by the modified 7-point Clinical Status ordinal scale, will be less in the telmisartan arm compared to the placebo arm

Secondary hypotheses:

- Telmisartan will be safe and well tolerated in symptomatic patients with COVID-19 over the 21 day study period
- Telmisartan will increase Ang(1-9), AngII and Ang(1-7); Elevated levels of these peptides in relation to angiotensin peptide receptors such as MasR, AT1R and AT2R expression will be important predictors of improved clinical outcomes
- Differences in biomarker levels will be seen between the 2 arms; Certain baseline values may predict clinical outcomes

Exploratory hypothesis:

- Loss of viral detectability will be faster in the telmisartan arm compared to the placebo arm

9.2 ANALYSIS DATASETS

The analysis dataset will include all subjects enrolled into the study with data from entry to the final day 21 study visit.

9.3 DESCRIPTION OF STATISTICAL METHODS

9.3.1 GENERAL APPROACH

This is a prospective, randomized, double-blind 3-week study of telmisartan vs placebo in symptomatic individuals diagnosed with COVID-19 disease. Subjects will be randomized 1:1 to receive telmisartan vs placebo for 3 weeks (21 days). A block randomization will be applied to ensure the balance of participant numbers and baseline severity between treatments.

The baseline characteristics of participants will be summarized by descriptive statistics and compared between the two groups to check any imbalance. The primary efficacy endpoint for the study is an ordinal outcome corresponding to the maximum clinical status of the study subject. The proportional odds model and logistic regression techniques will be applied to compare the ordinal outcome between treatments, based on odds ratios. There are several secondary efficacy endpoints defined for the study. For those measures, averages and rates will be compared between groups, appropriately. Longitudinal mixed-effects models will be utilized to handle longitudinal outcome measures observed at days 1, 4, 10, and 21. The covariate use in regression models will be limited due to the relatively small sample size. Tests of normality will be performed on continuous data and transformation applied where applicable. Type-I error for hypothesis tests will be fixed at 5% nominal level. All efficacy and safety estimates (e.g.

average and proportions) will be provided with 95% confidence intervals (95% CI). The multiplicity error in exploratory analyses will be corrected via the false discovery rate. All efforts will be taken to minimize loss-to-follow-up. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analysis with multiple imputations will be performed for confirming results. Statistical analyses will be performed using the R software 3.5.1 version.

9.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The efficacy primary endpoint of the study is the maximum clinical severity of disease as assessed by the clinical status ordinal scale. The primary efficacy analysis will be performed using a proportional odds model. This model allows comparing odds ratios on ordinal categories between the experimental treatment and the placebo via a set of regression parameters. The statistical significance of regression parameters will be tested using a one-sided test for the superior efficacy by telmisartan Alternatively, several ordinal categories can be combined to obtain a composite binary class outcome, in case if insufficient class representations observed. In this situation, group comparison with respect to a binary outcome can be performed using the logistic regression model.

In addition to the primary analysis, longitudinal outcomes obtained at baseline (day 1), days 4, 10, and 21 will be used in a generalized mixed-effect regression model (i.e., cumulative link mixed model) that contains treatment and days, and treatment: days interaction as fixed effects. In the model, treatment: days interaction represents the difference in longitudinal trajectories between the two treatment groups. The statistical significance of interactions will be determined. The regression models used for analysis can be further adjusted for any unbalanced covariates observed at baseline.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary efficacy endpoints for the study are given by a set of continuous/count measures observe at days 4, 10 and 21 (i.e., components of the RAS and blood biomarkers indicative of pro-inflammatory and coagulation disturbances, circulating T cell (CD4 and CD8), NK cell, and monocytes). A shift in distribution location parameter will be tested for the group companion, using two sample t-test or the Wilcoxon rank-sum test selected upon the outcome distributions. Additionally, longitudinal secondary outcomes obtained at baseline (day 1), days 4, 10, and 21 will be analyzed using generalized mixed effect models and together with a proper link function (i.e., identity, log, etc.). In those models, days: treatment interactions, will be tested for the differences in trajectories. Covariate adjustments will be applied if required.

AEs are categorical data. AEs will be summarized as frequencies and percentages within telmisartan and placebo groups. Chi-squared test or Fisher's exact test will be used to test for differences in proportions between two groups.

9.3.4 SAFETY ANALYSES

The number of adverse events will be tabulated by grade and symptom/lab parameters. Proportions and corresponding 95% exact confidence intervals will be provided.

9.3.5 ADHERENCE AND RETENTION ANALYSES

Participants compliance to study medication will be monitored at each study visit via Symptom Form that is completed by the participant daily. The participant is asked to enter the date and time they take the study medication each day on the Symptom Form. The number of subjects who discontinue study

drug, withdraw completely from the study, or are lost to follow-up will be summarized in a table as counts and proportions with 95% exact confidence intervals. The specific reasons for withdrawing or lost to follow-up will also be presented.

9.3.6 BASELINE DESCRIPTIVE STATISTICS

Demographic and clinical variables will be summarized using descriptive statistics. Continuous variables will be summarized with means and standard deviations. Categorical variables will be summarized with frequencies and proportions. To understand if imbalance at the baseline, clinical and demographic variables will be compared between two-groups, appropriately, using T-tests (or Wilcoxon Rank Sum test) and chi-squared test (or Fisher's exact test). Additionally, graphical techniques will be used to visualize longitudinal profiles of study participants, stratified by treatment groups.

9.3.7 PLANNED INTERIM ANALYSES

The proposed study will be a pilot study to explore early evidence for the clinical efficacy and safety of telmisartan in mitigating the pulmonary and cardiac severity of disease due to COVID-19. Since the study will be conducted using a relatively small sample size, the research team does not intend to propose a pre-planned interim analysis for stopping for the efficacy. However, the study can be stopped at any point for the safety of participants.

9.3.8 ADDITIONAL SUB-GROUP ANALYSES

Sub-group analysis by age, sex, race/ethnicity will be performed as possible within the relatively small sample size of this study. Average treatment effect differences among subgroups (e.g. baseline severity) will be summarized, along with 95% confidence intervals. Additionally, subgroup analysis results will be visualized using graphical techniques.

9.3.9 MULTIPLE COMPARISON/MULTIPLICITY

The multiplicity error in exploratory analyses will be corrected via the false discovery rate.

9.3.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual participant data will be listed by measure and time point.

9.4 SAMPLE SIZE

The sample size estimation for the proposed study is not provided considering that this is a pilot study. A total sample of 40 participants will be used in the study (20 per group). The above sample size was determined based on the feasibility assessment. Suppose, in the placebo group, the vector of probabilities for observing the ordinal scale outcomes is {0.40, 0.40, 0.05, 0.04, 0.04, 0.04, 0.03}, respectively for categories 1-7. If we assume the corresponding vector for the experimental treatment group as {0.76, 0.18, 0.02, 0.01, 0.01, 0.01, 0.01}, that will produce an odds ratio of 5.0 between the two groups. In this scenario, we will have about 80% power to detect a treatment difference using the proportional odds model at 5% type-I error. Also, the selected sample size will allow us to detect a standardized effect size of 0.9 at Cohen's d scale, above 80% power, for a mean comparison between two groups via a two-sample T-test for a Gaussian outcome.

9.5 MEASURES TO MINIMIZE BIAS

9.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

After signing the Informed Consent Form (ICF), the subject is assigned a unique patient identifier number (PID). At the time of enrollment (randomization), the subject is assigned a unique subject identifier number (SID). PIDs and SIDs are not re-assigned. Screening Numbers and Subject Numbers are not re-assigned. Subjects are randomly allocated (1:1) to active medication (telmisartan) or placebo.

Randomization may occur after verbal informed consent has been obtained from the subject or representative, and subject eligibility has been confirmed. A study enrollment form will be sent to the research pharmacist to initiate the randomization process and assign the treatment to the participant. The research pharmacist will obtain the randomized treatment allocation from a computer-generated randomized treatment list for the subject and the pharmacist or designated staff will prepare the study medication. The study medication will not be provided to the participant however until a written informed consent is obtained. The site research staff and investigators (with the exception of the research pharmacist) will not have access to the treatment assignments and investigational drug products are over-encapsulated to blind the study drugs.

Since the research pharmacist is unblinded in order to provide the assigned treatment, the research pharmacist will not be involved with the assessment of outcomes or data capture except as necessary to manage drug distribution, control and accountability.

9.5.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

9.5.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Blinded Treatment assignments will be made available to the Investigators only in the event of a medical emergency where knowledge of the blinded treatment is necessary for further medical management of the participant (for instance in the event of serious adverse event). The rationale for unblinding and circumstances supporting unblinding must be documented in the research record. A written request to unblind will be sent by the investigator to the research pharmacist or designated pharmacy staff. The treatment assignment will be revealed to the investigator in writing and documentation will be filed in the accountability record.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data is defined as information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. CRF will be designed by the research nurse coordinator and will serve as source documents for some of the required data except for the source data from participant's medical records, hematology, chemistry, and EKG results.

The research nurse coordinator and research pharmacist will maintain the source data, CRF, and all regulatory documents in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. The participant's research records will be stored in a locked file cabinet in the research unit's main office. PI, Co-I, research nurse coordinator, research pharmacist, and research staff working on the protocol or data analyses will have access to all documents and will adhere to all requirements for subject confidentiality as outlined in the ICF. QUALITY ASSURANCE AND QUALITY CONTROL

This section indicates the plans for quality management, the system for assessing the quality of processes within the study. Quality management will encompass quality assurance (QA) and quality control (QC). QA is defined as all planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (ICH E6 1.46). QC is defined as the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 1.47).

The research unit has a written QA and QC management plan that will be used for this protocol.

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be clarified/resolved by the PI in collaboration with the research nurse coordinator and research pharmacist.

The PI, research nurse coordinator, and research pharmacist will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, GLP).

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

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and the ICH E6.

11.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form by the IRB must be obtained before any participant is enrolled.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 INFORMED CONSENT PROCESS

11.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

IRB-approved informed consent document describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be required prior to starting intervention/administering study intervention.

The informed consent document for this study is submitted with this protocol.

11.3.2 CONSENT PROCEDURES AND DOCUMENTATION

For each study subject, an oral consent will be obtained prior to obtaining any patient information needed to determine eligibility requirements and for any specific protocol related information. A signed written informed consent will be obtained at the Entry visit. The process will be fully documented in the source documents.

The research nurse coordinator, PI or Co-I will explain orally the nature, duration, and purpose of the study, and the action of the drug in such a manner that the subject is aware of the potential benefits, risks, inconveniences, and adverse effects that may occur because of their participation. They will be informed that the subject may withdraw from the study at any time. They will receive all information that is required by federal, state, and local laws and regulations and ICH guidelines.

The participant will also be asked to read and review the IRB-approved informed consent document and to ask questions prior to signing. An opportunity will be given for the participant to discuss the study with their significant other and/or primary care physician or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to invasive procedures specifically for the study. The participant may withdraw consent at any time throughout the course of the trial.

The participant will retain the signed informed consent document and a photo will be taken of the signed consent for the research record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators and research staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without the permission of the Principal Investigator.

All subjects will be assigned a unique patient identifier number (PID) and at the time of enrollment (randomization), each subject will be assigned a unique subject identifier number (SID). PID and SIDs are not re-assigned. The log that links the subject's name to the PID is stored in a locked file cabinet. This information is also stored on a separate flash drive and not on a computer hard drive or server. The locked file cabinets housing these confidential documents will be stored in research unit's main office, which is in a 24-hour secured building. The only individuals who have access to these locked files are authorized personnel of the research staff directly involved in this study.

Representatives of the IRB or FDA may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

If the study participant elects to have their clinical laboratory data sent to their primary care providers, they will be asked to sign a separate consent covering release of his/her data to their physician.

The study participant's contact information will be securely stored in a locked file cabinet for internal use during the study. At the end of the study, all records will continue to be kept in a locked file cabinet in the main office of the research unit for as long a period as dictated by local IRB and Institutional regulations.

A study database containing de-identified study participant research data only will be utilized for the purposes of statistical analysis and scientific reporting. The database will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

11.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Intended Use of Stored Human Samples, Specimens, or Data: The ability to conduct studies on the mechanisms underlying COVID-19 pathologic effects by accessing the banked specimens together with de-identified data is an integral part of this clinical study. Therefore, the willingness to have specimens stored for future use is part of the permission we are seeking from participants prior to entry into this study.

Storage of Stored Human Samples, Specimens, or Data: Blood samples will be stored in the research unit's processing laboratory. Access to stored samples will be limited to laboratory staff of the research unit. No genetic testing will be performed.

Tracking of Stored Human Samples, Specimens, or Data: De-identified data will be tracked using subject's unique identifier code. Data will be kept in password-protected computers.

11.5 FUTURE USE OF STORED SPECIMENS

Stored specimens may be used for research of COVID-19.

12 DATA HANDLING AND RECORD KEEPING

12.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the PI, Co-I, research nurse coordinator, and research pharmacist at the site under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. ERASURE, OVERWRITE, OR USE OF CORRECTION FLUID OR TAPE ON THE ORIGINAL WILL NOT BE ALLOWED.

Copies of the CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap and/or Microsoft Excel, a 21 CFR Part 11-compliant data capture system provided by the University of Hawaii John A. Burns School of Medicine. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.2 STUDY RECORDS RETENTION

Study documents will be maintained and retained in accordance with applicable federal, state, and local laws, rules, regulations, guidelines, and regulatory requirements.

12.3 PROTOCOL DEVIATIONS

The following describes the managing of Non-Compliance that may affect the rights or welfare of human subject participants.

12.3.1 DEFINITIONS

Non-compliance is defined as conducting research involving human participants in a manner that disregards or violates federal regulations and/or the institutional human research protection program policies governing such research.

Continuing Non-Compliance is defined as a pattern of non-compliance that suggests the likelihood that, without intervention, situations of non-compliance will recur, a repeated unwillingness to comply, or a persistent lack of understanding of how to comply. **Serious Non-Compliance** is defined as non-compliance that adversely affects the rights or welfare of human research participants.

Protocol Violation is defined as a type of non-compliance, any deviation or departure from the IRB-approved protocol or proposal that does not have prior approval by the IRB unless the change is necessary to remove an apparent immediate hazard to one or more study participants.

- **Minor Protocol Violation (**also known as "Protocol Deviation") is defined as a protocol violation that does not impact the safety or welfare of study participants, compromise the integrity of

study data, or affect participants' willingness to participate in the study. Examples of protocol deviations include the following (not an all-inclusive list):

- Use of an outdated version of the consent form if risks to participants described in the form do not differ from those described in the current form.
- A study procedure conducted out of sequence.
- A study visit conducted outside the required time period.
- Failure to perform a required procedure, assessment, or lab test that, in the opinion of the PI, is unlikely to have an adverse impact on participant safety or welfare or the integrity of the data collected; and
- Enrollment of more than the IRB-approved number of participants.

- **Major Protocol Violation** is defined as a protocol violation that may impact the safety or welfare of study participants, compromises the integrity of study data, or affects participants' willingness to participate in the study. Examples of major protocol violations include the following:
  - Failure to obtain informed consent, or obtaining informed consent from a participant after initiation of study procedures.
  - Using an outdated version of the consent form when risks to participants described differ from those described in the current consent form.
  - Performing a study procedure not approved by the IRB.
  - Modifying a study without prior IRB approval unless to remove an apparent immediate hazard to one or more study participants.
  - Enrollment of a subject who did not meet any inclusion/exclusion criteria.
  - Failure to perform a required procedure, assessment, or lab test that, in the opinion of the PI, may affect the safety or welfare of one or more participants or the integrity of the data collected.
  - A drug dispensing or dosing error.
  - A study visit conducted outside of the required time period with a potentially adverse effect on the safety or welfare of one or more study participants.
  - Failure to follow applicable federal regulations or IRB policies and procedures, including those for reporting Unanticipated Problems and Adverse Events.
  - Failure to follow an IRB-approved safety monitoring plan.

Corrective Action Plan (CAP) is defined as a plan developed in response to a protocol violation that outlines the steps to be taken to: (1) reduce the risk to participants affected by the violation, and (2) prevent a recurrence of the violation.

12.3.2 PROCEDURES FOR REPORTING PROTOCOL VIOLATIONS

Minor Protocol Violations will not require reporting to the IRB at the time of each occurrence per institution Standard Operating Procedures (SOP).

The PI will provide to the IRB a summary of minor or major protocol violations that occurred during the prior IRB approval period at the time of ***continuing review*.**

Timeframe of Reporting Major Violations. The PI will notify the IRB of major protocol violations no later than 24 hours after the PI becomes aware of the event by phone or email, and report the event to the IRB no later than 10 business days after discovery of the violation using the protocol violation report form by a member of the study team.

Changes to Remove a Hazard. If a protocol change has been initiated to remove an apparent immediate hazard to one or more study participants, the PI will report this change to the IRB no later than 5 business days after initiation of the change.

12.4 PUBLICATION AND DATA SHARING POLICY

12.4.1 USE OF STUDY FINDINGS

This study is registered with www.clinicaltrials.gov (ID: NCT04360551) and will be updated as study findings become available.

It is also anticipated that if beneficial impact of telmisartan is seen in this study, grant applications proposing further research into the potential use of telmisartan in COVID-19 would be submitted.

12.4.2 PUBLICATION

It is anticipated that multiple publications will result from this study. The Investigative Team research-team will be responsible for assigning the primary author responsible for leading the writing of the manuscript, for developing publication procedures and resolving authorship issues.

13 STUDY ADMINISTRATION

13.1 STUDY LEADERSHIP

The clinical protocol will be implemented with Dr. Cecilia Shikuma as Principal Investigator and Dr. Dominic Chow as Physician Sub-Investigator.

14 CONFLICT OF INTEREST POLICY

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

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16 VERSION HISTORY

Version	Date	Significant Revisions
1.0	Approval: _____	Original