The Effect of Camostat Mesylate on COVID-19 Infection in Ambulatory Patients: An Investigator-Initiated Randomized, Placebo-Controlled, Phase IIa Trial

Short title: Camostat mesylate in COVID-19 Outpatients

Protocol Number: 2000027971

National Clinical Trial (NCT) Identified Number: NCT04353284

Principal Investigator: Geoffrey Chupp, M.D.

IND Sponsor: Geoffrey Chupp, M.D.

FDA IND #: 150074

Funded by: Yale University School of Medicine

Version Number: 8.0

18 August 2020

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STATEMENT OF COMPLIANCE

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

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this study 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 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

TITLE:	The Effect of Camostat Mesylate on COVID-19 Infection in Ambulatory Patients: An Investigator-Initiated Randomized, Placebo-Controlled, Phase IIa Trial
Study Description:	
Objectives:	Primary Objective: To determine whether camostat mesylate reduces SARS-COV-2 viral load in early COVID-19 disease. Secondary Objective: To determine the effect of camostat mesylate on COVID-19 symptom score.
Endpoints:	Primary Endpoint: 1. Change (reduction) from baseline to day 4 in respiratory (Nasopharyngeal swab, saliva RT-PCR) log_{10} viral load. Secondary Endpoints: 1. Change (reduction) from baseline to day 2 and to day 6 in respiratory (Nasopharyngeal swab, saliva RT-PCR) log_{10} viral load. 2. Difference in rate of a positive COVID-19 test result at day 6, 14 and 28 after enrollment 3. Change of COVID-19 symptom score from baseline to day 6 and to 14 4. To assess the safety of camostat mesylate 200 mg po QID Exploratory Endpoints: 1. Conversion of SARS-CoV-2 antigen detection (Quidel's Sofia assay) from Nasopharyngeal specimens from baseline to days 6 and 14; there is no specific *a priori* power analysis for this exploratory outcome because this assay is new (under an FDA EUA) and has not been used for serial assessment of outpatients and this exploratory analysis will provide data regarding the performance of this test in our outpatient context.

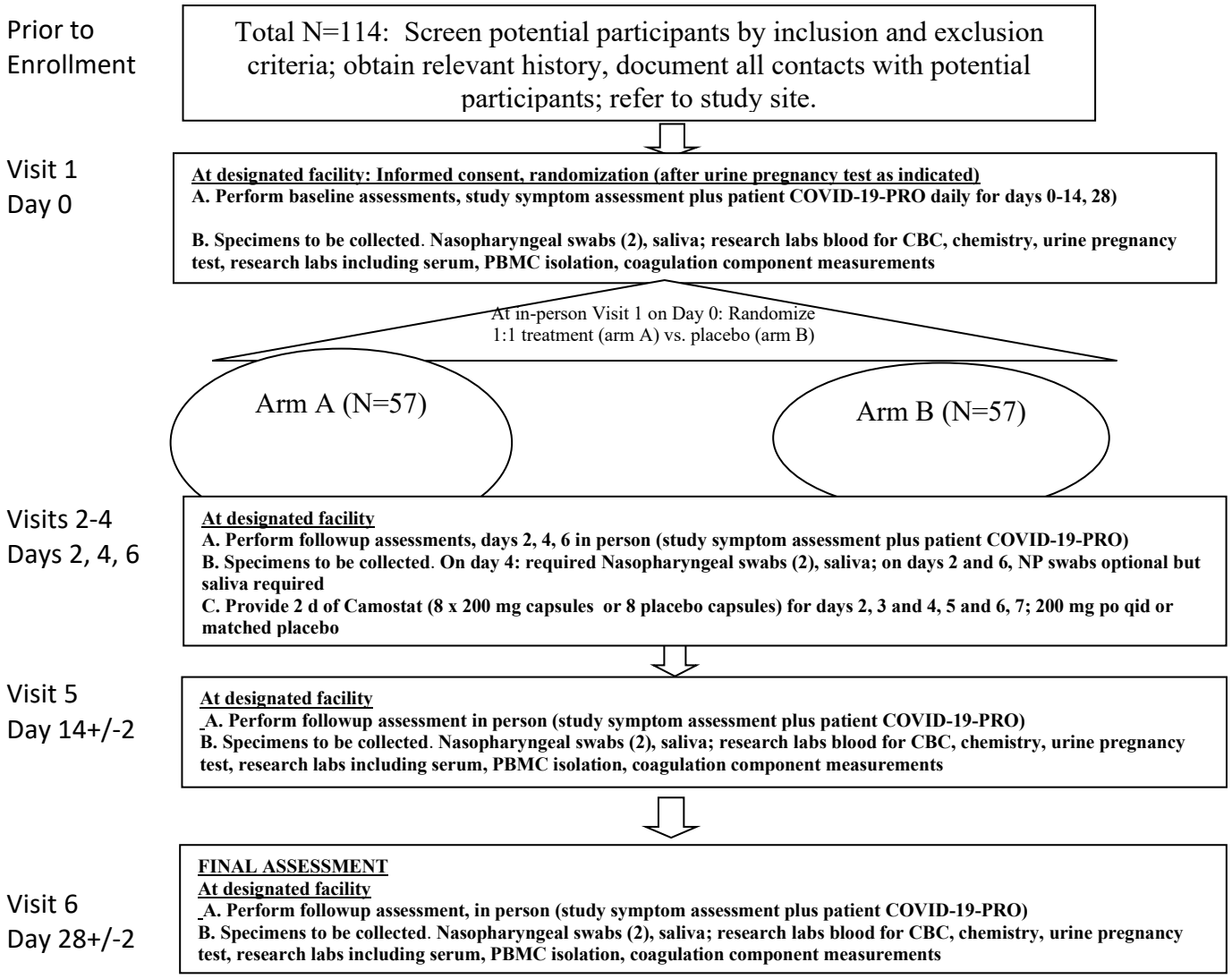
2. To gain insight into whether clinical outcomes might improve after treatment with camostat mesylate 200 mg po QID but this study is not powered to assess progression to hospitalization or other severe disease.

Population:	Male and female outpatients 18 and older with RT-PCR-confirmed COVID-19 recruited and enrolled from Yale New Haven Health System or referred/presenting for the study because of a positive COVID-19 test from an outside clinical laboratory. The subjects will not be stratified, hence will be undifferentiated as to general health status or geographic location.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Yale New Haven Health System
Description of Study Intervention:	Camostat mesylate 200mg po QID or placebo for 7 days
Study Duration:	1 year
Participant Duration:	4 weeks

1.2 SCHEMA

See below.

Flow diagram of randomized controlled trial



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Enrollment, Study Visit 1, Day 0	Study Visit 2 Day 2	Study Visit 3 Day 4	Study Visit 4 Day 6	Study Visit 5 Day 14+/- 2 days	Study Visit 6 Day 28+/- 2 days
Informed consent	X					
Demographics	X					
Medical history	X					
Randomization	X					
Administer study intervention: Subjects receive two days worth of drug/placebo on days 0, 2, 4 and one day of drug/placebo on day 6	X Drug/placebo For 2 days	X Drug/placebo For 2 days	X Drug/placebo For 2 days	X Drug/placebo For 1 day		
Nasopharyngeal swabs, saliva for COVID-19 RT-PCR and antigen testing	X	X Swabs optional	X	X Swabs optional	X	X
Physical exam: Vital signs, wt, pulse oximetry, other as clinically indicated	X	X	X	X	X	X
Urine pregnancy test (as indicated)	X					
Blood pregnancy test (as indicated)					X	
Hematology and coagulation	X				X	X
Blood chemistries	X				X	X
Adverse event review and evaluation	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Blood for research biorespository	X				X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X

All subjects, regardless of study arm (blinded to subjects and investigators), will be tracked for their health status through daily phone calls from days 0 to day 14 with routine, scheduled daily phone calls by study staff to help participants fill out symptom scores on the standardized COVID-19-PRO instrument. Any subject reporting concerning symptoms, particularly chest pain, shortness of breath, extreme prostration, change in mental status will be referred to for emergency care. Subjects will be given a contact phone number of PI or designee to contact for any concerns. If there is complete resolution of symptoms at the day 14 visit, then phone calls will not be routinely continued by our study staff to but subjects will be encouraged to call PI or designee for concerns or discussions.

2 INTRODUCTION

2.1 STUDY RATIONALE

SARS-CoV-2, one of a family of human coronaviruses, was initially identified in December 2019 in Wuhan city.[1] This new coronavirus causes a disease presentation which has now been named COVID-19. The virus has subsequently spread throughout the world and was declared a pandemic by the World Health Organization on 11th March 2020. In the United States, as of 12 April 2020, there were 532,339 confirmed cases with 21,418 deaths, with an estimated case-fatality rate of 4% for identified cases. At this time, there is no approved specific treatment for COVID-19 nor any drug or vaccine that could be used to prevent COVID-19. The current standard of care is limited to supportive treatment. The rationale of the present clinical trial is that an orally available drug given to outpatients that could reduce the viral burden in the upper respiratory tract could forestall complications of SARS-CoV-2 infection and reduce transmission from one infected individual to another.

Success in this trial, which focuses on the biological outcome of reduced viral load in the respiratory tract, would then lead to scaled-up clinical trials, for treatment in hospital inpatients and as prophylaxis for those at risk for infection. Alternatively, if camostat mesylate does not reduce viral load in the respiratory tract, then this drug would not be pursued for further clinical study.

2.2 BACKGROUND

Introduction

SARS-CoV-2, one of a family of human coronaviruses, was initially identified in December 2019 in Wuhan city.[2] This new coronavirus causes a disease presentation which has now been named COVID-19.[3] The virus has subsequently spread throughout the world and was declared a pandemic by the World Health Organization on 11th March 2020. In the United States, as of 12 April 2020, there were 532,339 confirmed cases with 21,418 deaths, yielding an estimated case-fatality rate of 4% for identified cases (which is surely an underestimate). Therapy for COVID-19 and the current standard of care is supportive treatment.

Patients infected with SARS-CoV can present with a range of symptoms from asymptomatic infection to severe respiratory failure, septic shock and multiple organ failure.[3] The most common symptoms are fever, cough, myalgia and dyspnea, though some patients present with headache, dizziness, nausea and vomiting. Viral pneumonia occurs in severe disease and leads to severe acute respiratory failure. Overall estimation of mortality rates vary from 0.039 and 7%, depending on the efficiency of population-based RT-PCR testing and and host demographic and baseline clinical status.

SARS-CoV-2 uses the angiotensin converting enzyme II (ACE2) as its cell entry receptor protein to access and infect human cells.[4] The interaction between ACE2 and the spike protein is not in ACE2's active site. This process critically uses the human epithelial cell (respiratory, gastrointestinal tract) surface-expressed serine protease TMPRSS2.[4] Utilizing previous research on severe acute respiratory syndrome coronavirus (SARS-CoV) and the closely related SARS-CoV-2 cell entry mechanism, it has been demonstrated that SARS-CoV-2 cellular entry can be blocked by camostat mesylate (Foipan, Ono Pharmaceuticals) *in vitro.*[5] *In vivo,* using a strain of SARS-Cov-1 adapted to causing lethal disease in a mouse model, camostat mesylate dosed at a concentration similar to the clinically achievable concentration in humans reduced mortality following SARS-CoV infection from 100% to 30-35% in this model.

Rationale for choice of study drug

Camostat mesylate is a proteolytic enzyme inhibitor that is used primarily in the treatment of postoperative reflux esophagitis and for acute, symptomatic exacerbations of chronic pancreatitis.[5] It has been used clinically since at least 2006 and is widely used in Japan for chronic-pancreatitis associated pain. Importantly, camostat mesylate is very well tolerated and has no known drug-drug interactions.

This randomized controlled trial will investigate the clinical effect of camostat mesylate on viral kinetics of SARS-CoV-2 in newly diagnosed COVID-19 in ambulatory patients. There are two arms named A and B. Arm A is the camostat mesylate arm which will provide drug in identical appearance as placebo by overencapsulation. Patients in group A will receive 200 mg camostat mesylate to be taken four times daily. Arm B is the placebo arm and will be given YNHH research pharmacy-formulated placebo 4 times a day. All patients will receive treatment or placebo for a total of 7 days.

There is no clinical experience in using camostat mesylate in humans to treat SARS-CoV-2. Camostat mesylate, approved for clinical use in Japan since 2006, has been used there for more than two decades to treat reflux esophagitis and acute-on-chronic pancreatitis, and it displays very little toxicity (detailed below). In animal studies, treatment with comparable human dosing reduces mortality (100% to 35% within the study period of 13 days) in mice exposed to SARS-CoV.

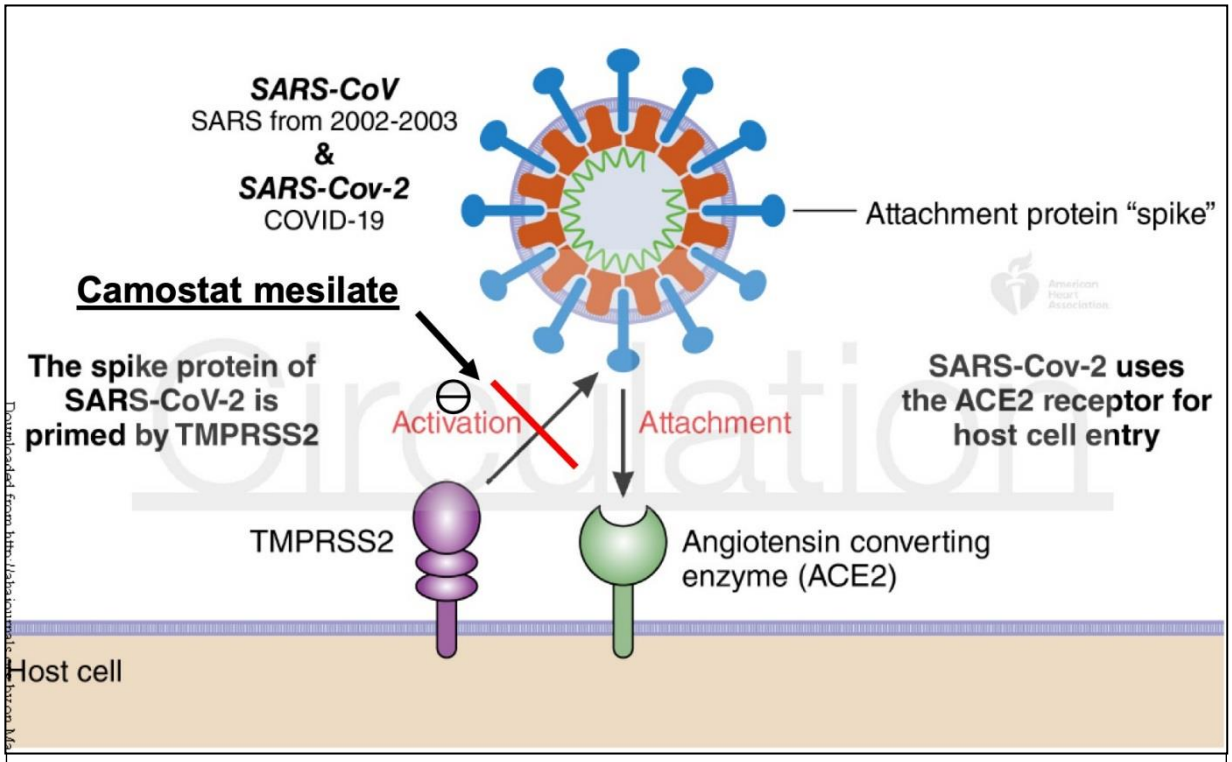


Figure 1. Camostat mesylate inhibits TMPRSS2-mediated priming of the SARS-CoV-2 spike protein which prevents the virus from cell entry. *Adapted from Clerkin et al. Circulation 2020*

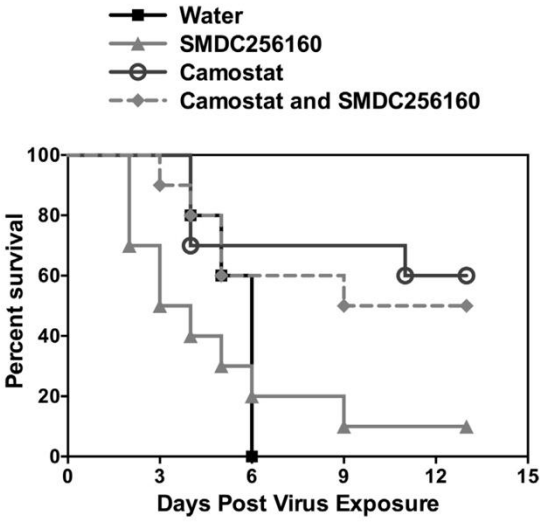


Fig. 3. Effects of per os administered SMDC256160 and/or camostat on survival of BALB/c mice infected with a lethal SARS-CoV. Ten mice per group were dosed twice a day by oral gavage with SMDC256160 and/or camostat or diluent alone (sterile water) for 9 days beginning 10 h prior to infection with 10,000 pfu of mouse-adapted SARS-CoV.

015) 76–84

In another study, camostat was found to have an EC_{50} of 87nM *in vitro*, a peak concentration achievable with oral camostat mesylate administration.[6]

Camostat mesylate is immediately and extensively hydrolysed in plasma to 4-(4-guanidinobenzoyl-oxy)phenylacetic acid (GBPA (FOY-251)), which is further degraded to 4-guanidinobenzoic acid (GBA). CM and GBPA have similar biological activity, while GBA is inactive.

Indication of absorption fraction after oral dosing is not available.

The Japanese manufacturer's summary of product characteristics describes a study in five healthy, fasting adults of a single oral dose of 200 mg. For GBPA Tmax is 40 min, Cmax 87.1 ng/ml, AUC 10,400 ng*min/ml and T½ 100min. Another study of four patients with complete gastrectomy given a single dose of 100 mg shows similar plasma curve changes including Cmax 30 ng/ml.

In another study, four healthy Caucasian males received a single dose of 40 mg camostat mesylate as intravenous infusion over 12 hours. The parent compound was not measurable in plasma, supportive of instantaneous degradation. PK parameters for the active metabolite, GBPA, were T_{max} 300 min (after infusion start), C_{max} 89.4 ng/ml, C_{ss} 83.6 ng/ml, AUC 966 ng.h/ml and T½ 1.0 hrs.

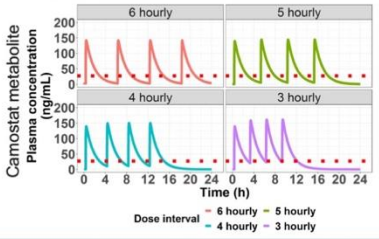
In a study of pancreatic function, twelve healthy individuals (6M/6F, median age 24.5 yrs) were given 500 mg four times daily for four weeks. Steady state concentration for GBPA at the end of week 1-4 were 19,600 ng/ml, 18,600 ng/ml, 19,000 ng/ml and 14,400 ng/ml.

Camostat mesylate is almost exclusively metabolized to GBPA and further on to GBA, by carboxyesterase and arylesterase. Neither parent compound nor metabolites affect CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Excretion is mainly renal as GBA (>95%).

The main metabolites of CM are renally eliminated, predominately 4-guanidinobenzoic acid (GBA) and to a much lesser extent 4-(4-guanidinobenzoyloxy)phenylacetic acid (GBPA). After a single oral administration of 200 mg in 5 healthy adults, the majority of these metabolites were excreted after 5-6 hours[10]. No PK studies have been located that have included patients with chronic kidney disease. However, the TACTIC trial, recruiting patients aiming at investigating the effect of CM against chronic pancreatitis in a western population, excludes patients with CKD stage IV (eGFR < 30 ml/min/1,73m2)[15]. This suggests that prior studies could potentially have documented the safety of CM use in patients with milder degrees of renal impairment.

In PK simulation modeling provided recently by Ono Pharmaceuticals, the new FDA suggested dosing of 200 mg QID of camostat would yield the following curves and time of blood levels exceeding the 87 nM EC_{50}.

Relationship between plasma concentration and viral inhibitory concentration



EC50 of camostat 0.087 μM
Hoffmann et al.(2020) AAC.

200mg QID Dose interval	Duration over 0.087 μM (hour/day)	Average concentration
6 hourly	10.4	0.12 μM
5 hourly	10.5	0.12 μM
4 hourly	10.6	0.12 μM
3 hourly	11.0	0.12 μM

Highly Confidential | Disclosed to: Any person involved in Camostat project | Responsible dept.: Clinical Pharmacology Department | Prepared on: 05/13/2020 | ONO PHARMACEUTICAL CO.,LTD. 1/3

Interactions with other drugs

There are no known interactions with other drugs and CM, GBA, GBPA. The drug and metabolites are not dependent on CYP metabolism.

Camostat mesylate is a serine protease inhibitor. The protease transmembrane protease serine S1 member 2 (TMPRSS2) activates the spike protein of the severe acute respiratory syndrome coronavirus (SARS-CoV) on the cell surface, and camostat inhibits TMPRSS2-dependent infection by SARS-CoV.[4]

According to the SmPC camostat is indicated for: Remission of acute symptoms of chronic pancreatitis (CP) 600 mg day/Postoperative reflux esophagitis (RE) 300 mg day. 3806 patients were evaluated in the Drug Use Investigation and observed for adverse reaction. The following has been reported.

Adverse Reactions (also shown in Table 1)

Abnormal laboratory test (1.3-1.8%), hepatic function abnormalities (Increased AST, ALT – 0.3%), Rash (0.4%), Pruritus (0.2%), nausea (0.1-0.3%), abdominal discomfort (0.2%), diarrhea (0.2%).

Clinical significant adverse reactions: (incidences unknown, thus rare)

Shock and anaphylactic symptoms (decreased blood pressure, dyspnea, pruritus)
Thrombocytopenia
Hepatic function disorder or jaundice
Hyperkalemia

Reported adverse effect are rare (<3%) and typically mild (such as pruritus, increased thirst and appetite and lightheadedness).

A phase 1/2 study was designed to study camostat mesylate as a treatment for chronic pancreatitis in the United States. The phase I study, investigated the pharmacokinetics and safety of 100, 200 and 300 mg doses and demonstrated safety in 18 subjects.[7] The phase 2 study was a double-blind, randomized, parallel-group, dose-ranging study and is underway to further assess the safety and efficacy of camostat versus placebo. May 2019: 63 subjects have completed the study out of 78 subjects enrolled into phase 2. A total of six serious adverse events (SAEs) have been reported in three subjects; none of these events were dose-limiting toxicities. In all but one case, the SAEs occurred during the follow-up period and none were considered related to study treatment. Only one subject has withdrawn due to an adverse event of nausea/vomiting while on treatment, which was considered as possibly related to treatment.

Adverse Reactions	0.5 – 0.1%	<0.1%	Incidence Unknown*
Hematologic	-	Leukopenia Erythropenia	Eosinophilia
Hypersensitivity	Rash Prutitus	-	-
Gastrointestinal	Nausea Abdominal discomfort Abdominal fullness Diarrhea	Anorexia Vomiting Dry mouth Heartburn Abdominal pain Constipation	-
Hepatic	Increased AST, ALT, etc.	-	-
Renal	-	Increased Blood Urea Nitrogen (BUN) Increased Creatinine	-

Others	-	Edema Hypoglycemia	-

Table 1. Summary of Safety Data for Camostat Mesylate tablets
Data summarized from the use of camostat mesylate for the indications of “Remission of acute symptoms of chronic pancreatitis” (83 ARs including abnormal lab.values observed in 69 (1.8%) of 3,806 patients) and “Postoperative reflux esophagitis” (75 ARs including abnormal lab.values observed in 57 (1.3%) of 4,224 patients).
Additional clinically significant ARs that may occur (incidences unknown*):
Shock or anaphylactoid symptoms, thrombocytopenia, hepatic function disorder or jaundice, hyperkalaemia.
*Incidence unknown: ADRs classified and collected from spontaneous reports.

Two case reports have been found. One about autoimmune hepatitis that may have occurred following drug-induced liver injury that may have been related to camostat treatment. Stopping the drug did not lead to complete remission, but low dose of corticosteroids completely cured the liver function[17]. Another case study reported eosinophilic pneumonia probably caused by 10 days treatment with camostat. The peripheral blood eosinophilia and eosinophilic infiltration into the alveolar space improved with the cessation of the drug[18].

Relevant monitoring of treatment is based on the knowledge about the reported clinically significant adverse reactions, which comprises: hyperkalemia, hepatic function disorder or jaundice, thrombocytopenia, eosinophilic pneumonia and shock/anaphylactic symptoms.

Safety in patients with reduced renal output or end-stage renal disease

Human data on camostat mesylate treatment and renal insufficiency.

Three studies have been found in Medline and/or Embase that address the safety of camostat mesylate administration in patients with renal insufficiency:

1. Onbe et al. J Diabet Complications 1991;5:167-8. 8 pts with nephrotic syndrome and diabetic nephropathy. CM 600 mg daily for 4 weeks. Reduced proteinuria, creatinine clearance stable throughout study.

2. Ikeda et al. J Diabetes Complications 1999;13:56-8

   3 pts with nephrotic syndrome and diabetic nephropathy. CM 600 mg daily for 4 weeks. Reduced proteinuria, no side effects reported.

3. Matsubara et al. Clin Nephrol 1989;32:119-23

   17 pts with heavy proteinuria caused by varous nephropathies. CM 600 mg daily for 4 weeks. Urine protein excretion diminished from week 2. No changes in serum creatinine during or after the study.

Collectively, the above-mentioned studies demonstrate the safety profile of camostat mesylate administration in patients with varying degrees of renal insufficiency. The studies found no evidence of a negative effect of camostat mesylate on renal function. Camostat mesylate administration was also not associated with an increased risk of adverse drug reactions.

In Japan, the approved doses for Foipan® are 100 mg three times daily for postoperative reflux esophagitis and 200 mg three times daily for symptoms of chronic pancreatitis. We propose in the present study dosing at 200 mg po QID, for which Ono has obtained safety data in early clinical trials (see below).[5] We will ask subjects to space out dosing over 24 hours as much as they can, taking sleep into account.

Much higher doses have been used in some studies without any severe adverse effects, i.e. 9 patients with severe oral carcinomas up to 7.2 g daily for several months as well as a study in healthy individuals of 2 g daily for four weeks.

Since use of the compound in SARS-CoV-2 setting is unchartered territory, we will use doses that are safe within the limits of the SmPC for camostat mesylate. In cell lines, camostat seems able to inhibit the serine-protease mediated maturation of the SARS Spike (S) protein. EC_{90} is about 5 uM and EC_{50} about 1 uM in that study. A more recent *in vitro* study showed an EC_{50} of 0.087 uM (87 NM).[6] In a mouse model of SARS-CoV-1 (the first SARS) virus, camostat mesylate (30 mg/kg x2) ameliorated progression to acute respiratory distress syndrome (ARDS). The reduction was from 100% to 35% lethality in the mouse model.[8, 9]

The rationale for the duration of treatment with camostat mesylate (i.e. 200 mg QID daily for 7 days) is in part based on the current treatment guidelines for other lower respiratory tract viral infections and also the known viral kinetics of SARS-CoV-2 in COVID-19 patients. For influenza, the standard recommendation is Tamiflu (oseltamivir 75 mg x 2) for 5 days in adults. Because participants in the proposed camostat trial are enrolled very early after outpatient diagnosis, we anticipate that the majority of them will present with mild to moderate disease. Therefore, we propose to follow the treatment principles for other lower respiratory tract infections of similar disease severity.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks of camostat mesylate (FOIPAN) are based on the package insert provided by Ono Pharmaceutics for the approved drug.[5]

In the first 7 days of participation in the study, minimal significant risks, either immediate or long-range risks to participants are anticipated from the physical, psychological, social, legal, economic, or other viewpoints by participating in the study that the Principal Investigator (PI) can foresee. Potential risks during the acute phase of COVID-19 infection and coming to the designated facility (outpatient study site) might be infection from others, or study personnel being exposed to active COVID-19 patients. These risks are mitigated by the participants being sampled by experienced staff wearing proper PPE and approved by EH&S during the first week of study participation, during which time they interact with study personnel obtaining respiratory swabs. Study personnel obtaining swabs will be dressed in YNHH system-approved PPE (N95 masks, goggles, face masks, gowns, gloves), and will change gowns, gloves, PPE sleeves between patients, as is standard practice.

At days 14+/-2 and 28+/-2 days, participants will return to the study clinic and NP swabs and saliva will be obtained. Blood will be drawn for standard blood tests (CBC and chemistries) plus that for research use. A maximum total of 125 mL of blood will be obtained at these two time points.

The guidance for maximum volume of blood draws that will be applied is for non-healthy adults, no more than 2.5% total blood volume in 24-period and no more than 5% total blood volume in 30 days. 70mL/kg must be used to calculate the appropriate blood draw volume per patient. The two blood draws of maximum 125 mL each for a total of 250 over two weeks, plus 30 ccs per visit for Visits 1-4 for a study total of 370ccs is still within the allowable amount.

2.3.2 KNOWN POTENTIAL BENEFITS

The anticipated potential benefits of receiving camostat mesylate treatment for patients with COVID-19 would be reduction of viral replication, which would be presumed to accelereate the reduction of COVID-19 disease symptomatology and reduce the contagiousness of the causative virus to others.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

According to what is known about COVID-19 disease and its potential for severe disease as well as transmission, and compared to the minimal risk of taking camostat mesylate, the potential benefits outweigh potential risks.

Risk of the study design itself, focused on the highly transmissible virus SARS-SoV-2 causing COVID-19 disease, mitigates risk both to subject and to study personnel during the acute phase of the study (days 0-6) and at days 14 and 28.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether camostat mesylate reduces SARS-COV-2 viral load within 2-3 days after laboratory-confirmed diagnosis of COVID-19 disease in ambulatory patients.	Primary Endpoint: 1. Change (reduction) from baseline to day 4 in respiratory (Nasopharyngeal swab, saliva RT-PCR) log_{10} viral load .	Per FDA recommendations and our own judgment, the timing of this primary endpoint was chosen because reduction of viral load in respiratory tract samples would be expected to be associated with anti-viral activity of the study drug, and would be expected to be associated with continued reduction of viral load during drug administration, hence potential reduction severity of COVID-19 disease and reduction of transmission by reducing infectiousness of infected individual. If we are able to achieve a reduction in viral load then a trial with clinical endpoints such as risk for progression to hospitalization and/or need for intensive unit care would be justified.
Secondary		
1. To determine whether camostat mesylate reduces SARS-COV-2 viral load within 7 days after laboratory-confirmed diagnosis of COVID-19 disease in ambulatory patients.	1. Change from baseline to day 2 and to day 6 in respiratory (Nasopharyngeal swab, saliva RT-PCR) log_{10} viral load. 2. Difference in rate of positive COVID-19 test at day 6, 14 and 28	As for the primary endpoints (above). We expect to see a time-dependent reduction of viral load, hence the second time point.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
2. To determine the effect of camostat mesylate on COVID-19 symptom score. 3. To evaluate the safety of camostat mesylate 4. Adverse events	3. Change of COVID-19 symptom score from baseline, to days 6 and 14 Assessment of safety by labs and history and physical, according to The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.	We expect to see a reduction in symptom score from baseline at day 6 and day 14 +/-2. If the secondary endpoints are not achieved, then a trial to examine the effect of camostat mesylate on COVID-19 would not be justified.
Tertiary/Exploratory		
To determine clinical outcome of COVID-19 treated with camostat mesylate To determine conversion of SARS-CoV-2 antigen from positive at baseline to negative at days 6 and 14.	As an exploratory endpoint in comparing treatment to placebo groups, we will assess time to clinical improvement and risk for hospitalization. Quidel's Sofia assay will be used for antigen detection.	A tertiary objective not powered by this study. We will explore, however, whether the treatment group clinically improves or has a lower, neutral, or greater risk of hospitalization. As the Quidel assay has not been used for serial assessment of outpatients, this exploratory analysis will provide data regarding the performance of this test in our outpatient context

4 STUDY DESIGN

4.1 OVERALL DESIGN

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should be consistent with the ***Protocol Synopsis (section 1.1) and Protocol Schema (section 1.2)*** *and include:*

Hypothesis: Camostat mesylate, a serine protease inhibitor shown to inhibit SARS-COV-2 replication *in vitro* and to reduce mortality in a mouse model of SARS, inhibits SARS-COV-2 replication in early stage, laboratory-confirmed, ambulatory COVID-19 patients.

Trial phase*:* This is a phase II trial of camostat mesylate, a drug approved for clinical use in Japan for treatment of pancreatitis and postoperative reflux esophagitis.

Trial design*:* Randomized, double-blind, placebo-controlled clinical trial

Methods to minimize bias: Participants will be randomized equally to camostat mesylate or identical appearing placebo using a permuted-block design with variable block size. Actual treatment assignment will be concealed from the investigators and the participants.

Number of study groups/arms and study intervention duration: Two arms: Group A, study drug (camostat mesylate); Group B, placebo. Duration of study: 7 days. Duration of involvement by participants: 28 days.

Number of Sites: one

Name of study intervention: Camostat mesylate

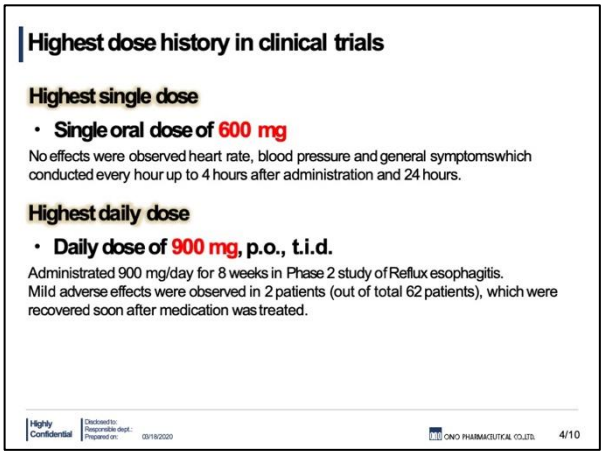
Stratification: None

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rationale for placebo is that there is no known effective treatment for COVID-19 disease. The natural history of viral shedding in infected patients varies substantially among patients. Generally viral replication appears within about 5 days after exposure, and an asymptomatic phase may or may not be present for days prior to the onset of symptoms, most often described as progressive symptoms of fever, cough, malaise and shortness of breath. Because there is no available animal model in which to study the anti-SARS-CoV-2 viral effect of camostat mesylate, infected humans must be studied. Because respiratory viral burden varies substantially (orders of magnitude ranging from 10^2-10^9/swab) among COVID-19-affected individuals, in order to demonstrate an antiviral effect of any drug on SARS-CoV-2, serial samples and measurement of viral load on respiratory samples must be compared between placebo and experimental groups. We will also perform viral load testing on saliva because recent studies have suggested that saliva may be more reliable; however the nasopharyngeal swab remains the gold standard. Because enrollment will be based on an initial positive COVID-19 test on a nasopharyngeal swab and participants randomized in a double-blinded way, experimental and placebo groups are expected to be comparable without bias.

4.3 JUSTIFICATION FOR DOSE

The standard dose of camostat mesylate as approved in Japan for patients with chronic pancreatitis is 600mg/day (200 mg po tid). We will increase the dose to 800mg/day (200 mg po QID) which has been shown to be safe. This choice of dosage is consistent with PK simulation data (shown above) and Ono's safety data as seen below, and the FDA IND approval letter suggested a dose of 800mg/day (200 mg po QID). The placebo control will be produced by the Yale New Haven Hospital research pharmacy to be a look-alike.



Highest dose history in clinical trials

Highest single dose

- **Single oral dose of 600 mg**

No effects were observed heart rate, blood pressure and general symptomswhich conducted every hour up to 4 hours after administration and 24 hours.

Highest daily dose

- **Daily dose of 900 mg, p.o., t.i.d.**

Administrated 900 mg/day for 8 weeks in Phase 2 study of Reflux esophagitis.
Mild adverse effects were observed in 2 patients (out of total 62 patients), which were recovered soon after medication was treated.

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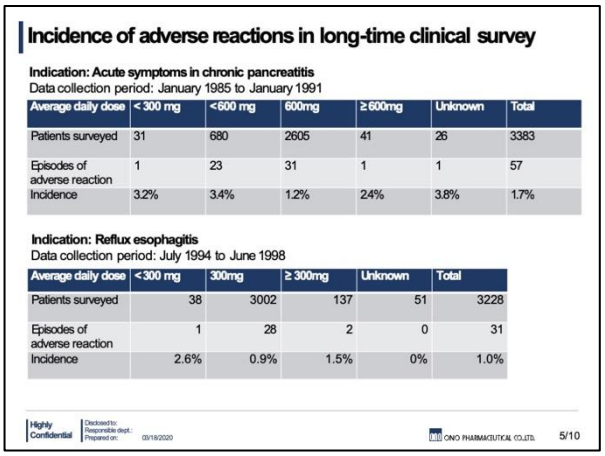

Incidence of adverse reactions in long-time clinical survey

Indication: Acute symptoms in chronic pancreatitis
Data collection period: January 1985 to January 1991

Average daily dose	< 300 mg	<600 mg	600mg	≥600mg	Unknown	Total
Patients surveyed	31	680	2605	41	26	3383
Episodes of adverse reaction	1	23	31	1	1	57
Incidence	3.2%	3.4%	1.2%	24%	3.8%	1.7%

Indication: Reflux esophagitis
Data collection period: July 1994 to June 1998

Average daily dose	<300 mg	300mg	≥ 300mg	Unknown	Total
Patients surveyed	38	3002	137	51	3228
Episodes of adverse reaction	1	28	2	0	31
Incidence	2.6%	0.9%	1.5%	0%	1.0%

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4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Consecutive participants testing positive for COVID-19 at the Sargent Drive testing center, any other YNHHS site, or external COVID-19 testing facility will be eligible for enrollment.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Be enrolled within 3 days of being notified of their first positive COVID-19 test result.
2. Evidence of a recent active COVID-19 infection, as evidenced by the positive test results being associated with at least one COVID-19-compatible symptom such as fever, upper respiratory symptoms, cough, chills, loss of taste/smell, etc.(see COVID-19-PRO symptom score sheet), or a recent high-risk exposure to COVID-19
3. Provision of informed consent
4. Stated willingness to comply with all study procedures and availability for the duration of the study
5. Male or female, aged 18 and older
6. Diagnosed with COVID-19 within past 3 days and not exhibiting manifestations requiring hospitalization such as extreme shortness of breath or severe prostration. Nurses at the study site will assess such severe conditions requiring hospitalization, which would preclude enrollment.
7. Ability to take oral medication and be willing to adhere to the camostat mesylate regimen.
8. For men and women of reproductive potential: use of condoms or other methods to ensure effective contraception with partner during study drug administration.
9. Agreement to adhere to Lifestyle Considerations (birth control measures) throughout the 7-day duration of study drug administration.
10. English and Spanish speaking subjects as well as patients speaking any language for which we can find appropriate translators will be enrolled. A short form with interpretation will be used for anyone speaking a language for which a translated informed consent form is not currently available in accordance with local site IRB policies, including developing certified translations as necessary.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Presence of COVID-19 disease manifestations that would require referral for consideration of hospitalization.
2. A previous positive COVID-19 test reported more than 7 days before, which would indicate likelihood of non-culturable, nonreplicating virus
3. A positive COVID-19 test without a known recent exposure that would indicate an active infection, hence an unknown chance of non-culturable, non-replicating virus being present (i.e., asymptomatic COVID-19 infection of unknown duration)
4. Known pregnancy or lactation; a positive urine pregnancy test done at the enrollment (day 0 visit) for women with child bearing potential.
5. Known allergic reactions to components of camostat mesylate.

   With regard to inclusion or exclusion of women of child-bearing potential, women who tell us they know they are pregnant are excluded. All women of child-bearing potential who test positive for pregnancy by urine test at first visit are excluded. A day 14 followup blood pregnancy test will be done on appropriate enrolled women (i.e. those who had a negative urine pregnancy test on day 0 for further safety assessment.

5.3 LIFESTYLE CONSIDERATIONS

Female subjects with potential for childbearing will be asked to maintain at least two forms of birth control during the 7 days of study drug/placebo administration, including but not limited to abstinence from sexual intercourse, condom use and/or using oral contraceptives.

During this study, participants are asked to comply with State public health requirements and the U.S. Centers for Disease Control and Prevention in terms of social distancing and discontinuing home isolation (https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html), which will be provided in written form to participants.

5.4 SCREEN FAILURES

The study design is expected to minimize screen failures because enrollment will be based on consecutively diagnosed COVID-19+ individuals. Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Special circumstances must prevail for recruitment and retention in this study given the contagiousness potential of COVID-19.

Target study sample size: 114, with no pre-specified breakdown by gender, race, ethnicity, or age;

Anticipated accrual rate: 1-5 participants weekly, may take longer

Anticipated number of sites: one, Yale School of Medicine/Yale New Haven Health, New Haven, CT

Source of participants: Persons with a positive SARS-CoV-2 test recorded at the clinical site, referral from healthcare personnel due to a positive SARS-CoV-2 test, or self-referral after receiving a positive SARS-CoV-2 test.

How potential participants will be identified and approached: Participants who are diagnosed within the YNHH Health System will be identified via a daily JDAT data output that will identify new COVID-19 outpatients who have not opted out of being contacted for Yale research studies. Approved study personnel will use this list to identify subjects that fulfill inclusion criteria and are not excluded according to exclusion criteria, and then contact potential subjects to ask if they might be willing to participate in the study. If so, the study will be explained and the informed consent process initiated.

Alternatively, physicians/APRNs/HCWs may refer a potential participant based on a new positive COVID-19 test, or patients may self-refer themselves for potential participation.

Participants will be offered compensation . Free parking or reimbursement for parking will be provided for outpatient visits. Study site staff will make efforts to arrange and pay for safe transportation to and from the study site if a participant meeting eligibility criteria otherwise cannot make their appointments.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study intervention*:* camostat mesylate 200mg po qid vs. placebo. Commercially available in Japan, but not in the United States.

6.1.2 DOSING AND ADMINISTRATION

Camostat mesylate 200 mg po qid vs. placebo for 7 days.
Two days of study drug or placebo will be provided every other day in the study clinic at the time of check-in, prior to being swabbed and obtaining saliva samples.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Ono Pharmaceutical, Japan, will provide Camostat mesylate 100 mg tablets as FOIPAN. The Yale New Haven Hospital research pharmacy will receive and store the drug within 15-30°C range according to protocol storage requirements.

Microcrystalline Cellulose NF (PH-102) for placebo formulation will be acquired from Fagron.

Empty gelatin capsules Size 0, for over-encapsulation will be acquired from Fagron.

Before Ono Pharmaceutical can send the drug, an IND will be obtained from the FDA.

The Sponsor-Investigator and the Yale New Haven Hospital research pharmacy will keep accountability records for all investigational products acquired, dispensed, used and disposed.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

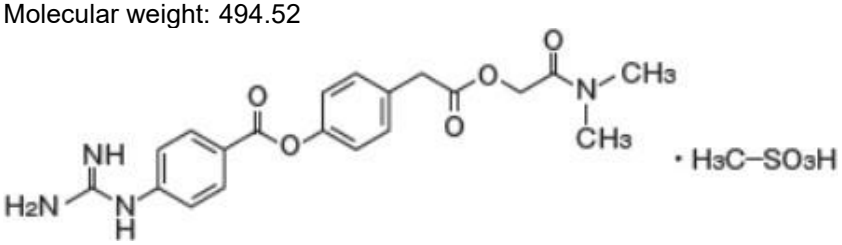
Camostat mesylate will be provided by Ono Pharmaceuticals as 500 tablets/bottle in glass bottles. Each tablet contains 100 mg of Camostat mesylate. For study administration two tablets will be combined (by investigational pharmacy) into one 200 mg capsule (see page 23) and subjects will take one capsule qid of either study drug or placebo. Placebo will be formulated to be similar in appearance to the study drug and provided in similar plastic containers.

Chemical name: 4-[[4-[(Aminoiminomethyl)amino]benzoyl]oxy]benzeneacetic acid 2-(dimethylamino)-2-oxoethyl ester methanesulfonate.

International Nonproprietary Name (INN): Camostat

Molecular formula: $C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$

Molecular weight: 494.52



Structural formula

6.2.3 PRODUCT STORAGE AND STABILITY

The study drug Camostat is stable at 25°C and should be kept at ambient (15-30°C) temperature for long term storage. For short term storage (up to 30 days) to facilitate daily dispensing of the drug it will be kept at ambient office or clinic temperature.

Placebo for Camostat will also be stored at ambient (15-30°C) temperature for long term storage. For short term storage (up to 30 days) to facilitate daily dispensing of the drug it will be kept at ambient office or clinic temperature.

Drug will be stored in locked cabinets at ambient (15-30°C) temperature at all times other than during active dispensing.

6.2.4 PREPARATION

Encapsulated Camostat 200 mg Capsules

For blinding, two intact active camostat 100 mg tablets will be placed in a capsule shell, back filled with sufficient quantity of microcrystalline cellulose, and closed. The capsules are visually inspected and packed into polypropylene bottles.

Placebo for Encapsulated Camostat 200 mg dose Capsules

Matching placebo will be compounded, using a matching empty capsule filled with sufficient quantity of microcrystalline cellulose. The capsules are visually inspected and packed into polypropylene bottles.

Assigned beyond use date is not later than the time remaining until the earliest expiration date of any ingredient or 6 months.

Master formulation record and compounding record will be kept for the compounding. Compounding, packaging and labelling will be carried out by Investigational Drug Service Pharmacy, Yale-New Haven Hospital.

Labeling:
Camostat 200 mg dose Capsules (Active) Compounding Date:
Lot: Exp Date:
Qty:
Protocol #
Storage Condition (Room Temp 15-30°C)
"Caution: New Drug--Limited by Federal (or United States) law to investigational use."

Placebo for Camostat 200 mg Capsules Compounding Date:
Lot: Exp Date:
Qty:
Protocol #
Storage Condition (Room Temp 15-30 °C)
"Caution: New Drug--Limited by Federal (or United States) law to investigational use."

Dispensing:
For dispensing, 8 capsules of overencapsulated Camostat 200 mg per capsule or identically appearing Placebo for camostat mesylate 200 mg will be packaged in a polypropylene bottle and given to enrolled research participants every other day. The bottles will be labeled with dispensing label containing patient name, administration instructions, and provider information per state pharmacy regulations.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Consecutive consenting COVID-19+ patients will be recruited as participants, who will be randomized equally to camostat mesylate or placebo using a permuted-block design with variable block size. Actual treatment assignment will be double-blind, concealed from the investigators and the participants. The YCCI statistical group (YCAS) will generate the randomization scheme and provide it to the pharmacy. Research pharmacy staff will prepare study drug and placebo for dispensing and assign and record which subject are assigned to receive them. The study site team will record what each participant receives according to assigned kit #.

6.4 STUDY INTERVENTION COMPLIANCE

The study design is built around obtaining respiratory swabs and saliva from participants. To encourage compliance with study protocol, study drug/placebo will be provided every other day (prior to swabbing and saliva collection) and verbal assessment of whether study drug/placebo was taken as prescribed will be done.

Participants will have the option of not being swabbed again or providing saliva, even after receiving study drug, but lack of day 0 and 4 NP swabs would be a protocol deviation although they would be retained in intention to treat analysis. NP swabs are required at days 0, 4, 14, 28; optional swabs at days 2 and 6. Saliva will be collected at all study visits.

6.5 CONCOMITANT THERAPY

Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications (oral and parenteral), over-the-counter medications and supplements. There are no restrictions. We will track all concomitant medications that subjects take.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Reasons why a study subjects may be withdrawn from the study intervention include, but are not limited to:

Subject request (withdrawal of consent)
Protocol violation, i.e. declining to take drug or be swabbed or providing saliva for viral load two times.
AE or reactions
Any condition, interaction, or contraindication where continued participation in the study will result in an unacceptable risk for the subject, as assessed by the Investigators or advisers
Discontinuation of the study by the Sponsor
Lost to follow-up

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention
- The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who provide informed consent and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two or more visits and is unable to be contacted by the study site staff; if a subject is hospitalized outside the YNHHS we will attempt follow for clinical outcomes and concomitant medications.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one day and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Biological specimen collection and laboratory evaluations.

On study days 0, 2 (NP swab optional, saliva required), 4 (NP swab and saliva both required) and 6 (NP swab optional, saliva required), 14+/-2 (NP swab and saliva both required) and 28+/-2, (NP swab and saliva both required), samples will be obtained and analyzed by an FDA-authorized COVID-19 RT-PCR assay coordinated through the YNHH Clinical Virology Laboratory, and Yale Department of Pathology. Additional testing including antigen detection may be done on an NP swab, nasal swab or saliva.

On study days 0, 14+/-2 and 28+/-2, blood will be collected for 1) clinical surveillance→complete blood count, blood chemistries and coagulation including electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, HS-CRP, LDH and alkaline phosphatase, PT, INR, d-dimer, fibrinogen; 2) research testing including obtaining serum, plasma and peripheral blood mononuclear cells for research studies. A maximum of 125 mL of blood will be requested to be collected on days 0, 14 and day 28 (total of 375 mL over four weeks) for these purposes.

Respiratory swab and saliva RT-PCR testing will be done by YNHHS or YNHHS-designated send-out laboratories. Quidel's Sofia platform will be use at the study site for antigen detection. Positivity and Ct values will be recorded and $\log_{10}$ viral loads back-extrapolated from $\log_{10}$ being equivalent to 3.3 C_t units or as determined using a concomitant standard curve.

Blood chemistries and CBCs (and an FDA-approved POC urine pregnancy test will be done on site prior to enrollment for appropriate women as required) will be done by YNHHS laboratories and recorded, and results reported to patients.

Remaining blood samples will be stored in a biological specimen repository approved by Yale University as follows:

Investigator:	Stephanie Halene
Type of Review:	Modification/Update
Title of Study:	Specimen Repository for Hematologic Diseases
IRB Protocol ID:	1401013259
Submission ID:	MOD00029770
Committee Name:	IRB 0-Ad Hoc Committee

Final Approval Date: 3/29/2020
Expiration Date: 2/17/2021

Remaining respiratory tract samples (NP swabs, saliva) processed by the YNHH Virology laboratory will be overlabelled with unique identifiers (to de-identify the samples) and conserved for future use in the Vinetz laboratory which has been approved to handle such COVID-19 specimens by EH&S.

8.2 SAFETY AND OTHER ASSESSMENTS

At study visits, vital signs including pulse oximetry will be obtained. Physical examination will not be performed routinely on participants unless dictated by signs or symptoms. Any patient experiencing symptoms requiring medical examination will be referred to hospital..

On all study days, participants will be asked to answer specific questions that relate to known potential adverse effects of camostat mesylate. The previously determined incidence of adverse effects (when drug administered for at least two weeks) are:

Symptom	0.1 to 0.5%	<0.1%	
Rash	0.4		
Pruritus	0.2%		
Gastrointestinal	0.1 to 0.5% (nausea, abdominal discomfort or fullness, diarrhea)	Anorexia, vomiting, dry mouth, heartburn, abdominal pain, constipation	

Included in the informed consent form are concerns about rare side effects. Study personnel will specifically elicit whether there are symptoms concerning for severe allergy such as jaundice, anaphylaxis or anaphylactoid reactions will be determined on a daily basis by study personnel who will ask about such symptoms (yellow eyes, weakness, wheezing, shortness of breath, tongue swelling, hives, rash) during the first 7 days of the study. Laboratory evidence of adverse effects such as thrombocytopenia, hyperbilirubinemia, or hyperkalemia will only be able to be determined at day 14.

Participants will be informed on study day 28 of all available research-specific study results to date. Results that return after day 28 will be communicated with the participant within 2 weeks of such results. If there are actionable results of routine/standard of care lab tests including CBC, chemistries and coagulation studies, they will be reported to participants in a timely manner, otherwise they will be discussed at the day 28 visit or if they become available after day 28, within 2 weeks of when new results become available.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used to characterize adverse events.

The study involves a repurposed drug in routine clinical use in Japan and is an investigational new drug in the United States.

The study involves the use of placebo in a population with diagnosed COVID-19, which is justified because there is no drug approved for its treatment, nor is there a current outpatient study for treatment of diagnosed COVID-19.

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event 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)).

Adverse events in this study will be assessed by verbal report, and specifically sought according to the approval package insert.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used to characterize adverse events.

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The PI and co-investigator team will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention (i.e. the package insert approved in Japan).

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

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

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (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.

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.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 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.

8.3.5 ADVERSE EVENT REPORTING

An external DSMB will be appointed to oversee this study, to assess safety and to determine early evidence of efficacy or futility at a planned interim data examination. The PI and co-investigators will record all adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.
All AEs will be reported to regulatory authorities, IRB, and investigators in accordance with all local applicable laws and regulations.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician(s) will report to the Sponsor-Investigator within 24 hours of awareness of the event, any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

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

The Sponsor-Investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information and within 15 days for all other serious unexpected suspected adverse reactions (SUSARs), in an Investigational New Drug (IND) safety report.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Given that the duration of study drug administration is one week, a new pregnancy is unlikely to be reported. If so, the participant so reporting a new pregnancy will be stopped from receiving study drug/placebo. Other followup may be continued.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems 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 Institutional Review Board (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.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). 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:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 2 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 2 days.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable to the study population.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

All tests performed will be tests of superiority.
For the primary endpoint, we will test the hypothesis that camostat mesylate results in a significantly greater change from baseline to day 4 in respiratory (Nasopharyngeal swab, saliva RT-PCR) log_{10} viral load compared to placebo.
Similarly, for secondary endpoints we will test the hypothesis that camostat mesylate will result in a significantly greater change from baseline to days 2 and 6 in respiratory (nasopharyngeal swab, saliva RT-PCR) log_{10} viral load compared to placebo; that camostat mesylate will reduce log_{10} of a positive COVID19 test at days 2 and 6 (optional swabs), rate of positive tests at days 6, 14 (required), and 28 (required); and that camostat mesylate will result in lower symptom burden at days 6 and 14.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculation is based on the primary outcome of interest: change in log_{10} respiratory (nasopharyngeal swab, saliva swab RT-PCR) viral load from baseline to day 4 post-randomization. Given the limited data on the variability of the change in log_{10} viral load, we have powered the study based on detecting a moderate standardized effect size of 0.3 using an analysis of covariance (ANCOVA), adjusting for baseline log_{10} viral load. To put into context, one scenario that would produce a 0.3 standardized effect size would be a change of 4 in log_{10} viral load in the camostat mesylate group compared to a change of 1 in log_{10} viral load in the placebo group assuming a standard deviation of 5.0. (NOTE: For ANCOVA, the effect size is the standard deviation of the treatment means divided by the pooled standard deviations of the observations.) To be conservative we assume a R-squared of 0 between the log_{10} viral RNA at 4-days and baseline log_{10} viral RNA. With a power of 90%, and a type I error rate of 10% (2-sided), we would be able to detect the hypothesized 0.3 standardized effect size with 98 total patients - 49 patients per group with a 1:1 randomization. Increasing this sample size by 15%, 5% for an efficacy and futility look at 50% information (i.e. when half of the patients have been enrolled) and 10% to account for loss to follow up, gives a total of 114 participants (57 per treatment arm).

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat Analysis Dataset: Participants will be analyzed based on their treatment assignment.

Per Protocol Analyses Dataset: All participants completing the study who complied with the protocol.

Safety Analysis Dataset: all study participants.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All primary analyses will be performed as intent-to-treat analyses with a type I error rate of 10% (two-sided). Parametric distributional assumptions will be checked. If assumptions fail, other distributions will be considered prior to transformations and non-parametric methods. SAS (version 9.4) or the latest version of R (currently 3.6.3) will be used to analyze the data.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis will be according to intent-to-treat and conducted using ANCOVA, adjusting for baseline $\log_{10}$ viral load (or conversion from Ct value assuming 1 $\log_{10}$ = 3.3 Ct units). We will use the t-statistic for the treatment effect to determine whether the treatment is statistically different from the placebo at the overall 10% level of significance, controlling for baseline $\log_{10}$ viral load. Because of the interim analysis (see below), a p-value of 0.06 (2-sided), corresponding to an efficacy boundary value of 1.875 at the last look, will be used for the level of significance for the primary outcome at the final analysis. In sensitivity analyses, we will also adjust for age and time since onset of symptoms. We will also conduct a per-protocol analysis as a secondary analysis. We will assess the missing mechanism and the impact of missing data. Sensitivity analyses under either missing at random or missing not at random will be considered, as appropriate.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes of interest include: change in $\log_{10}$ respiratory (nasopharyngeal swab, saliva RT-PCR) viral load from baseline (day 0) to days 2 and 6 post-randomization; $\log_{10}$ and risk for a positive COVID-19 test at day 6, 14 and 28; and change of COVID-19 symptom score from baseline (day 0), as measured at days 6 and 14 +/- 2 days after enrollment (day 0). The same ANCOVA analysis as proposed for the primary endpoint will be used to analyze two and six day change in $\log_{10}$ for the secondary endpoint. Risk for positive COVID19 test at day 6, 14 and 28 will be compared using an exact binomial distribution. Linear mixed models will be used to describe trajectories of change in the symptom score. The models will include fixed effects for treatment, time and the interaction of treatment and time. An unstructured covariance pattern will allow for correlation between repeated observations. Differences in means at each timepoint will be estimated along with 90% confidence intervals. All statistical tests will be conducted at 10% level of significance (two-sided) with no adjustment for multiple testing.

The COVID-19 PRO daily self score tool, derived almost entirely from a validated influenza symptom scoring. Tool (FLU-PRO)10 consists of 39 items that are answered daily. Items 1-33 are Likert scale questions (rated 0-4) where 0 = not at all,11, 12 and 4 = very much. These items are summed to score the severity of symptoms- where a total score of 132 would indicate the greatest severity of symptoms and a score of 0 would indicate no severity of symptoms. Items 34-38 are also Likert scale questions (rated 0-4) that measure the frequency of specific daily symptoms where 0 = 0 times and 4 = 4 times or more. These items are summed to score the frequency of symptoms- where the highest score for the frequency of symptoms (20) indicates the greatest burden of symptom frequency. The last question (39) asks patients for their highest temperature in Fahrenheit.

9.4.4 SAFETY ANALYSES

Safety will be reported by treatment arm using descriptive statistics (means and standard deviations or frequencies and counts) and assessed by comparing the adverse events in the treatment group using Type I error of 5% (2-sided); no control for multiplicity will be done for safety outcomes. We will consider Wilcoxon rank sum tests or two-sample t-tests for continuous outcomes and the exact binomial distribution for proportions.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics (including demographic, lab, and clinical variables) will be presented by treatment group (camostat mesylate and placebo). Means and standard deviations will presented for continuous variables and frequencies and proportions will be presented for categorical variables. No inferential statistics will be presented.

9.4.6 PLANNED INTERIM ANALYSES

Interim monitoring for safety, efficacy and futility will be conducted. When 50% of the participants have accumulated the primary endpoint, we will conduct an interim analysis to assess for efficacy and futility using the group sequential method with asymmetric boundaries. We will use a Pocock boundary for efficacy and will consider stopping early for efficacy if the t-statistic for the treatment effect is greater than the critical value of 1.875; we propose stopping for futility if the drug is trending in the wrong direction, and have set a futility boundary value of -1. Safety will be assessed by comparing the rate of adverse events in the treatment group using Type I error of 5% (2-sided); no control for multiplicity will be done for safety outcomes.

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

9.4.9 EXPLORATORY ANALYSES

Exploratory endpoints will include area under the $\log_{10}$ viral RNA curve; time to complete absence of symptoms the components of the symptom assessment scale (e.g. nose, throat, cough); and hospitalization. Also we are going to use Quidel's Sofia's antigen detection test in this study. Area under the curve (AUC) will only be calculated for participants with at least three follow-up $\log_{10}$ viral load measurements, and will account for the follow-up time. Mean AUC values will be compared using a two-sample t statistic. Time to complete absence of symptoms will be analyzed using the Cox model and event-free rates determined by Kaplan-Meier. Individuals will be administratively censored at 28 days. Those who die will be censored at time of death. We will conduct sensitivity analyses using death as a semi-competing risk. Twenty-eight day hospitalization rates will be compared using an exact binomial distribution. We will also consider additional biomarkers (using similar methods as described for the primary and secondary outcomes) and the individual components of the symptoms (using similar methods as described above).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and documentation of informed consent is required prior to administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Obtaining and documenting informed consent. Due to the contagiousness of COVID-19 patients and the desire to minimize face-to-face time between staff and subjects, the process of obtaining written informed consent will be carried out as follows. 1) Prior to the first study visit, a member of the study team will contact, by telephone, the potential participant on the basis of a positive COVID-19 test and explain the study, according to the attached script. 2) The informed consent form will be provided by email if the participant has an active email address, or provided in paper form if the participant prefers at the first study visit for discussion. 3) On arrival to the first study visit, the participant will again provide verbal assent and will receive a written informed consent form. Verbal assent will be witnessed by a health care worker and/or a study researcher, recorded, and entered into the participant's electronic medical record (EPIC).

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation.

Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Language regarding long-term storage of samples and genetic testing have been included in the informed consent form. An opt-out check box is provided in the informed consent form, as well as the possibility that commercializable, for-profit products may result from their specimens, with no compensation to the subject.

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the Yale Center for Clinical Investigation's Forte Electronic Data Capture (EDC), which is 21 CFR Part 11 compliant. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Yale Center for Clinical Investigation research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Yale Center for Clinical Investigation or its designate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in the PI's private office. After the study is completed, the de-identified, archived data will be transmitted to and stored at at the Yale Center for Clinical Investigation and/or its designees, for use by other researchers including those outside of the study. Permission to transmit data to the Yale Center for Clinical Investigation and/or its designees will be included in the informed consent.

Stored specimens will include nasopharyngeal swabs, saliva and blood and will be have coded identifiers with identities only known to study-approved personnel. No identifiers will be provided to researchers. The future use of these samples is intended to include possible genetic, immunological and virological analysis. Genetic studies may include single gene sequencing, whole genome sequencing, and T and B cell repertoire studies to look at genetic predisposition to COVID-19 and/or specificity of immune responses, including production of biologics derived from such studies, and for for-profit uses. These uses are described in lay terms in the informed consent form and include language that there will not be financial rights or compensation for genetic or immunological uses.

After the study is completed, the de-identified, archived data stored at at the Yale Center for Clinical Investigation and/or its designees, will be made available for use by other researchers including those outside of the study.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Biorepository supervised by Dr. Stephanie Halene at 300 George St. with the same goal as the sharing of data with the YCCI. These samples could be used to research the causes of COVID-19, its complications and other conditions for which individuals viral infections are at increased risk, and to improve treatment. The Halene Biorepository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Halene Biorepository or Vinetz laboratory.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Sponsor-Investigator.

Sponsor-Investigator		
Geoffrey Chupp, M.D., Professor of Internal Medicine		
Yale School of Medicine Division of Pulmonary, Critical Care & Sleep Medicine		
300 Cedar Street TAC 441-B New Haven, CT 06520-8057		
203-737-5405		
geoffrey.chupp@yale.edu		

An independent COVID Data and Safety Monitoring Board (DSMB) will monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to review efficacy information. The COVID DSMB will perform periodic safety reviews throughout the study as outlined in the COVID DSMB charter. The board will also meet to review interim data. The COVID DSMB will consist of a minimum of four members including the chair, at least one infectious disease physician, at least one biostatistician and investigators with expertise in current clinical trials conduct and methodology. The COVID DSMB responsibilities, authorities, and procedures will be documented in a separate charter.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a collaboration between the PI and a DSMB . The DSMB will be independent from the study conduct and free of conflict of interest; measures will be in place to minimize perceived conflict of interest. The DSMB will meet according to a regular schedule to assess safety and efficacy data on each arm of the study. The PI and DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the the PI and medical monitors. At this time, each data element that they need to assess will be clearly defined. The DSMB will provide input to the Yale School of Medicine via the PI.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the PI/Sponsor and an independent site monitor.

The Sponsor-Investigator-designated monitor(s) will conduct monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits while subjects are on study, and a site close-out visit at the site. Following each site visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of informed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- GCP compliance
- Investigational Drug and Placebo Storage and Accountability (including quantity and disposal procedures)
- Laboratory Facilities
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Sponsor-Investigator and the appointed independent clinical monitor will define the required study monitoring activities in a Study Monitoring Plan.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management by the appointed Site Monitor.

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical

Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

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

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the Yale Center for Clinical Investigation's Forte Electronic Data Capture (EDC), a 21 CFR Part 11-compliant data capture system.The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The

noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within two working days of identification of the protocol deviation, or within one working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies, and to the Yale Center for Clinical Investigation data management staff for inclusion in the study database. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

Even though this study is not supported by the NIH, we will follow the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research, even though this study is not funded by the NIH. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Even though this study is not funded by the NIH, this study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers immediatelyafter the completion of the primary manuscript by contacting the Yale Center for Clinical Investigation.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the appropriate NIH Institute or Center will have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health

NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
6.0	May 21, 2020	N/A – first version approved by IRB	N/A
7.1	June 11, 2020	Increase dosing from TID to QID and change in primary endpoint evaluation from Day 2 to Day 4 Operational changes as a result of institutional changes at Yale (eg different clinic) Clarifications of procedures	Feedback from FDA Yale institutional operational refinements

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