A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Camostat Mesilate Compared to Standard of Care in Subjects With Mild-Moderate COVID-19

Study Protocol and Statistical Analysis Plan

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PROTOCOL SIGNATURE PAGE

Protocol Title: **A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Camostat Mesilate Compared to Standard of Care in Subjects with Mild-Moderate COVID-19**

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Protocol Version/Date: Version 4.0 / 04 DEC 2020

Sponsor Name: Stanford University School of Medicine, Stanford, CA 94305

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____
Date (MM/DD/YYYY)

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List of Abbreviations

ACE2 angiotensin-converting enzyme 2
ADR adverse drug reaction
AE adverse event
ALP alkaline phosphatase
ALT alanine aminotransferase
AST aspartate aminotransferase
CBC complete blood count
CDC Centers for Disease Control and Prevention
Cmax maximum plasma concentration
CMC chemistry, manufacturing, and controls
COVID-19 Coronavirus Disease 2019
CTRU Clinical and Translational Research Unit
CYP cytochrome P450
DSMC Data and Safety Monitoring Committee
ED emergency department
FDA Food and Drug Administration
FOY-251 4-(4-guanidinobenzoyloxy)phenylacetic acid
GMP Good Manufacturing Practice
HHS Department of Health and Human Services
HPLC high performance liquid chromatography
IC50 half maximal inhibitory concentration
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND Investigational New Drug
IRB Institutional Review Board
IUPAC International Union of Pure and Applied Chemistry
JP Japanese Pharmacopeia
LD50 median lethal dose
LFT liver function test
NOAEL no-observed-adverse-effect level
NOEL no-observed-effect level
NSAID nonsteroidal anti-inflammatory drug
p.o. oral (per os)
PSUR Periodic Safety Update Report
PTP press through packaging
qPCR quantitative polymerase chain reaction
RH relative humidity
SAE serious adverse event
SARS severe acute respiratory syndrome
T1/2 half-life
TID 3 times daily
TLC thin layer chromatography
U.S. United States

1 SYNOPSIS

Title	**A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Camostat Mesilate Compared to Standard Supportive Care in Subjects with Mild-Moderate COVID-19**
Design	This is a Phase 2 **Double Blinded, Placebo Controlled Study** evaluating the efficacy and safety of oral camostat mesilate in adult subjects with PCR-positive, mild-moderate COVID-19 infections. Subjects will be randomized to receive either camostat mesilate +current Standard of Care (SOC) or SOC + placebo. Study participants will be randomly assigned 1:1 to two tablets of oral camostat mesilate (100 mg/tablet) four times a day plus SOC or SOC plus placebo for 10 days. Subjects in the SOC arm will receive placebo. The total anticipated duration of the study for each patient is 28 days.
Objectives	**Primary Objective** To evaluate the efficacy of oral Foipan (camostat mesilate, 200 mg, four times a day for ten days) compared with placebo plus current standard of care in reducing the area under the curve (AUC) through day 10 of viral shedding of SARS-CoV-2 virus in patients with mild-moderate COVID-19. **Secondary Objectives** 1. To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus current SOC in reducing the AUC up through day 28 of viral shedding of SARS-CoV-2 virus in patients with mild-moderate COVID-19. 2. To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus current SOC in reducing the duration of viral shedding of SARS-CoV-2 virus in patients with mild-moderate COVID-19. 3. To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus SOC in reducing the duration of symptoms, hospitalizations or ED visits, or mortality in patients with mild-moderate COVID-19. 4. To evaluate the proportion of individuals with a negative SARS-CoV2 RT PCR test on days 7, 14 and 28. 5. To assess the safety and tolerability of camostat mesilate in this subject population. 6. To assess the development of antibodies against SARS-CoV-2 7. To determine drug levels at one time point on day 5 using the current dosing scheme.
Endpoints	**Primary Endpoint:**

	AUC of shedding of SARS-CoV-2 virus calculated using the RT-PCR measures of viral load from self-collected nasal swabs on days 1-10. **Secondary Endpoints** 1. AUC of shedding of SARS-CoV-2 virus calculated using the RT-PCR measures of viral load from self-collected nasal swabs on days 1-10, 14, 21, and 28. 2. Time until cessation of shedding of SARS-CoV-2 virus, defined as the time in days from randomization to the first negative RT-PCR result of self-collected nasal swabs that is followed by only negative results (i.e. no later positive results are observed). 3. RT-PCR results from oropharyngeal swabs collected on Days 1, 5, 10 and 28 4. Clinical worsening of COVID-19 in symptomatic subjects (clinical worsening defined the development of respiratory distress or symptoms that require hospitalization) 5. Adverse events AEs and clinical laboratory tests for systemic safety including hematology and clinical chemistry 6. Mortality 7. Development of antibodies to SARS-CoV-2 8. Time until resolution of symptoms (resolution of symptoms defined as absence of moderate or severe symptoms for at least 24 hours for those reporting moderate or severe symptoms at baseline). 9. Drug level on day five, one hour after a dose taken on an empty stomach.
Study Sites	Stanford University School of Medicine
Planned Enrollment	120 (60 in the camostat mesilate + SOC group and 60 in the placebo + SOC group)
Study Population	Adults with confirmed SARS-CoV-2 who are experiencing mild-moderate symptoms
Subject Entry Criteria	**Inclusion Criteria (all questions must be answered YES)** 1. Adults (18-80) 2. Diagnosis of COVID-19 disease: a. Presence of mild-moderate symptoms without signs of respiratory distress (as defined by SpO2 <=94% on room air, RR >=24, HR >=110), with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from initial swab to the time of commencing informed consent: Disease is defined as having at least 2 of the following symptoms that are of moderate or higher severity as scored on the COVID Outpatient Symptom Scale (COSS): i. Fever (>98.7F)

	ii. **Cough** iii. **Shortness of breath** iv. **Fatigue** v. **Headache** vi. **Body ache** vii. **Joint pain** viii. **Chest pressure** ix. **Abdominal pain** x. **Sore throat** xi. **Nasal congestion** xii. **Chills** xiii. **Feeling hot or feverish** xiv. **Runny nose** xv. **Loss of taste** xvi. **Loss of smell** xvii. **Diarrhea** xviii. **Nausea** xix. **Vomiting** xx. **Rash** b. The date of onset of the first of the above symptoms will be documented. 3. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures. 4. If male, subject must fulfill one of the following criteria: a. Be sterile (e.g., have had a vasectomy at least 6 months prior to Day 1 dosing), OR, b. Agree not to donate sperm during the study and for seven days following the last dose of study medication, AND, c. Agree to strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication: i. Abstain from sexual intercourse ii. Use a condom during sexual intercourse with a female of child-bearing potential. In addition, the female partner must use another form of contraception (e.g. intrauterine device [IUD], diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).

	5. If female, subject must fulfill one of the following criteria: a. Be unable to bear children (have not had a period for ≥ 12 consecutive months, have had her uterus or ovaries removed, or have had a tubal ligation), OR, b. Must ensure that their male partner is incapable of fathering a child (e.g., has had a vasectomy at least 6 months prior to study entry), OR, c. If she is of childbearing potential will strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication: i. Abstain from sexual intercourse, OR, ii. Must ensure that their male partner agrees to use a condom during sexual intercourse and agree to use an approved method of contraception (e.g., IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants). d. Agrees to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy. e. Has a negative urine pregnancy test at screening. 6. When such testing is available, subject will be confirmed to be SARS-CoV2 infected using a rapid (<30 minute) SARS-CoV2 point-of-care test; if such a test is not available, this step of screening will be omitted. 7. Subject agrees to maintain home or other quarantine as recommended by the study physician, except to visit the study site as required by the protocol. 8. Subject agrees to take daily nasal swabs (anterior nares) for Day 1 to Day 10 and Day 14, 21, and 28 using the study provided material and bring these to their follow up visits on days 5, 10 and 28. 9. Subject agrees to record daily symptoms, temperature, and oxygen saturation using the study provided materials. 10. Subject agrees to return to the study site for follow-up visits on Day 5, 10 and 28. The study site will be staffed by trained healthcare providers wearing full personal protective equipment and study site equipment will be disinfected between patients according to the same protocols as a clinical setting. Subjects will be wearing masks, will be appropriately spaced, and the number of subjects assessed at each time will be limited. 11. Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met. **Exclusion Criteria (all questions must be answered NO)** 12. Subject has a concomitant bacterial respiratory infection as documented by a respiratory culture with microbiologic growth.

	NOTE: Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who are positive for SARS-CoV-2, are allowed in the study. 13. Previous use of antiviral drugs that may be active against Covid-19. 14. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers). **NOTE:** Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrollment into other clinical studies that evaluate investigational agents for COVID-19. 15. Subject has gout, a bleeding disorder, or a serious chronic disease (e.g., uncontrolled human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, and/or moderate or severe hepatic insufficiency). 16. Subject uses an anticoagulant medication including heparin, coumadin, a factor Xa inhibitor (xarelto, apixaban) or a thrombin inhibitor (Pradaxa). Aspirin is not an indication for exclusion 17. Has previously received camostat mesilate within the past 30 days. 18. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). 19. Has liver impairment greater than Child Pugh A. 20. Has a history of alcohol or drug abuse in the previous 6 months. 21. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year. 22. Has taken another investigational drug within the past 30 days. 23. Is deemed by the Investigator to be ineligible for any reason.
Randomization	Following consent, those subjects meeting all entry criteria will be randomized in a 1:1 ratio. Treatment Arm: camostat mesilate dose + SOC Control Arm: placebo + SOC Randomization will be stratified by age (>=50 and <50 years old) and sex

Treatment Regimen for Camostat mesilate (Standard dose)	• Camostat mesilate and placebo tablets will be administered orally, one hour prior to eating, and at bedtime. • The total duration of treatment is expected to be 10 days.
Duration of Study Participation	The total anticipated duration of the study for each patient is 28 days.
Statistical Methods	To address our primary objective, the AUC SARS-CoV2 viral RNA levels during follow-up will be estimated using the linear trapezoidal method, and mean AUC levels compared between groups using a linear regression model regressing log(AUC) on treatment arm, site, age, and sex. The test will be performed at the two-sided alpha = 0.05 level of significance. Time until viral shedding cessation will be compared between the two treatment arms using a two-sided Wald test derived from a Cox proportional hazards model adjusted for age and sex. The test will be performed at the two-sided alpha = 0.05 level of significance. The hazard ratio for shedding cessation will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. We will use this same approach to model the secondary endpoints of clinical worsening and mortality. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption. The log rank test will also be performed. The distribution of viral shedding cessation will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Median time to shedding cessation along with 95% confidence intervals will be presented for each treatment arm. Median time to resolution of symptoms will be estimated along with 95% confidence intervals by each arm. The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set. An interim analysis for safety and overwhelming efficacy will be performed once 50% of patients have 24 hours of follow-up complete.
Individual Stopping Rule	A subject should be removed from camostat mesilate treatment if one of the following criteria is met: • AST or ALT > 8 x ULN • ALT or AST > 3 x ULN AND total bilirubin > 2X ULN • AST or ALT > 3 x ULN AND patient has right upper quadrant pain or eosinophilia • Platelet count <75,000 cells/mm^3

	• Absolute neutrophil count <800 cells/mm^3 • Hemoglobin <11 g/dL for women and <12 g/dL for men • Serum creatinine concentration ≥1.5× ULN • Confirmed creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault • Hypersensitivity • Shock or anaphylactoid symptoms • Hepatic function disorder or jaundice (both incidences unknown). • Hepatic function disorder accompanied by remarkable increase of γ-GTP, Al-P, or jaundice. • Hyperkalemia (incidence unknown). Severe hyperkalemia may occur. A subject whose treatment is terminated should remain in the study for appropriate follow up assessments.
Study Measurements: Efficacy, Safety	**Primary Measurement (Efficacy):** 1. Nasal swab for RT-PCR taken daily from Day 1 to Day 10, and Days 14, 21, and 28. **Secondary Measurements (Safety and Efficacy)**: 2. Symptom improvement or worsening: Subjects will fill in a diary daily, recording the following symptoms: a. Cough b. Sore throat c. Headache d. Nasal congestion e. Body aches and pains f. Fatigue g. Oral temperature taken at a consistent time each day and at least four hours after ingesting the most recent antipyretic (acetaminophen or NSAID) h. Dyspnea i. Shaking chills j. Loss of taste k. Loss of smell l. GI symptoms including nausea, vomiting, and/or diarrhea m. Chest pain 3. Safety as assessed by: a. Observed and reported adverse events b. Clinical laboratory evaluations of blood on Days 1, 5, and 10 c. Physical Examination at screening (pre-dose Day 1), Days 5, 10 and 28 d. Daily vital signs: pulse oximetry, heart rate, and temperature.

	4. Blood for determination of antibodies to SARS-CoV-2 will be obtained on Days 1 and 28.

2 INTRODUCTION

2.1 Background Information

Coronaviruses have been widely identified as causing respiratory and intestinal infections in humans after the outbreak of severe acute respiratory syndrome (SARS) in Guangdong, China in 2002 and 2003 (Zhong et al., 2003; Cui et al., 2019; Khan et al., 2020). Recently, a novel coronavirus has been identified as the causative pathogen of a rapidly spreading infection associated with pneumonia and severe acute respiratory syndrome. COVID-19, originally identified in Wuhan in the Hubei province of China, has now spread across the globe and has been declared by the WHO as a global pandemic. While the majority of infected patients display mild symptoms if any, death rates of up to 4% due to development of severe acute respiratory syndrome (COVID-19 SARS), have been reported in patients with co-morbid conditions and in the elderly population. The only available treatment for COVID-19 illness is remdesivir but its use is currently limited to hospitalized patients with severe disease under an emergency use authorization from the FDA. With the unprecedented global health and economic threats imposed by COVID-19, development of therapies to suppress or eradicate this emerging pathogen has become an urgent unmet medical need.

The mechanisms associated with the infectiousness of SARS-CoV-2 are not clear; however, structural analysis suggests it is likely entering human cells through the ACE2 receptor (Zhou et al., 2020). Considering the adverse outcomes of the current COVID-19 epidemic, developing effective therapeutic strategies is necessary to cope with the lack of effective drugs, high mortality rate, and the potential of the virus to cause further epidemics (Khan et al., 2020).

2.2 Preclinical and In Vitro Experiences

The hypothesis that the transmembrane serine protease TMPRSS2 plays a critical role in the life cycle of SARS-CoV-2 is supported primarily by 2 lines of evidence. Using a panel of established human cell lines, Matsuyama et al. (2020) have shown that SARS-CoV-2 infection is enhanced by TMPRSS2 expression in a host cell. Independently, Hoffmann et al. (2020) have shown that SARS-CoV-2 cell entry depends on the ACE2 receptor and TMPRSS3 activity, the latter resulting from the ability of the protease to prime the viral spike (S) protein. The case for camostat as a pharmacologic inhibitor of TMPRSS2 also stems from 2 lines of evidence. In the same study cited above (Hoffmann et al., 2020), camostat was shown to block viral entry in vitro. Furthermore, because the same mechanism involving ACE2 and TMPRSS2 is also in the entry of the closely related SARS-CoV coronavirus in human cells, animal studies with this respiratory virus are also relevant to COVID-19 therapy. Zhou et al. (2015) have shown that camostat was effective in protecting mice against death due to a lethal infection by SARS-CoV, with a survival rate of ~60%. Together, these findings suggest that camostat may be an effective treatment and prophylactic for patients infected with SARS-CoV-2. The inhibitory effects of camostat on various proteases were compared with those of FOY-251 (the major metabolite of camostat). As compared to camostat, the inhibitory effect of FOY-251 on trypsin-catalyzed hydrolysis of TAMe was 1/2, that on

caseinolysis was 1/5, that on plasmin catalyzed fibrinogen degradation was 1/3, thrombin-catalyzed fibrin coagulation was equivalent, and those on plasma kallikrein and pancreatic kallikrein were 1/7 and 1/2, respectively.

Decreased locomotor activity, convulsions, loss of righting reflex, external irritation, hypersensitivity, and dyspnea were observed in rats at extremely high doses of 3,000 mg/kg or higher orally (p.o.). However, no effects were observed on the central nervous system at doses up to 2,000 mg/kg, p.o., in mice, or on the autonomic nervous system at doses ranging between 100 and 500 mg/kg, p.o., in rats. No changes in blood pressure were observed in rats at doses ranging between 10 and 1,000 mg, p.o. Inhibitory effects were observed in vitro on contraction of the isolated smooth muscles in the gastrointestinal tract, trachea, and blood.

2.3 Clinical Experience

Camostat/Foipan has been extensively used in pancreatitis patients for more than 20 years in Japan. The clinical development program in Japan consisted of the following studies:

- A Phase I tolerability study was conducted in which camostat mesilate was administered postprandially at doses of 50, 100, 200, 300, 400, and 600 mg to 6 healthy adult males aged between 24 and 39 years. Pulse rate, blood pressure and clinical symptoms were monitored every hour for 4 hours post-dose and at 24 hours post-dose.

- A dose-response exploratory early Phase II study in remission of acute symptoms of chronic pancreatitis. This preliminary clinical study was conducted in which camostat mesilate 300mg/day and 600 mg/day was administered 3 times daily after each meal for 6 consecutive weeks in patients with chronic pancreatitis.

- A Phase II double-blind comparative study was conducted in which patients with postoperative reflux esophagitis received FOIPAN 300 mg/day (Group L), 600 mg/day (Group M), and 900mg/day (Group H) for 8 weeks.

- A Phase II double-blind comparative clinical study was conducted in which patients with postoperative reflux esophagitis, subjective symptoms, endoscopically observed erosion, hemorrhage, ulcer, white film, redness, etc., received FOIPAN 300 mg/day (Group H) and 90mg/day in unidentifiable tablets containing 30 mg of this product (Group L) for 8 weeks.

- A Japanese double-blind controlled study for emission of acute symptoms of chronic pancreatitis was conducted using FOIPAN 600 mg/day (Group F) and placebo (Group P) in patients diagnosed with chronic pancreatitis by histological examination, morphologic examination, or pancreatic function test based on diagnostic criteria of the Japan Pancreas Society, and who had an elevated serum/urine amylase level and acute symptoms of upper abdominal pain and/or tenderness, and were capable of taking oral medication. The treatment period was 2 weeks and the observation period was 4 weeks until 2 weeks after the end of treatment.

- A Japanese double-blind controlled study for emission of acute symptoms of chronic pancreatitis was conducted using FOIPAN 600 mg/day (Group F) and placebo (Group P) in patients diagnosed with chronic pancreatitis by histological examination, morphologic

examination, or pancreatic function test based on diagnostic criteria of the Japan Pancreas Society, and who had an elevated serum/urine amylase level and acute symptoms of upper abdominal pain and/or tenderness, and were capable of taking oral medication. The treatment period was 2 weeks and the observation period was 4 weeks until 2 weeks after the end of treatment.

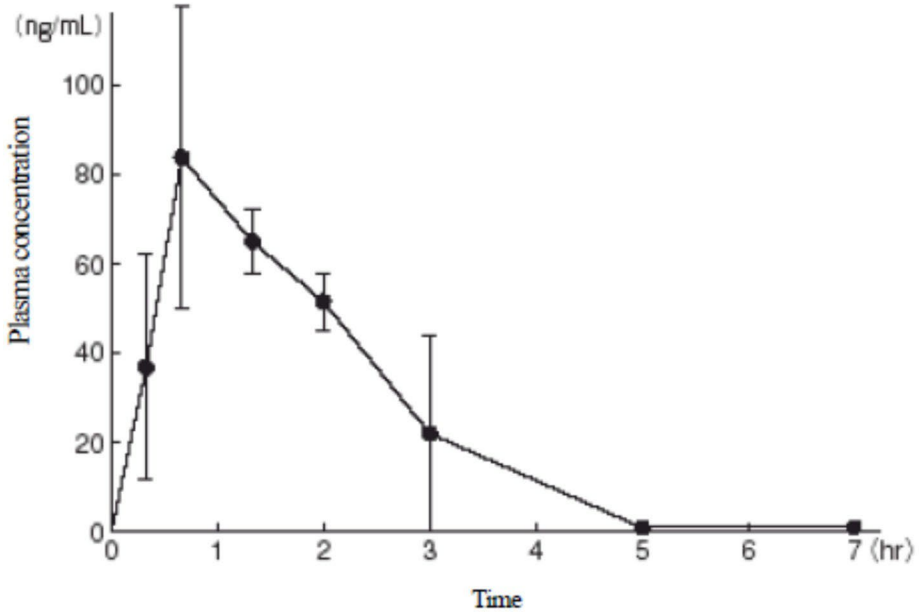
A Phase I study in 14 healthy young men of 2400 mg per day for seven days with the dose given 30 minutes or one hour pre-prandially. Fasting and non-fasting drug levels were compared and subjects were assessed for adverse events and to compare drug levels in fasting state, at 30 and 60 minutes before eating and with food.

Implementation of a controlled study as a Phase III study was considered but based on the results of comparison of the Group H (300 mg/day) with the Group L (90 mg/day) in the Phase II double-blind controlled study, it was determined that a placebo-controlled study was not necessary.

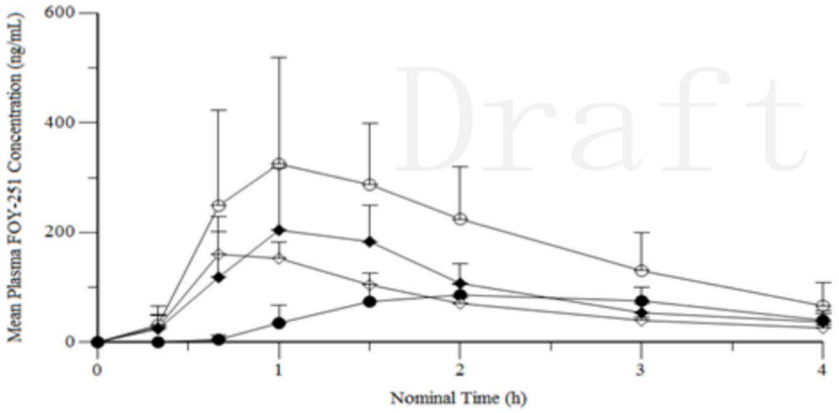
2.4 Phase 1 Study Steady State Exposure

Plasma concentrations of camostat mesilate were determined by HPLC after single dose of 200 mg was orally administered with about 100 mL of water to 5 healthy adult male volunteers in a fasted state. The unchanged drug concentration in plasma was below the limit of quantitation, but the active metabolite 4-(4-guanidinobenzoyloxy)phenylacetic acid (hereafter abbreviated as FOY-251) was detected. The plasma concentration of the active metabolite FOY-251 reached a maximum at 40 minutes post-dose, with a maximum plasma concentration (Cmax) of 87.1 ng/mL and a half-life (T1/2) of approximately 100 minutes. The time course of the blood concentration of the active metabolite FOY-251 is provided below.

Figure 3 Time Course of Blood Concentration of FOY-251



○ : Cohort 1 Day 1 (Single dose in the fasted state), ● : Cohort 1 Day 3 (Single dose after the meal), ◇ : Cohort 2 Day 1 (Single dose, 30min before the administration), ◆ : Cohort 2 Day 3 (Single dose, 60min before the administration)



Data are presented as the mean ± standard deviation except that Tmax is shown as the median.

Tmax (min)	Cmax (ng/mL)	AUC (ng·min/mL)	$T_{1/2}$ (min)
40	87.1±29.5	10400±1400	100±40

2.5 Rationale for 200 mg dose four times per day given one hour before meals

In a recent study, the IC50 for camostat for coronavirus was found to be 4.3 nM (Hoffmann et al. 2020 *Preprint)*. In the presence of serum, however, camostat rapidly degrades to GBPA which has an IC50 of 70.3. This is similar to previous reports of an IC50 of 87. The Cmax of Camostat and GBPA in blood noted above (87.1 ng/ml) with a 200 mg dosing is thus barely sufficient to reliably inhibit the virus. There is precedent, however, in US for using a higher dose of 200 mg four times daily; a trial of camostat for Covid-19 currently underway at Mayo Clinic is using this 800 mg dose (NCT04470544). Moreover, providing the drug one hour before meals can maximize the Cmax as is evident in the figure below using a 600 mg dose. Thus, we feel the best dosage for Camostat is 200 mg one hour before and two hours after meals and at bedtime.

2.6 Rationale for 10-day Dosing Regimen

The indicated dose of camostat/Foipan has been extensively used in pancreatitis patients for more than 20 years in Japan.

2.7 Rationale for the Current Study

There is a global pandemic caused by the SARS-CoV-2 virus, which threatens the lives of many and the economic stability of the world. Therapeutic approaches are badly needed, and an orally available, well tolerated small molecule agent could play a critical part in preventing and ameliorating COVID-19.

People with COVID-19 who are or experiencing mild symptoms that do not require hospitalization have no proven option other than supportive care. The safety profile of camostat mesilate is well-established. It is generally safe and well-tolerated. Furthermore, reducing viral shedding may decrease household and community transmission of SARS-CoV2. Thus, the risk to benefit assessment of treatment with camostat mesilate in the face of COVID-19 is clearly in favor of potential study subjects.

This study will assess the time course of cessation of viral shedding, and gather clinical benefit information, in patients with COVID-19 treated with camostat mesilate plus SOC as compared to placebo plus SOC. Data from this trial is expected to support a larger study which will demonstrate clinical benefit and serve as a pivotal trial for approval. The information gathered from this study will also help define the safety profile in this setting and enable expansion into other patient populations such as those who have been exposed but who are not yet ill. This could have a significant impact on public health.

3 DESIGN

This is a Phase 2 double blinded and placebo controlled randomized trial evaluating the efficacy and safety of camostat mesilate in adult subjects with PCR-positive, mild-moderate or COVID-19 infections.

Subjects will be randomized to receive either camostat mesilate + current Standard of Care (SOC) or SOC + placebo.

Study participants will be randomly assigned 1:1 to two tablets of oral camostat mesilate (200 mg) four times a day or current standard of care for 10 days.

Subjects in the SOC arm will receive a placebo. The total anticipated duration of the study for each patient is 28 days.

4 OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus SOC in reducing the AUC through day 10 of shedding of SARS-CoV2 virus in patients with mild-moderate COVID-19 disease.

4.2 Secondary Objectives

1. To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus current SOC in reducing the AUC up through day 28 of viral shedding of SARS-CoV-2 virus in patients with mild-moderate COVID-19.
2. To evaluate the efficacy of oral camostat mesilate plus SOC compared with placebo plus current SOC in reducing the duration of viral shedding of SARS-CoV-2 virus in patients with mild-moderate COVID-19.
3. To evaluate the efficacy of oral camostat mesilate plus SOC compared SOC plus placebo in reducing the duration of symptoms, hospitalizations or ED visits, or mortality in patients with mild-moderate COVID-19 disease.
4. To evaluate the proportion of individuals with a negative SARS-CoV2 RT PCR test on days 7, 14 and 28.

5. To assess the safety and tolerability of camostat mesilate in this subject population.
6. To assess the development of antibodies against SARSCoV-2
7. To determine drug levels using the current dosing scheme.

5 SUBJECT POPULATION

5.1 Inclusion Criteria

All criteria must be confirmed as "YES":

1. Adults (18 to 80 years old inclusive)
2. Diagnosis of COVID-19 disease:
    a. Presence of mild-moderate symptoms without signs of respiratory distress (as defined by SpO2 <=94% on room air, RR >=24, HR >=110), with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from swab to the time of commencing informed consent. Mild-moderate disease is defined as having at least 2of the following symptoms that are of moderate or higher severity as scored on the COVID Outpatient Symptom Scale (COSS)::
        i. Fever (>98.7F)
        ii. Cough
        iii. Shortness of breath
        iv. Fatigue
        v. Headache
        vi. Body ache
        vii. Joint pain
        viii. Chest pressure
        ix. Abdominal pain
        x. Sore throat
        xi. Nasal congestion
        xii. Chills
        xiii. Feeling hot or feverish
        xiv. Runny nose
        xv. Loss of taste
        xvi. Loss of smell
        xvii. Diarrhea
        xviii. Nausea
        xix. Vomiting
        xx. Rash
    b. The date of onset of the first of the above symptoms will be documented.
3. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures.
4. If male, subject must:

a. Be sterile (e.g., have had a vasectomy at least 6 months prior to Day 1 dosing), OR,
b. Agree not to donate sperm during the study and for seven days following the last dose of study medication, AND,
c. Agree to strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication:
   i. Abstain from sexual intercourse.
   ii. Use a condom during sexual intercourse with a female of child-bearing potential. In addition, the female partner must use another form of contraception (e.g. intrauterine device [IUD], diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).

5. If female, subject must:
   a. Be unable to bear children (have not had a period for ≥ 12 consecutive months, have had her uterus or ovaries removed, or have had a tubal ligation), OR,
   b. Must ensure that their male partner is incapable of fathering a child (e.g., has had a vasectomy at least 6 months prior to study entry), OR,
   c. If she is of childbearing potential will strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication:
      i. Abstain from sexual intercourse, OR,
      ii. Must ensure that her male partner agrees to use a condom during sexual intercourse and agree to use an approved method of contraception (e.g., IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).
   d. Agrees to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy.
   e. Has a negative urine pregnancy test at screening.
   f. Has not had unprotected sexual intercourse within the past month.
6. When such testing is available, subject will be confirmed to be SARS-CoV2 infected using a rapid (<30 minute) SARS-CoV2 point-of-care test; if such a test is not available, this step of screening will be omitted.
7. Subject agrees to maintain home or other quarantine as recommended by the study physician, except to visit the study site as required by the protocol.
8. Subject agrees to take daily nasal swabs (anterior nares) for Day 1 to Day 10 and Day 14, 21, and 28 using the study provided material and bring these to their follow up visits on days 5, 10 and 28.
9. Subject agrees to record daily symptoms, temperature, oxygen saturation, and pulse using the study provided materials.
10. Subject agrees to return to the study site for follow-up visits on Day 5, 10 and 28. The study site will be staffed by trained healthcare providers wearing full personal protective equipment and study site equipment will be disinfected between patients according to the same protocols as a clinical setting. Subjects will be wearing masks, will be appropriately spaced, and the number of subjects assessed at each time will be limited.
11. Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met.

5.2 Exclusion Criteria

All criteria must be confirmed as "NO":

1. Subject has a concomitant bacterial respiratory infection, as defined by positive respiratory culture

   NOTE: Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who are positive for SARS-CoV-2, are allowed in the study.
2. Previous use of antiviral drugs that may be active against COVID-19.
3. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers).

   NOTE: Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrolment into other clinical studies that evaluate investigational agents for COVID-19.
4. Subject has gout, a bleeding disorder, or a serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, moderate or severe hepatic insufficiency and/or unstable renal, cardiac, pulmonary, neurologic, vascular, or endocrinologic disease states requiring medication dose adjustments within the last 30 days).
5. Subject uses an anticoagulant medication including heparin, coumadin, a factor Xa inhibitor (xarelto, apixaban) or a thrombin inhibitor (Pradaxa). Aspirin is not an indication for exclusion
6. Has previously received camostat mesilate within the past 30 days.
7. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
8. Has liver impairment greater than Child-Pugh A.
9. Has a history of alcohol or drug abuse in the previous 6 months.
10. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year.
11. Has taken another investigational drug within the past 30 days.
12. Is deemed by the Investigator to be ineligible for any reason.

5.3 Removal of Subjects from Treatment

The participation of a subject in the study or the administration of treatment may be terminated at any time for one of the following reasons:

- The subject desires to discontinue study treatment.
- The subject withdraws consent to participate in the study.
- The subject is unwilling or unable to comply with the safety procedures.
- The subject is discovered to be pregnant.
- The subject experiences a medical emergency that necessitates withdrawal.
- The subject is withdrawn at the discretion of the Investigator for medical reasons or non-compliance.

- AST or ALT > 8 x ULN
- ALT or AST > 3 x ULN AND total bilirubin > 2X ULN
- AST or ALT > 3 x ULN AND patient has right upper quadrant pain or eosinophilia
- Hypersensitivity
- Shock or anaphylactoid symptoms
- Absolute neutrophil count <800 cells/mm^3
- Hemoglobin <11 g/dL for women and <12 g/dL for men
- Serum creatinine concentration ≥1.5× ULN
- Confirmed creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault
- Platelet count <75,000 cell/mm^3.
- Hepatic function disorder or jaundice (both incidences unknown).
- Hyperkalemia (incidence unknown). Severe hyperkalemia may occur.

A subject whose treatment is terminated should remain in the study for appropriate follow up assessments whenever possible.

6 STUDY TREATMENT - CAMOSTAT MESILATE

6.1 Study Drug

Camostat will be supplied as 100mg unprinted tablets to be stored at controlled room temperature (15°C to 30°C [59°F to 86°F]). Ono Pharmaceuticals has prepared matched placebo tablets, which they will also supply to us along with camostat tablets. Matching placebo will be provided in tablet form to be stored at controlled room temperature (15°C to 30°C [59°F to 86°F]).

Standard Dose
Subjects randomized to the camostat mesilate + SOC arm will be administered. Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as soon as possible after the subject's eligibility has been confirmed.

Subjects randomized to the SOC + placebo arm will be administered. Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as soon as possible after the subject's eligibility has been confirmed.

6.2 Administration of Camostat mesilate or placebo

The tablets will be dispensed in appropriately sized amber prescription containers with child-resistant caps. The prescription container and caps are manufactured from PP (polypropylene plastic).

Camostat mesilate is provided as 100 mg tablets and dosed orally. Subjects will be instructed to take their doses at least two hours after a meal and one hour before the next meal, and at bedtime.

Subjects who vomit during or immediately after dosing, should not be re-dosed.

6.3 Outpatient Camostat mesilate Dosing

Subjects in the camostat mesilate + SOC arm, will be dispensed sufficient camostat mesilate to ensure continued dosing until their next study visit.

Subjects will also be instructed that if they miss a dose, they should follow the guidelines:

1) If more than 1/2 the time until their next dose has elapsed, they SHOULD NOT take the dose. They should just take the next dose at the normal scheduled time.
2) If less than 1/2 the time until their next dose has elapsed, they should take the missed dose immediately.
3) In both cases, they should then return to their regular dosing schedule.

6.4 Drug Accountability

The Investigator must maintain adequate records showing the receipt, dispensation, or other disposition of camostat mesilate including the date, quantity and identification of subjects (study ID) who received camostat mesilate. Drug supplies will be inventoried and accounted. Unused supplies of all camostat mesilate will be returned to the Sponsor or destroyed on site in accordance with local procedures upon approval of the Sponsor.

6.5 Treatment Compliance

The pharmacy will provide bottles of camostat mesilate for outpatient use (Exact dispensing instructions for outpatients will be described in the pharmacy instructions). Assessment for compliance with each dose will be monitored and recorded in accordance with site standard operating procedures.

6.6 Treatment Precautions

An overdose is defined as any dose of study drug given to a subject or taken by a subject that exceeds the dose described in this document. In the event of an overdose, the subject's symptoms should be treated, and the Sponsor informed.

6.7 Clinically Significant Adverse Reactions

As indicated on the FOIPAN label (Japanese approved product), the below listed clinically significant adverse reactions may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing the administration should be taken.

- Shock or anaphylactoid symptoms (both incidences unknown). If any symptoms such as decreased blood pressure, dyspnea, and pruritus are observed, administration should be discontinued and appropriate measures be taken.
- Thrombocytopenia (incidence unknown).
- Hepatic function disorder or jaundice (both incidences unknown).
- Hepatic function disorder accompanied by remarkable increase of AST (GOT), ALT (GPT), γ-GTP, Al-P, or jaundice may occur.
- Hyperkalemia (incidence unknown). Severe hyperkalemia may occur.

6.8 Other Adverse Reactions

Incidence[1]/Adverse Reaction	0.1%-0.5%	<0.1%	Unknown
Hematologic		Leukopenia, erythrocytopenia	Eosinophilia
Hypersensitivity[2]	Rash, pruritus		
Gastrointestinal	Nausea, abdominal discomfort, abdominal fullness, diarrhea	Anorexia, vomiting, dry mouth, heartburn, abdominal pain, constipation	
Hepatic	Increased AST (GOT), ALT (GPT), etc.		
Renal		Increased BUN, increased creatinine	
Other		Edema, hypoglycemia	

[1] The incidences are calculated by including reports from the drug use surveillance

[2] If such symptoms are observed, administration should be discontinued.

6.9 Prohibited Concomitant Therapy

The following may interact with camostat mesilate and risks and benefits should be carefully considered prior to treatment with the following:

- Any other anti-viral medication whether investigational or approved.

7 STUDY PROCEDURES

Refer also to Section 14: Schedule of Assessments

7.1 Day 1 (PRE-DOSE)

- Obtain informed consent.
- Verify eligibility per the inclusion and exclusion criteria. (See Sections 5.1 and 5.2)
  - Review and record medical history to ensure there are no exclusionary illnesses.
  - Review and record concomitant medications for possible prohibited medications. (See Section 6.7)
  - Record date of onset of symptoms
- If subject is female of child-bearing potential and meets inclusion criteria 5.e, obtain urine pregnancy test and proceed if result is negative.
- Measure and record vital signs (BP, HR, Temp, Resp).

- Collect and record SPO2 by Finger Sensor
- Perform Physical exam (may be done by the Principal Investigator or their designee)
- Collect oropharyngeal swab for virologic testing by RT-PCR and resistance testing.
- Collect blood samples for:
  - Antibodies to SARS-CoV-2.
  - Hematology and clinical chemistry laboratory analyses
  - Biobanking
- Perform subject randomization (via EDC) to establish treatment arm (camostat mesilate + SOC or SOC + placebo).
- Explain in home procedures for the study (self-sampling of nasal swabs, temperature, SPO2, completing the daily questionnaire).
- Provide supplies to research subject and review the calendar of return visits

7.2 Day 1 (FIRST DOSE AND POST-DOSE)

NOTE: Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as quickly as possible after the subject's eligibility has been confirmed.

- Administer first dose (200 mg camostat mesilate or placebo) at time 0.
- Monitor patient for 30 minutes after their first dose.

7.3 Days 5, 10, 28 (Follow-up) or Early Termination

- Conduct and record the results of a Physical Exam.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- Measure and record vital signs (BP, HR, Temp, Resp).
- Collect and record SPO2 by Finger Sensor
- Collect blood samples for:
  - Antibodies to SARS-CoV-2. (28)
  - Biobanking (Day 10 and Day 28)
  - Hematology and clinical chemistry laboratory analyses (Day 5, 10, 28)
  - Drug level one hour after dosing (Day 5)
- Assess and record clinical status according to the following study-specific 7-point scale:
  1. Not hospitalized
  2. Hospitalized, not requiring hospital care due to lack of housing
  3. Hospitalized, not requiring supplemental oxygen
  4. Hospitalized, requiring supplemental oxygen
  5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
  6. Hospitalized, on invasive mechanical ventilation or ECMO

7. Death

- Collect oropharyngeal swab for virologic testing (RT-PCR) and resistance analysis.
- Collect and record adverse events (see Section 8.3 for detailed instructions).

8 EFFICACY, PHARMACOKINETICS AND SAFETY ASSESSMENTS

8.1 Efficacy Assessments

Primary Measurement (Efficacy):

1. Nasal swab for PCR taken daily from Day 1 to Day 10, and Days 14, 21, and 28.

Secondary Measurements (Efficacy):

1. Symptom improvement or worsening: Subjects will fill in a diary daily (see Appendix A2), recording the following symptoms:
    a. Cough
    b. Sore throat
    c. Headache
    d. Nasal congestion
    e. Body aches and pains
    f. Fatigue
    g. Oral temperature taken at a consistent time each day and at least four hours after ingesting the most recent antipyretic (acetaminophen or NSAID)
    h. Dyspnea
    i. Shaking chills
    j. Loss of taste
    k. Loss of smell
    l. GI symptoms including nausea, vomiting, and/or diarrhea
    m. Chest pain
2. Blood for determination of antibodies to SARS-CoV-2 will be obtained on Days 1 and 28.
3. Number of subject hospitalizations, emergency department visits, incidence of respiratory failure, deaths, and proportions of subjects alive, not hospitalized, and free of respiratory failure on day 28

8.2 Required Resistance Testing

Resistance testing, as required in clinical trials of anti-viral drugs will be performed at each time point that oropharyngeal swabs are taken.

8.3 Safety Assessments

Abnormal clinical laboratory values that are clinically significant and all reported adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Safety will be assessed by the collection of observed and reported adverse events, physical exams, vital signs and the following clinical laboratory tests:

- **Hematology**

Hemoglobin (Hgb)	Hematocrit (Hct)
Platelet count	Red blood cell count
White blood cell count with differential	

- **Chemistry**

Blood Urea Nitrogen (BUN)	Creatinine
Total bilirubin	Alkaline Phosphatase
Aspartate transaminase (AST)	Alanine transaminase (ALT)
	Lactic dehydrogenase (LDH)
Glucose	Albumin
Total protein	Bicarbonate
	Sodium
Potassium	Chloride
Calcium	
Urate	C-reactive protein

NOTES:

- All clinical laboratory assessments listed above (hematology and chemistry) will be conducted at the Stanford University Medical Center clinical laboratory.
- If coagulation assays are ordered as part of the SOC, the results should be added to the EDC.

Including Clinical Laboratory Testing, subjects will undergo four planned venipunctures during this study.

8.3.1 Adverse Events

Treatment-emergent AEs will be defined as those occurring coincident with start of treatment through 28 days post-treatment.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Investigator (and/or designee) must document all AEs reported through completion of the Day 28 visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or, if in the camostat mesilate arm, 14 days after last dose. The Investigator will document available follow-up information on the subject's source documentation and CRF

8.3.2 Definition of an Adverse Event

The FDA Safety Guidance, referencing 21CFR312.32(a), defines an Adverse Event as follows:

> *Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*
>
> *An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.*

Adverse Events are **NOT**:

- **Clinical events related to the progression of COVID-19.**
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

8.3.3 Evaluating and Reporting of Adverse Events

All AEs (i.e. a new event or an exacerbation of a pre-existing condition) that occur after dosing with camostat mesilate and after completion of baseline assessments in the SOC + placebo arm, must be recorded as an AE or SAE (if applicable), on the Adverse Event eCRF and SAE form, as applicable. The Investigator must follow all AEs until the AE resolves, or until the Investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the Investigator and Medical Monitor will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All subjects who have received at least one exposure to study therapy will be evaluated for safety of study treatment.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

All AEs must be promptly documented on the Adverse Event eCRF and assessed by the Investigator. Details of the event must include the dates of onset and resolution, severity, relationship to study drug, seriousness, and whether the event caused the subject to withdraw from the study, outcome and timing with regard to administration of the study drug. We will categorize the AES using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Severity: Severity should be graded and recorded as follows:

- Grade 1 Mild: No or minimal interference with usual activities; intervention not indicated
- Grade 2 Moderate: Greater than minimal interference with usual activity; intervention indicated
- Grade 3 Severe: Inability to carry out usual activity, incapacitating; requires intervention or hospitalization
- Grade 4 Potentially life-threatening: Inability to perform self-care; intervention indicated to prevent permanent impairment, disability or death
- Grade 5 Death

Relationship: The relationship of the Adverse Event to the study drug will be determined by the Principal Investigator, and assessed using the following definitions:

- **Related:** There is a distinct temporal relationship between the event onset and administration of the study drug. There is a known reaction to agent or chemical group or predicted by known pharmacology. The event cannot be explained by subject's clinical state or other factors.
- **Unrelated:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

8.3.4 Serious Adverse Events (SAEs)

All SAEs as defined below and that occur after the first dose of camostat mesilate and up to Day 28 must be reported to the Sponsor as soon as the site becomes aware of them. Any SAEs occurring after Day 28 and considered at least possibly drug-related must also be reported.

8.3.5 Definition of Serious Adverse Events

An SAE is an AE from this study that results in any of the following outcomes:

- Death **(even if caused by COVID-19 all deaths are recorded as SAEs)**
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug

NOTE: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject *and* may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A life-threatening AE is defined as any adverse experience that places the subject in the view of the Investigator, at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

"Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time with a minimum one overnight stay. Presentation and care within an emergency department does not necessarily constitute an SAE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, it is an SAE.

8.3.6 SAE Reporting Requirements to the Sponsor

The procedure for reporting SAEs, regardless of causal relationship, is as follows:

- Within 24 hours of the Investigator's knowledge of an SAE, the site must notify the Sponsor by phone call to their site monitor, medical monitor or other Sponsor representative. They should also immediately complete the AE eCRF and select "Serious".
- This initial reporting of an SAE should contain as much information as is available to the Investigator. Submission of the SAE via the EDC should not be delayed in order to collect additional information to complete the form.
- Follow-up SAE reports may be generated in cases in which additional information becomes available. Hospital records, autopsy reports, and other documents may become available and scanned copies can be provided to the Sponsor when applicable. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated, whether

the blind was broken or not, and whether the subject continued or withdrew from study participation.

- The Sponsor will distribute completed SAE forms, which may be used to notify the IRB when applicable, via a secure internet-based document depository.
- The Investigator should notify the IRB of Serious Adverse Events occurring at the site and other adverse reports received from the Sponsor in accordance with local procedures.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF. However, treatment medication should only be recorded in the narrative description section of the SAE form.

8.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR carries specific and time-based reporting requirements for the Sponsor of a clinical trial. Thus, after an Investigator reports an SAE, the FDA expects the Sponsor will determine whether it meets the definition of a SUSAR.

A SUSAR is defined according to 3 criteria:

1. The AE is deemed a "suspected adverse reaction" if there is a reasonable possibility that the study drug caused the AE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and adverse event.
2. The AE is "Serious" if it meets the definition of an SAE provided in section 8.3.5
3. The AE is deemed "unexpected" if it is not listed in the Investigator's Brochure (IB) or if in the IB, has not been reported at the severity observed.

In cases where the Sponsor deems a SUSAR has occurred, it must file an IND Safety Report with the FDA. Sponsorwill require the assistance and cooperation of the Investigator and staff to provide accurate and complete information on the subject and observed SAE so that reporting requirements to the FDA can be met.

8.4.1 Reporting SUSARs to the FDA: IND Safety Reports

IND safety reports are used to submit reports of SUSARs to the FDA. There are 2 types of reports:

- A "15-day report" is used when the reported SAE is a SUSAR and requires that as much information as is available to the investigator and the sponsor, be submitted to the FDA in on the appropriate form. For US trials, the appropriate form is the FDA Form 3500A also commonly known as a "MedWatch" form.
- A "7-day report" is used when the SUSAR is considered to be fatal or life-threatening.

The 7-day and 15-day timelines begin the day that the Investigator learns of the event and are counted in calendar days – not business days. Therefore, it is important that the investigator carefully follow the reporting requirements described in section 8.3.6.

8.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs unless considered to be clinically significant by the site clinician. An abnormal laboratory result will be considered an AE if it

induces clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g. discontinuation of the study drug, dose modification) or when the event is requiring treatment or other therapeutic intervention (e.g. iron supplements, blood transfusion, etc.).

The Investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significant abnormal laboratory results will be followed until they return to normal or become stabilized.

8.6 Handling of Overdose

An overdose is defined as any dose greater than the highest daily dose included in this document. Any overdose must be recorded. If the overdose is associated with an AE, that AE must be recorded, assessed for seriousness, and reported as an SAE.

9 STATISTICAL METHODS

Complete details of all statistical analyses, including methods for handling missing data, will be included in a formal statistical analysis plan (SAP), to be completed as soon as possible.

9.1 General Considerations

For the primary comparison, the following will be tested:

- Null hypothesis: AUC of viral shedding through day 10 is equal in control and treatment;
- Alternative hypothesis: AUC of viral shedding through day 10 differs between control and treatment.

Hypothesis tests will be two sided and conducted at an overall alpha = 0.05 level of significance.

The number of hospitalizations and emergency department visits will be estimated for each arm, with 95% confidence intervals. The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

9.2 Sample size justification

Approximately 120 patients will be enrolled.

Assuming 1:1 randomization and the use of a two-sided log rank test at the alpha=0.04999 level of significance for the final analysis, 120 patients (60 per arm) events will provide 80% power to detect an effect size of 0.5 using two-sample t-test. This leaves alpha=0.00001 to check for overwhelming efficacy after 50% of participants have completed 24 hours of follow-up.

9.3 Demographic and Baseline Characteristics

Summary statistics will be provided per treatment group for demographic (e.g., age, height, weight, body mass index [BMI], race, gender) and other initial subject characteristics (e.g., medical history,

concomitant diseases) will be provided per treatment group and for the total group. The ITT population will be used for the summaries.

9.4 Analysis Populations

The following analysis populations will be defined for the study:

The intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed according to their assigned treatment arm. All efficacy analyses will be completed in the ITT population.

The safety population will include all patients who receive study treatment. Patients will be analyzed according to actual treatment received. All safety analyses will be completed in the safety population.

9.5 Stratification, Subgroup Analysis and Pooled Analysis

Following consent, those subjects meeting all entry criteria will be randomized in a 1:1 ratio

Treatment Arm: camostat mesilate + SOC

Control Arm: placebo + SOC

Randomization will be stratified by age (>=50 and <50 years old) and sex.

Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met. Because this is a double-blind, placebo-controlled trial, subjects from the same household will be randomized just as any other subject.

9.6 Efficacy Endpoint Analysis

9.7 Descriptive analyses

Descriptive statistics (proportions for categorical variables, means, medians, standard deviations and interquartile ranges for continuous variables) will be reported for all key patient variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status. Data that are missing on key patient characteristics and the outcome will be fully described, including any patterns of missingness (i.e., any relationships between missingness of a variable and patient characteristics).

A CONSORT diagram displaying the number of patients screened, eligible, and consented along with reasons for ineligibility will be provided. Graphical tools such as histograms, boxplots, and scatterplots will be created to assess quality of data and to display patterns over time.

9.8 Primary efficacy analysis

To address our primary objective, the AUC SARS-CoV2 viral RNA levels during follow-up will be estimated using the linear trapezoidal method, and mean AUC levels compared between groups using a linear regression model regressing log(AUC) on treatment arm, site, age, and sex. If more than 3 sites are included to address the objectives, we will employ a mixed effects

model, with a random effect for site. The test will be performed at the two-sided alpha = 0.05 level of significance.

9.9 Secondary efficacy analyses

Time until shedding cessation will be compared between the two treatment arms using a Cox proportional hazards model adjusted for site, age, and sex. Time of cessation will be defined as the first negative result that is followed only by negative results. If more than 3 sites are included to address the objectives, we will employ a stratified Cox model, stratified by site, allowing each site to have its own baseline hazard. The hazard ratio for shedding cessation will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption

The distribution of shedding cessation will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to shedding cessation at the end of the study period along with 95% confidence intervals will be presented for each treatment arm.

The distribution of time to resolution of symptoms will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to resolution of symptoms at the end of the study period along with 95% confidence intervals will be presented for each treatment arm. The hazard ratio for resolution of symptoms will be estimated, along with its 95% confidence intervals, from a Cox proportional hazards model. Time to resolution of symptoms will be determined by analysis of daily questionnaires (see Appendix A2). Resolution of symptoms requires that symptoms are mild or absent for at least 24 hours. The analysis of symptom resolution will be conducted on the symptomatic ITT population, i.e. participants who report moderate or severe symptoms at baseline. These analyses will be repeated in a second analysis considering only respiratory symptoms, i.e. fever, cough, shortness of breath, sore throat, headache, and nasal congestion/runny nose. This analysis will be performed on the subset of patients who report moderate or severe respiratory symptoms at baseline.

The number of hospitalizations, emergency department visits, incidence of respiratory failure, deaths, and proportions of subjects alive, not hospitalized, and free of respiratory failure will be estimated for each arm, with 95% confidence intervals. Respiratory failure is defined as the need for mechanical ventilation, ECMO, non- invasive ventilation, or high-flow oxygen

Our analyses will use multiple imputation methods that assume data are missing at random by including all baseline characteristics, treatment assignment, and reasons for missingness in the imputation model. This approach will be applied to any analysis involving endpoints or key variables where any missing data occurs in order to adhere to the ITT principle. Assumptions regarding missingness will be addressed in sensitivity analyses.

9.10 Safety Analysis

The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

The original exact terms in the electronic data capture (EDC) system used by Investigators to identify AEs other than symptoms of COVID-19 will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be defined as those occurring coincident with start of treatment and through 28 days post-treatment. TEAEs will be summarized overall and by treatment group and by MedDRA body organ system and preferred term, severity, relatedness, and seriousness.

An overall summary of TEAEs will be presented by treatment, with subject counts and percentages of subjects with the event. This summary will include subjects with any TEAE, any treatment-related TEAE, any serious TEAE, any treatment-related serious TEAE, TEAEs leading to study infusion discontinuation, treatment-related TEAEs leading to study infusion discontinuation, TEAEs leading to death, and treatment-related TEAEs leading to death. The difference in proportions between treatment groups in each of these categories will be calculated.

Summaries of changes over time in laboratory parameters, as well as counts and percentages of laboratory parameters that are Low, Normal, and High compared to the reference ranges will be presented by treatment at each visit and time point. Shift tables will be presented for laboratory parameters with defined severity grades.

10 DATA SAFETY MONITORING

10.1 Data and Safety Monitoring Committee

A DSMC will be established by the study team in cooperation with the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate the trial. The DSMC will operate according to guidelines documented in a DSMC charter. Minutes will be taken to provide a written record of the DSMC meetings, including interim results; these will be available for review when the trial is complete. The DSMC will be a separate entity from the Institutional Review Board (IRB). The independence of the DSMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. DSMC members will be external to Stanford University, will not participate in the study as investigators, and will not have conflicts of interest regarding the study or the investigational product. The composition of the DSMC will include at minimum:

- DSMC Chair, having experience and expertise in clinical trials
- Scientist with expertise in viral infectious diseases.
- Biostatistician with expertise in clinical trials.

The DSMC will meet before the study and during an interim analysis to review progress of the clinical trial and safety data. A formal interim analysis for overwhelming efficacy is planned for the interim analysis. There are no plans to stop for futility. the DSMC may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. Any recommendation by the DSMC to stop the trial early will be based on a balanced review of safety and efficacy data and a consideration of whether an adequate amount of information is available to reach a conclusive decision.

The study PI will distribute study information to the DSMC prior to a scheduled meeting. The DSMC may request additions and other modifications to this information on a one-time or continuing basis. This information will consist of two parts: (1) information on study progress such as accrual, baseline characteristics, and other general information on study status and (2) any confidential data on study outcomes, including safety data. A formal report from the DSMC should be supplied to the PI within 3 days of each meeting. Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A recommendation to terminate the study should be transmitted to the PI and IRBs as rapidly as possible, by immediate telephone and fax if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMC report.

10.2 Interim Analysis

An interim analysis for safety and overwhelming efficacy will be performed once 50% of patients have 24 hours of follow-up complete. The DSMC will meet within a week after 50% enrollment is reached to review the safety data collected within the first 24 hours of follow-up on all enrolled patients. We additionally expect blood count labs collected at day 5 to be available in approximately 25% of patients at the time of the DSMC review.

The DSMC will also review the efficacy data on all randomized participants at this meeting. The interim efficacy analysis will use the same methods as are planned for the final analysis using the ITT analysis. Based on the results of the interim analysis, the DSMC will either recommend to the sponsor to terminate the study for overwhelming efficacy ($p<0.00001$ at the interim analysis), terminate the study for safety concerns, modify the study, or continue the study as planned. No formal stopping rules for futility are planned.

11 RECORDING AND COLLECTION OF DATA

11.1 Case Report Form

The Investigator or designee will record all data collected on the electronic Case Report Form (eCRF) provided for that purpose. For this study, REDCAP cloud will be the eCRF. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures.

All site entries will be made in a secured web site and the Principal Investigator will review the record for completeness. Upon completion of the review, the PI will sign electronically in the signature page of the eCRF.

The Investigator or designee will make necessary eCRF corrections. The investigator must authorize the corrections to the entered data on eCRF.

Specific instructions on use of the EDC system and guidelines for data entry and correction will be provided to the sites.

11.2 Study Files and Subject Source Documents

Subject confidentiality is strictly held in trust by the participating investigators, research staff, the Sponsor and their designees. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Authorized representatives of the Sponsor 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 subjects in this study. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a subject identification number to maintain confidentiality.

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original subject clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Subject clinical source documents may include, but are not limited to, subject hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, and consultant letters. The Investigator must assure that all original source documents are available to support monitoring activities.

11.3 Monitoring

Due to the restrictions imposed on clinical and hospital visits by the COVID-19 pandemic, all monitoring of this study will be conducted remotely. Monitors will work with the Study Coordinator at each site to determine times for "joint" remote monitoring – meaning that the monitor and the SC will review data together over the telephone.

Remote monitoring will be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Investigator will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of remote monitoring and by prompt attention to any matters brought to his/her attention by the monitor.

11.4 Audit

ICH guidelines for GCP require independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The Investigator

and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by the Sponsor that will be suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies. The Investigator understands and agrees to give access to the necessary documentation and files.

11.5 Retention of Data

All records connected with this clinical study will be retained for at least two years following the date of an approved marketing application [21 CFR 312.62(c)]; or at least three years from the formal discontinuation of camostat mesilate development; or seven years from the end of the study, whichever is longer. All local laws regarding retention of records must also be followed. Study sites are required to retain all records until written notification allowing destruction is received from the Sponsor.

12 ETHICS

12.1 Ethics Committee

A properly constituted, valid IRB/IEC must review the treatment plan and procedures, the Investigator's informed consent document, and related subject information. It is the responsibility of the Investigator to ensure that all aspects of institutional review are conducted in accordance with current regulations governing the jurisdiction where the study is conducted. The Sponsor (or designee) must receive a letter documenting IRB/IEC approval that specifically identifies the title of the treatment plan, subject information sheet, and ICF.

12.2 Subject Information and Consent

It is the responsibility of the Investigator to ensure that written informed consent is obtained from the subject or legal representative before any activity or procedure is undertaken that is not part of routine care. The informed consent must comply with local regulations.

The background of the study, the procedures, the potential benefits and risks of the treatment, and the fact that treatment is voluntary for the subject must be explained to the subject or legal representative. The subject or representative must be given sufficient time to consider whether to receive compassionate treatment. A copy of the ICF, signed and dated by the subject/representative and the Investigator (or designee), must be given to the subject/representative. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any treatment with camostat mesilate.

Each consent form should contain an authorization allowing the Investigator and the Sponsor (or designee) to use and disclose protected health information (PHI) (i.e., subject-identifiable health information) in compliance with local law. The signed consent form will be retained with the treatment records.

13 GENERAL CONSIDERATIONS

13.1 Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at any time for any reason.

13.2 Use of Information and Publication

All information concerning camostat mesilate, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, formulation, and other information supplied by the Sponsor to the Investigator and not previously published is considered confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only to treat this patient and will not use it for other purposes without written consent of the Sponsor.

The information obtained in this study will be used by the Sponsor in connection with the continued development and, if approved, commercialization of camostat mesilate. Thus, Sponsor may disclose such information as required to other clinical Investigators, contractors, and government regulatory agencies.

Publication or other public presentation of results from this study and related information is subject to the provisions of the Clinical Trial Agreement between Sponsor and the Study Site.

14 SCHEDULE OF ASSESSMENTS

Day of study	**Assessment in the study clinic** (Physical Exam, Vital at each visit Clinical Status 7-scale,SPO2)	**Administration of study drugs**	**Self-collected nasal swab and self-assessment**	**Oropharyngeal swab**	**Blood collected by phlebotomy for clinical labs** (CBC, Chem 7, LFTs)	**Blood collected for drug level**	**Blood collected by phlebotomy for biobanking/immunology studies**
1	X	X	X	X	X		X
2		X	X				
3		X	X				
4		X	X				
5	X	X	X	X	X	X	
6		X	X				
7		X	X				
8		X	X				
9		X	X				
10	X	X	X	X	X		X
14			X				
21			X				
28	X		X	X	X		X

15 APPENDIX

Appendix A: Subject Status

1. ECOG Performance Status

GRADE	**ECOG PERFORMANCE STATUS**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up an about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hour
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

2. Study Specific Daily Symptom Status Questionnaire

COVID-19 Outpatient Symptom Scale (COSS):

The below is a copy of a sample self-assessment a participant will be required to assess:

Please take your oral temperature and assess your oxygen saturation with your pulse oximeter.	Oral temperature.	_____ F
	Time temperature was obtained.	_____ AM/PM
	Blood oxygen saturation.	_____ %
	Did you take a nasal swab today (study day 1-10,14,21,28)?	Yes / No
	Have you taken your study drug as prescribed in the last 24 hours? (study day 1-10)	Yes / No
	If it is written on your schedule (clinic visit day 3, 14, 28): did you collect your stool sample for your next visit?	Yes / No

daily.

COVID-19 Outcome Symptom Scale (COSS) Daily Questionnaire

The following questions are about how you feel and how things have been during the past 24 hours compared to your typical health. Give the one answer that comes closest to the way you have been feeling. Select "None" if you have not had this symptom.

Cough?			
□ None	□ Mild; just a few coughs per day	□ Moderate; frequent but I can tolerate it	□ Severe; I am very uncomfortable
Shortness of breath (difficulty breathing)?			

□ None	□ Mild; just short of breath with exercise	□ Moderate; I get short of breath doing daily activities	□ Severe; I feel I can't get enough air even at rest
Fatigue (low energy)?			
□ None	□ Mild; I go about my day normally	□ Moderate; I rest more and restrict activity	□ Severe; I am staying in bed I'm so tired
Headache?			
□ None	□ Mild; I can ignore it	□ Moderate; I need to take medication	□ Severe; it is markedly limiting my life
Body Ache?			
□ None	□ Mild; I can ignore them	□ Moderate; I need to restrict some activities	□ Severe; they are markedly limiting my life
Joint pain?			
□ None	□ Mild; I can ignore them	□ Moderate; I need to restrict some activities	□ Severe; they are markedly limiting my life
Chest pressure?			
□ None	□ Mild; I feel it occasionally but can ignore it most of the time	□ Moderate; I notice it a lot and it limits my activity	□ Severe; I have bad pain and pressure that bothers me most of the time
Abdominal pain?			
□ None	□ Mild; I can ignore it	□ Moderate; it is limiting my activities	□ Severe; it hurts a lot. I may need to see a doctor
Sore Throat?			
□ None	□ Mild; I can ignore it	□ Moderate; it is painful to swallow and speak	□ Severe; it is limiting my ability to swallow or speak
Nasal Congestion?			
□ None	□ Mild; I can ignore it	□ Moderate; I notice it a lot	□ Severe; it is markedly limiting my life
Chills?			
□ None	□ Mild; I can ignore it	□ Moderate; I notice it a lot	□ Severe; I am very uncomfortable
Feeling hot or feverish?			
□ None	□ Mild; I can ignore it	□ Moderate; I notice it a lot	□ Severe; I am very uncomfortable
Runny Nose?			
□ None	□ Mild; I can ignore it	□ Moderate; frequent but I can tolerate it	□ Severe; I am very uncomfortable
Taste?			
□ None	□ Mild; tastes aren't as strong as usual	□ Moderate; I've noticed I can't taste certain foods	□ Severe; I cannot taste my food at all
Smell?			
□ None	□ Mild; smells aren't as strong as usual	□ Moderate; I've noticed I can't smell certain odors	□ Severe; I cannot smell anything at all
Diarrhea? (loose or watery stools in 24 hours)			
□ None	□ Mild; less than 3 times	□ Moderate; 3-6 times	□ Severe; more than 6 times
Nausea (feeling like you want to throw up)?			
□ None	□ Mild; I'm eating and ignoring it	□ Moderate; I don't want to eat and can't ignore it	□ Severe; I am feeling quite uncomfortable

Vomiting?			
□ None	□ Mild; only once or occasionally	□ Moderate; 3-4 times per day	□ Severe; I am having trouble keeping food down
How many times have you vomited today?			_____
Do you have a rash?			Yes / No
The rash is (check all that apply):			□ No rash □ Covering a small amount of my body □ Extensive covering of my body □ Involving the inside of my mouth or lips □ Itchy □ Itchy with hives
In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?			Yes / No

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