COVID-19 Outpatient Pragmatic Platform Study (COPPS): Camostat Sub-Protocol

A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19

Study Protocol and Statistical Analysis Plan

NCT04662073

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COVID-19 Outpatient Pragmatic Platform Study (COPPS): Sub-protocol: Camostat Mesilate

Document History		Notes
Version 1	Date: 06 October 2020	Initial Approval
Version 2	Date: 17 November 2020	PIND recommendations
Version 3	Date: 20 January 2021	Multisite & Endpoint changes
Version 4	Date: 04 May 2021	Inclusion criteria updated, interim analysis
Version 5	Date: 07 July 2021	Interim analysis
Version 6	Date: 21 September 2021	Schedule of assessments

CONTACT INFORMATION:

Sub Protocol Principal Investigator:
Julie Parsonnet, MD,
Professor, Stanford University, Division of Infectious Diseases and Geographic Medicine
Lane Building, [redacted], 300 Pasteur Drive, Stanford, CA 94305
Email: parsonnt@stanford.edu
Phone: 1-650-725-4561

Chaitan Khosla, Ph.D.
Baker Family co-Director, Stanford ChEM-H
Professor of Chemistry and Chemical Engineering
Email: khosla@stanford.edu
Mobile phone: [redacted]

SUMMARY OF CHANGES FROM VER 5 TO VER 6

- Updated schedule of assessments to align with Master Protocol Ver 9

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0. Summary paragraph for body of platform protocol

Camostat/Foipan has been extensively used in pancreatitis patients for more than 20 years in Japan. The clinical development program in Japan consisted of multiple clinical trials. The hypothesis, in brief, is that the transmembrane serine protease TMPRSS2, plays a critical role in viral entry of SARS-CoV-2 into host cells. 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. In the same study cited above (Hoffmann et al., 2020), camostat was shown to block viral entry in vitro.

1. Background

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.

Structural analyses indicate that SARS-CoV2 begins the process of infection when the spike (S) protein binds to the host's ACE2 receptors (Zhou et al., 2020). The S spike protein then requires processing by themTMPRSS2 serine protease to successfully enter the cell and complete its replication cycle. Blocking TMPRSS2 is thus considered a promising target for antivirals. 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).

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.

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.

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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

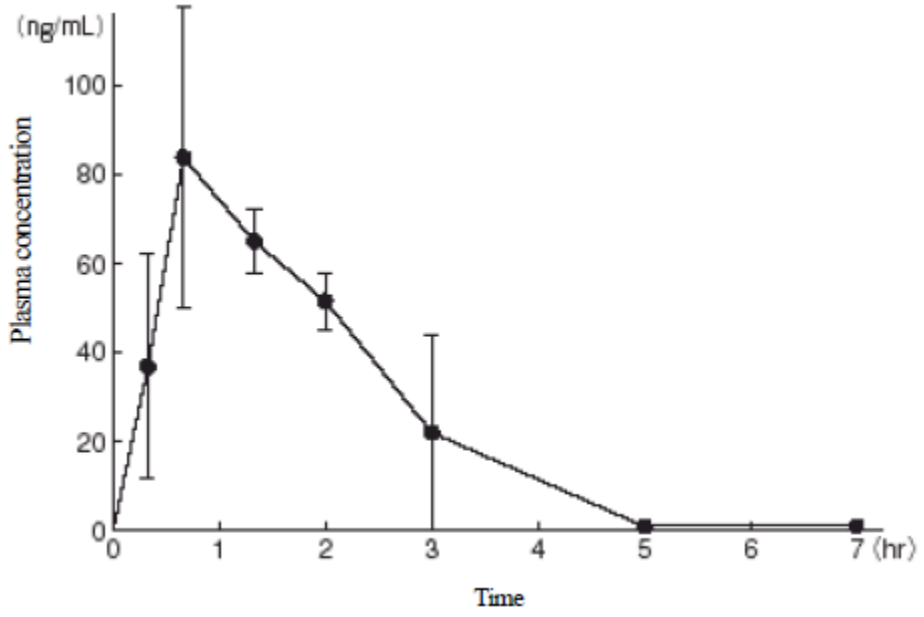
- A recent Phase I study in 14 healthy young men of 2400 mg per day x 7 days. The medication was well tolerated with an aphthous ulcer appearing in one patient. 8/14 subjects developed asymptomatic Grade 1 hyperuricemia and 5/14 developed asymptomatic Grade 1 abnormalities in coagulation (PT or aPTT).

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.

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



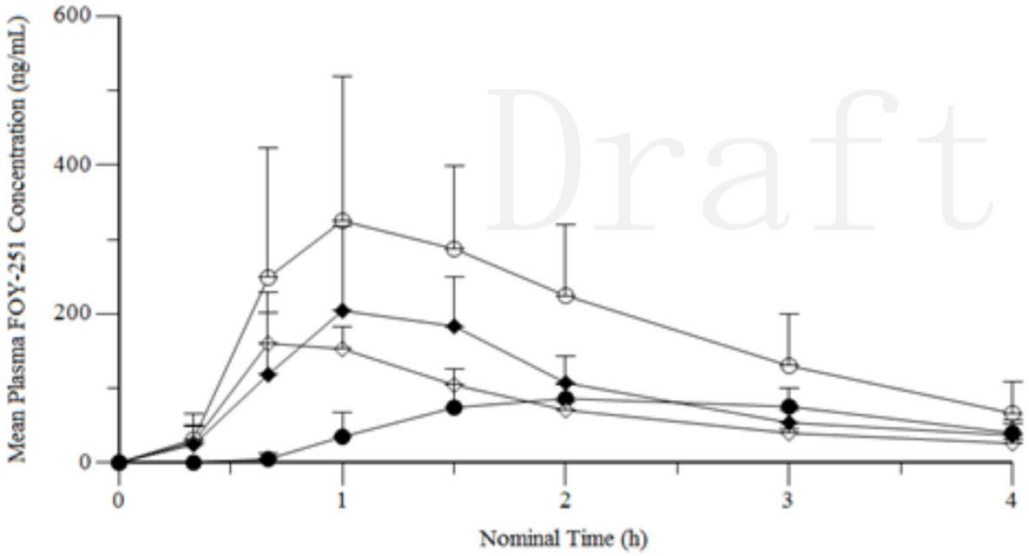
Data are presented as the mean ± standard deviation except that Tmax is shown as the median.

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

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 meals and at bedtime.

○ : 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)



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.

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.

2. Additional Inclusion/Exclusion Criteria

The below participant criteria is necessary for camostat mesilate in addition to criteria already stated above in the platform protocol:

Inclusion

1. 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).
2. 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.

Exclusion

1. Subject has received their first dose of any COVID-19 vaccine greater than 10 days prior to their Day 1 visit.
2. Subject is eligible for monoclonal antibody treatments for COVID-19 under EUA (see “NOTE” in Master protocol under section 3.2 for further details).

3. Subject has a history of gout or coagulation disorders.

4. 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.
5. Has previously received camostat mesilate within the past 30 days.

Note: Clinical screening laboratory evaluations will be performed locally by the site or site-designated laboratory.

3. Camostat Treatment

Standard Dose

Subjects randomized to active camostat mesilate will receive 200mg one hour before meals (breakfast, lunch, and dinner) and before bedtime, for 800mg total in a day over 4 dosing periods. Those under the placebo group will receive inactive placebo.

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.

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.

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.

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.

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. During the days 5 and 28 in-person visits, participants will be asked to bring their prescribed medication with them to track participant compliance.

Management of Progression of Disease

Should the patient be admitted to the hospital, they will follow protocol for inpatient procedures at the hospital, which usually includes the IV antiviral drug remdesivir. The clinical team for the patient will make a recommendation as to whether drug must be stopped or unblinded.

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.

Table 1. Camostat Sub-protocol Assessments																
Day of study	**1**	**2**	**3**	**4**	**5 ±1**	**6**	**7**	**8**	**9**	**10 ±1**	**14**	**21**	**28** +7	**120 ±7**	**210 ±7**	**300 ±7**
Assessments in the clinic	X				X					X			X			
Physical exam	X				X					X			X			
Vitals	X				X					X			X			
Clinical status	X				X					X			X			
SpO2	X				X					X			X			
Urine Pregnancy Test	X															
Self-collected nasal swab	X	X	X	X	X	X	X	X	X	X	X	X	X			
COSS self-assessment	Every day from days 1-28 inclusive													X	X	X
Oropharyngeal swab	X				X					X			X			
Blood collected by phlebotomy for clinical labs	X				X					X			X			
Blood collected by phlebotomy for biobanking	X[1]												X[1]			
Blood collected by phlebotomy for PK					X[1]											
Telehealth visit														X	X	X[2]
Administration of drug - Camostat sub-protocol	X	X	X	X	X	X	X	X	X	X						

1-Denotes optional assessment for sites external to Stanford University.
2-Denotes additional telehealth visit if needed for following any ongoing AEs.

4. Known product related Adverse Events

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.

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.

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.

5. Additional Endpoints (Safety, Secondary, and Exploratory)

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)
Glucose	Lactic dehydrogenase (LDH)
Total protein	Albumin
Potassium	Bicarbonate
Calcium	Sodium
Urate	Chloride
	C-reactive protein

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

Pharmacokinetic testing will be performed at day 5. Participants will be asked to take their dose in the clinic on day 5 for their in-person appointment. PK testing to sites external to Stanford University are optional.

Additional secondary endpoint:

1) To evaluate the proportion of individuals with a negative SARS-CoV2 RT-PCR test on days 14 and 28

6. Deviations to timing of measurements

Not applicable for camostat mesilate.

7. Preparation, Handling, and Storage

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]).

8. Interim analyses

A futility analysis will be conducted on both the virologic and on the clinical endpoints in addition to the interim efficacy analysis to be performed after 50% of the patients have been treated. The futility analysis will be based on the same Wald test using the estimated hazard ratio from the primary Cox proportional hazards model. Stopping for futility should be considered if the Z-statistic for the estimated hazard ratio is < 0.25, corresponding to a conditional power of 30%, for both the virologic and clinical endpoints.