COMBO Trial (Camostat with bicalutamide for COVID-19)

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1. Background

An important observation that has emerged from the global COVID-19 pandemic has been that men have a more severe course and higher mortality following infection with SARS-CoV-2 (Cao et al., 2020; Zhou et al., 2020). This gender disparity was also seen in the previous SARS and MERS outbreaks (Alghamdi et al., 2014; Karlberg et al., 2004; Leong et al., 2006). All three of the pathogens share a unique requirement for activation by the trypsin-like serine protease TMPRSS2 for infectivity and viral spread (Hoffmann et al., 2020a). TMPRSS2 has been demonstrated to proteolytically process and prime the S protein to mediate viral entry into host cells and is essential for viral spread and pathogenesis, making it a prime target for treatment (Hoffmann et al., 2020). Two strategies for blocking TMPRSS2 activity are (1) to inhibit proteolytic activity and (2) to downregulate expression of the protein. We hypothesize that a combination of these two strategies together would improve outcomes compared to Camostat alone or standard of care without either of these two drugs.

1.1. Camostat

Camostat mesilate is a serine protease inhibitor. It is approved for use in Japan for the treatment of chronic pancreatitis and reflux esophagitis (ONO Pharmaceutical, 2009). It has been shown in vivo to inhibit TMPRSS2 thereby blocking viral entry into host cells (Hoffmann et al., 2020a). In similar disease of SARS, caused by SARS-CoV, which uses similar mechanism of entry, camostat treatment also improved survival times in a mouse model of SARS-CoV infection (Zhou et al., 2015). We hypothesize that inhibition of TMPRSS2 with camostat, by treating early in the disease course when patients are diagnosed as outpatients, will decrease the percentage of people who end up hospitalized from COVID-19.

1.2. Bicalutamide

TMPRSS2 is an androgen regulated transmembrane serine protease that is highly expressed in prostate cells, which have the highest expression of this protein in humans. TMPRSS2 is also expressed in other tissues including the lung and gastrointestinal tract. While we do not have direct evidence of antiviral activity of bicalutamide against SARS-CoV-2, the rationale for using bicalutamide in patients infected with SARS-CoV-2 is based on strong scientific rationale and safety data as described in detail below. In brief, our hypothesis is that the SARS-CoV-2 must be proteolytically processed by a human protease known as TMPRSS2. Inhibition or blocking expression of TMPRSS2 inhibits SARS-CoV-2 infection. The expression level of the TMPRSS2 protease is regulated by androgen. Treatment with an antiandrogen such as bicalutamide downregulates expression of TMPRSS2. This downregulation should reduce proteolytic activation of SARS-CoV-2 and help to limit severity of infection and subsequent morbidity and mortality.

Recent experimental data has demonstrated that the human protease Transmembrane Serine Protease 2 (TMPRSS2) plays an important role in COVID-19 infection. Hoffman et al demonstrated that TMPRSS2 proteolytic activity is able to prime the spike protein (S protein) of SARS-CoV-2 (Hoffmann et al., 2020a). Proteolytic priming by TMPRSS2 allows for binding of the virus to the angiotensin-converting enzyme 2 (ACE2) as the entry receptor. TMPRSS2 is also capable of activating Influenza A and B, MERS and SARS-CoV (Böttcher et al., 2006; Matsuyama et al., 2010). Hoffman et al demonstrated that cells lacking TMPRSS2 expression were less susceptible to SARS-Co-V2 infection and inhibition of TMPRSS2 proteolytic function could block SARS-CoV-2 infection (Hoffmann et al., 2020a).

TMPRSS2 is highly expressed by human prostate tissue but is also expressed by many normal human epithelial cells including the colon, stomach and lung (Bertram et al., 2012; Lin et al., 1999; Lucas et al., 2008, 2014; Mikkonen et al., 2010). Previous studies demonstrated that TMPRSS2 is an androgen-regulated gene whose expression could be downregulated by androgen withdrawal and antiandrogens, **Figure 1A, B** (Bühler et al., 2010; Lin et al., 1999; Semaan et al., 2019).

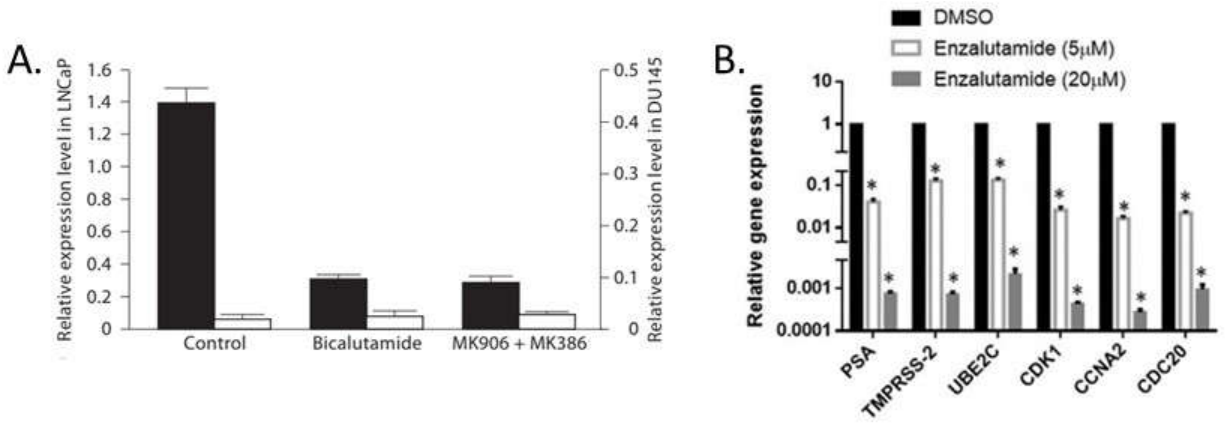


Figure 1. TMPRSS2 expression is downregulated by antiandrogens.
(A) Bicalutamide induces a 7-fold decrease in expression of TMPRSS2 in human AR-positive LNCaP prostate cancer cell line. (Bühler P, et al. Urol Int. 2010;84(2):203-11.)
(B) The antiandrogen enzalutamide induces marked down-regulation of androgen regulated genes PSA and TMPRSS2 in human AR-positive VCaP prostate cancer cell line. (Semaan L, et al. BMC Cancer. 2019 Oct 21;19(1):972.)

Mikkonen et al demonstrate the presence of androgen receptor expression in murine lung tissue from both male and female mice and in a human lung cancer cell line (Mikkonen et al., 2010). Androgen exposure in this lung cancer line cell line resulted in an ~ 3-fold increase in expression of TMPRSS2, **Figure 2A**. Bertram et al further demonstrated strong TMPRSS2 expression in both human lung epithelium and human sinus, **Figure 2B** (Bertram et al., 2012).

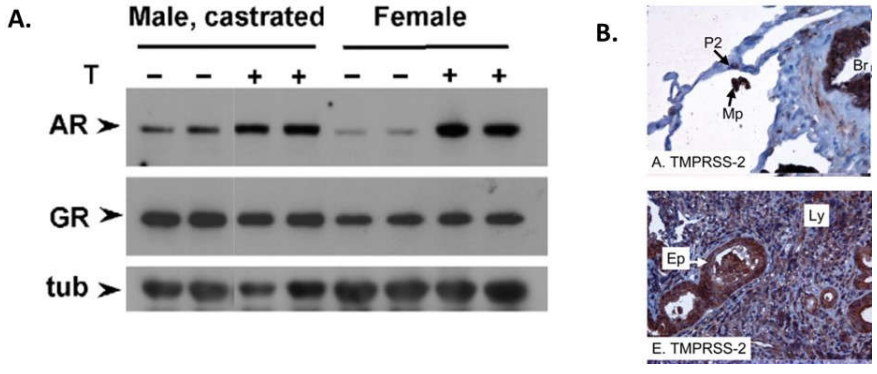


Figure 2. (A) Androgen receptor expresssion in murine lung from castrate male mice and female mice. AR expression is increased in both castrated male and female mice in response to androgen (From Mikkonen et al Mol Cell Endocrinol. 2010 Apr 12;317(1-2):14-24.); (B) TMPRSS2 is expressed in human lung and sinus (From Bertram et al. PLoS One. 2012;7(4):e35876

Anti-androgens, such as bicalutamide, effectively downregulate expression of the TMPRSS2 in the normal prostate and prostate cancer cells and other tissues. TMPRSS2 is also

downregulated in the prostate by estrogen receptor beta (ER- beta) stimulation by estrogens (Setlur et al., 2008; Tomlins et al., 2005). Bicalutamide is an oral non- steroidal antiandrogen that downregulates TMPRSS2. It is well tolerated, widely available, and inexpensive. It is currently FDA approved for the treatment of prostate cancer and has also been used in women for the treatment of hirsutism, polycystic ovarian disease, and breast cancer (Gucalp et al., 2013; Moretti et al., 2018).

Additionally, ACE2 receptor is located on the X-chromosome and also escapes X inactivation (Gheblawi Mahmoud et al., 2020). Previous research found that ACE2 is primarily expressed in the kidney where there is greater activity in the male kidney compared to females. (Liu et al., 2010) More recently, it has also been demonstrated that in the lung, where ACE 2 is also expressed albeit at lower levels, estradiol downregulates ACE2 expression as seen in **Figure 3**. (Stelzig et al., 2020)

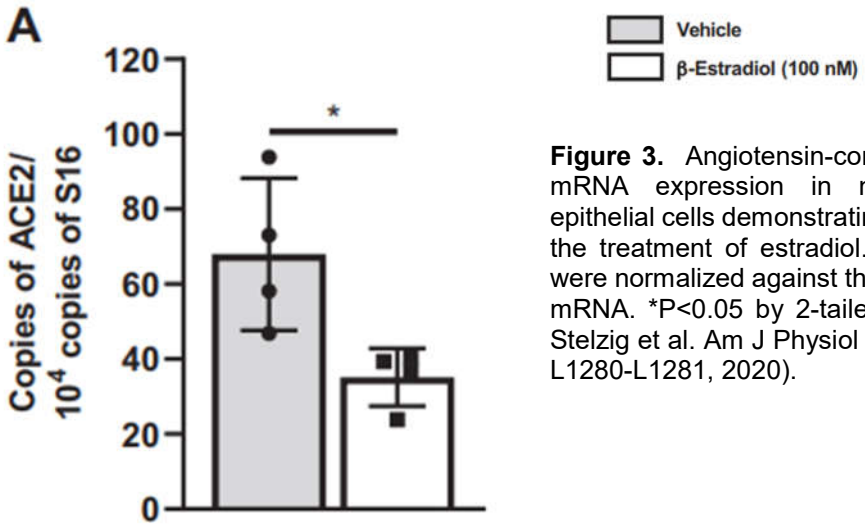


Figure 3. Angiotensin-converting enzyme 2 (ACE2) mRNA expression in normal human bronchial epithelial cells demonstrating reduced expression with the treatment of estradiol. The quantities of ACE2 were normalized against that of ribosomal protein S16 mRNA. *P<0.05 by 2-tailed Student's *t* test. (From Stelzig et al. Am J Physiol Lung Cell Mol Physiol 318: L1280-L1281, 2020).

Since AR, and ER are also expressed in lung tissues, we hypothesize that these receptors, through regulation of TMPRSS2 expression, may contribute to the higher morbidity and mortality among men with COVID-19. In prostate cancer patients, bicalutamide effectively downregulates expression of the androgen regulated serine protease Prostate-Specific Antigen (PSA). Decline in PSA following bicalutamide therapy is used as a biomarker of efficacy in men with prostate cancer.

A second important component is regulation of the host immune response to SARS-CoV-2 infection as this is likely to be a major contributor to COVID-19 disease manifestations (Chen et al., 2020). Progression of the disease to late stages including pneumonia and acute respiratory distress syndrome (PNA-ARDS) appears to exhibit characteristics similar to many forms of viral mediated PNA- ARDS, including unremitting lung inflammation and tissue injury that can be disproportionate to pathogen load at late stages. There is published literature showing regulation of Treg numbers and activity by estrogens and Estrogen Receptor (ER) (Tai et al., 2008), promoting activity to suppress inflammatory damage. In strong preliminary data from the labs of team members Drs. D'Alessio and Damico, these effects were mediated by ER-beta, and use of the estrogen Estradiol (E2) or selective ER-beta agonists led to

significant Treg amplification and pro-repair functions to strongly accelerate resolution of ARDS in a murine pneumonia model. Bicalutamide, is an anti-androgen that crosses the blood brain barrier inhibiting AR in the hypothalamus (unpublished data). This leads to a feedback release of LHRH that leads to increased levels of pituitary LH stimulating subsequent increased production of testosterone by the testes which is subsequently aromatized to estradiol. Androgen receptor signaling has known effects on many antiviral immune responses, including type 1 IFN activity, CD8+ T cell frequencies, subsets of CD4+ T cells, including Tregs, and humoral immunity. We hypothesize that these estrogenic effects in enhancing the immune response may also mediate some of the sex differences in COVID-19 PNA-ARDS and treatment with bicalutamide would improve outcomes.

Notably, we are including women. While men have a more severe course and higher mortality, women still are suffering and dying from SARS-CoV-2 infection. We do think that the proposed mechanism of benefit is applicable to both men and women for the following reasons:

(1) TMPRSS2 and ACE2, are expressed in the lung epithelial tissue of both men and women, albeit at varying levels. Asselta et al used genotype tissue expression (GTEx database (https://gtexportal.org/home/) and Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/geo/) and showed that TMPRSS2 expression is also present in women, albeit at lower levels in women compared to men (**Figure 4**).

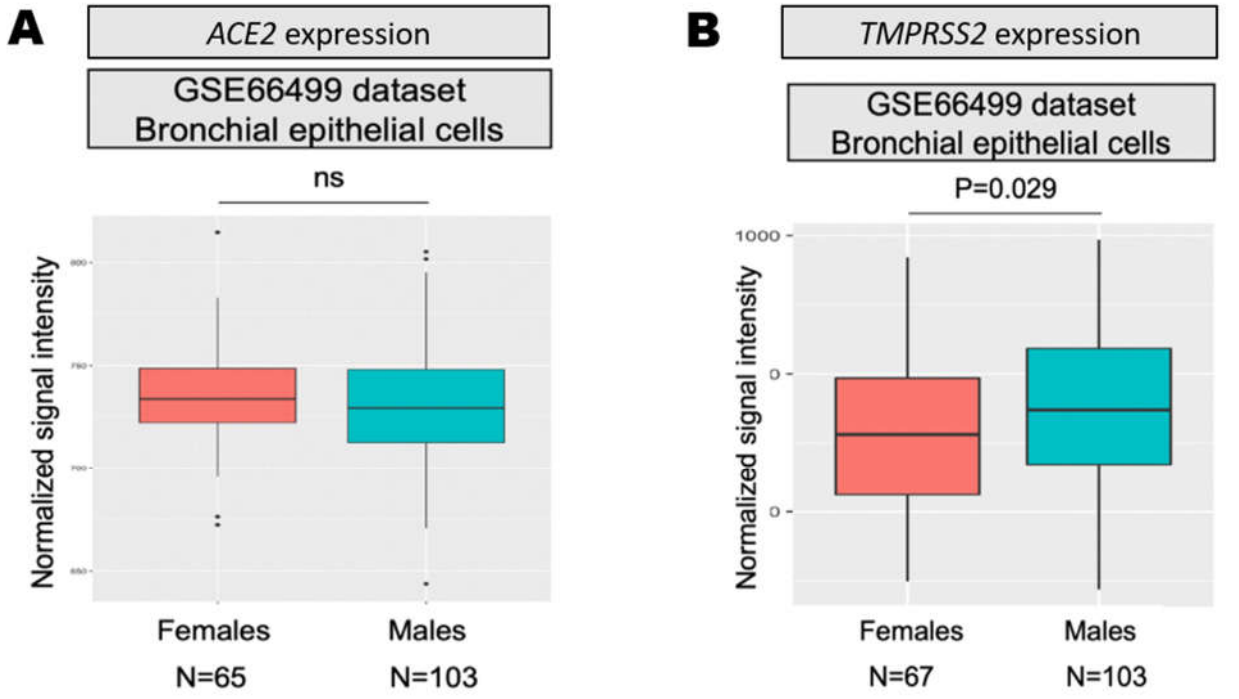


Figure 4. (A) ACE2 and (B) TMPRSS2 expression mRNA expression levels in human normal lung samples, stratified by sex (From Asselta, et al. *Aging*. 2020 Jun 5;12(11):10087-10098).

(2) The androgen receptor is also expressed in men and women at varying levels. Previous studies demonstrated that TMPRSS2 is an androgen-regulated gene whose expression could be downregulated by androgen withdrawal and antiandrogens (Bühler et al., 2010;

Lin et al., 1999; Semaan et al., 2019). Mikkonen et al demonstrate the presence of androgen receptor expression in murine lung tissue from both male and female mice and in a human lung cancer cell line (Mikkonen et al., 2010). Androgen exposure in this lung cancer line cell line resulted in an ~ 3-fold increase in expression of TMPRSS2, **Figure 5A**.

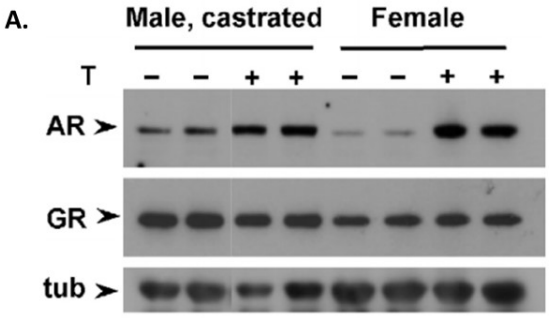


Figure 5. (A) Androgen receptor expresssion in murine lung from castrate male mice and female mice. AR expression is increased in both castrated male and female mice in response to androgen (From Mikkonen et al 2010)

(3) There is significant heterogeneity in levels of circulating androgens in women across age groups, albeit at lower levels than men. We hypothesize that the reason women do not have such severe disease is due to lower levels of circulating androgens compared to men (**Figure 6**). This subsequently affects TMPRSS2 levels and viral spread. However, women do have androgens, at variable levels, throughout the lifespan (Khosla et al., 1998) and therefore, would potentially also perceive benefit from treatment with an anti-androgen.

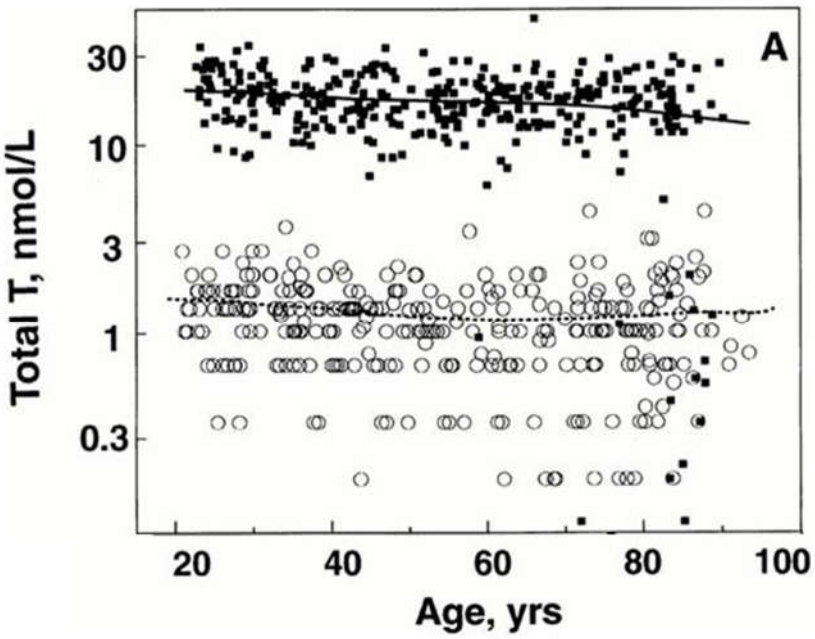


Figure 6. Testosterone levels in men (square) are higher than in women (circles), and present even in older women. (From Khosla, 1998).

(4) There is no justifiable reason to exclude them as bicalutamide has been used in women, at this dose, with no new safety signals. In terms of risk-benefit, bicalutamide has been given to women in clinical studies for treatment of hirsutism, particularly in the context of

polycystic ovarian syndrome, a dysmetabolic disorder that occurs in women due to excess androgen levels (Azziz et al., 2016). The major side effects noted were in the context of long term exposure, and risk to women should be greatly mitigated in this study due to the short course of exposure (7 days). Additionally it has been studied, at the dose of 150mg daily, for the treatment of androgen receptor (AR) positive triple negative breast cancer. In a phase II study by Gucalp at all, 426 patients were screened and 28 had AR+ disease and started treatment. There were no grade 4 of 5 events. There were 3 grade 3 liver related adverse events (AST elevation, hyperbilirubinemia, and alk phos elevation) and these all occurred in a single patient who known liver metastases and disease progression. Two patients had dose delays due to liver function test grade 2 abnormalities and these also were related to cancer progression. One patient had a dose reduction due to cerebrovascular ischemia that was thought to be related to hypertension and she continued on therapy (Gucalp et al., 2013). Thus, even in this sick patient population with metastatic breast cancer, bicalutamide, at this dose, did not demonstrate any unexpected or severe side effects in women.

2. Objectives

2.1. Primary objective

To determine if bicalutamide + camostat decreases the rate of hospitalization in outpatients diagnosed with COVID-19.

2.2. Secondary objectives

To determine if bicalutamide + camostat:

- Decrease the proportion of people with symptoms at day 7 and day 21
- Are safe to give in outpatients with COVID-19
- Decrease all-cause mortality at 60 days

2.3. Exploratory objectives

To determine if bicalutamide + camostat:

- Decrease the duration of hospitalization (defined as number of calendar days in the hospital)
- Decrease the % of patients needing upgrade to the intermediate care unit (IMC)
- Decrease the duration of IMC stay
- Decrease the % of patients needing upgrade to the intensive care unit (ICU)
- Decrease the duration of ICU stay
- Decrease the need for mechanical ventilation
- Decrease the duration of mechanical ventilation
- Alter development of SARS-CoV-2 antibodies
- Alter systemic cytokine profiles
- Alter hormone levels

2.4. Primary endpoint

Percentage of people who are hospitalized or die by day 28.

2.5. Secondary endpoints

- Proportion of people with symptoms at day 7 and day 21

- Proportion of drug-related AEs and SAEs
- All-cause mortality at day 60

2.6. Exploratory endpoints

Attenuation in disease course/inflammatory response –*resources permitting*

- Change from baseline in white blood cells, platelets, D-dimer, AST, ALT, CK, CRP, ESR, ferritin
- Change from baseline in hormones and hormone regulated gene expression
- Immunophenotyping of PBMCs with fluorescence-activated cell sorting (FACS): to understand the immune response and to determine the source of critical cytokines (resources permitting)
- SARS-CoV-2 antibody analysis, including IgM to IgG transition and virus-neutralizing antibodies

Clinical exploratory endpoints

- Duration of hospitalization (defined as number of calendar days in the hospital)
- % of patients needing upgrade to the intermediate care unit (IMC)
- Duration of IMC stay
- % of patients needing upgrade to the intensive care unit (ICU)
- Duration of ICU stay
- % of patients with need for mechanical ventilation
- Duration of mechanical ventilation

3. Patient Selection

A total of 40 patients will be recruited.

3.1. Inclusion Criteria

1. ≥ 60 years of age
2. COVID-19 infection, confirmed by polymerase chain reaction (PCR) test <=5 days from enrollment done in the ambulatory setting
3. Able to provide informed consent
4. Symptom related to COVID-19. This includes: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea or other symptom recognized by the Centers for Disease Control to be a symptom of COVID-19.

3.2. Exclusion Criteria

1. Patients who undergo asymptomatic screening test that is positive and remain asymptomatic during the eligible time window
2. Patients who have had one or more positive tests more than 5 days prior to enrollment but within 60 days of enrollment (ex. If a patient has a positive test 10 days prior to enrollment and then a second positive test the day referred for enrollment, that patient would be excluded. If a patient had a positive test 5 months ago, and then another positive test the day he/she was referred for enrollment, that patient would be eligible.)
3. Unable to take oral medication

4. Male patients with female partners of reproductive potential who are unable to maintain effective contraception during the recommended time period (during treatment and for 130 days after the final dose)
5. Symptoms requiring hospitalization or immediate referral to hospital
6. Taking bicalutamide, any systemic hormonal therapy, or camostat within one month of study entry
7. Known hypersensitivity to bicalutamide, or camostat, or its components.
8. On coumadin anticoagulation (because of drug-drug interaction with bicalutamide)
9. Self-reported past medical history of chronic liver disease or cirrhosis
10. Self-reported myocardial infarction within 6 months or past medical history of congestive heart failure with known ejection fraction < 40%
11. Taking any other investigational treatment for COVID-19 or COVID-19 prophylaxis (COVID-19 vaccines and treatments allowed under FDA Emergency Use Authorization are allowed.)

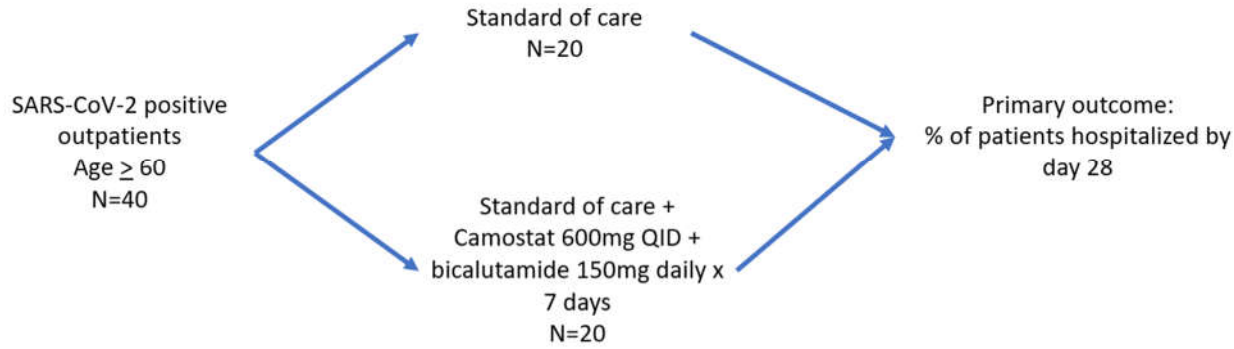
3.3. Inclusion of Women and Minorities

Women and people from all ethnic and race groups are eligible for this study.

4. Treatment Plan

4.1. Study design

This will be a randomized, open-label study to determine if camostat+ bicalutamide decreases the proportion of people with COVID-19 who require hospitalization, compared to historical controls. Patients with symptomatic COVID-19, diagnosed as outpatients, will be randomized 1:1 stratified by gender and receipt of SOC drugs/vaccine, to treatment with standard of care alone or with camostat+bicalutamide . The schema is shown below:



4.2. Study treatments

4.2.1. Camostat and Bicalutamide

Patients randomized to camostat and bicalutamide arm will receive 600mg of camostat mesilate (six 100mg tablets), four times a day on an empty stomach [one hour before a meal (e.g. 6:00, 11:00, 16:00, and 21:00)] and 150mg of bicalutamide daily for a total of 7 days. Bicalutamide will be given as three 50mg tablets.

Rationale for dose: Bicalutamide is well tolerated at 50mg and 150mg. It is frequently given at a dose of 150mg when used as a single agent, rather than the 50mg dose which is usually given in combination with medical or surgical castration. Bicalutamide 150mg

daily is approved for use in the European Union for the treatment of prostate cancer (European Medicines Agency, 2018). Bicalutamide has been extensively tested at a higher dose of 150 mg per day as monotherapy for prostate cancer, although it is not FDA-approved at this dose. Pharmacokinetic studies demonstrate an approximate doubling of the Cmax, Css and AUC and when bicalutamide is administered at this 3-fold higher dose.(Cockshott, 2004) Thus, we are using the higher dose bicalutamide of 150 mg/day compared to lower dose of 50 mg/day in order to achieve maximum androgen receptor blockade over the short 7-day exposure period proposed in this trial

Should any patient enrolled on the study miss a scheduled dose for whatever reason, the patient will be allowed to take the scheduled dose up to a maximum of 12 hours after that scheduled dose time. If greater than 12 hours, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. Patients should also be advised to avoid conceiving for 3 months after the last dose of bicalutamide.

Rationale for duration of bicalutamide and camostat:

Both drugs are generally used for long periods of time, with bicalutamide safely given for years at a time. Trough concentrations of 150 mg/day bicalutamide at 7 days exceed the steady state trough levels of 50 mg/day bicalutamide after 28 days. Additionally, an increase in estradiol has been demonstrated at one week of starting bicalutamide at this dose. (Verhelst et al., 1994)

Additionally, respiratory infections are commonly treated for up to 7 days. For example, the Infectious Disease Society of America (IDSA) guidelines for the recommendation of treatment of influenza is for 5 days of anti-viral therapy in outpatients, with consideration of longer duration for certain populations. Given this trial is in patients at least 60 years old and the severity of the disease, we believe a longer duration is warranted. This, in combination with the data presented above, is why we believe 7 days is safe, likely to be effective, and in line with other treatment paradigms.

4.3. Supportive care guidelines and general concomitant medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided that their use is documented in the medical records. The administration of any other therapies intended to treat the primary condition are permitted if considered the standard of care. The use of other concurrent investigational drugs is NOT allowed during the screening and treatment period. Patients should receive appropriate supportive care measures as deemed necessary by the Investigator and treating physicians.

4.4. Drug compliance documentation

Compliance will be recorded on a Diary of Treatment.

4.5. Prohibited and restricted therapies

- Any COVID-19 investigational agent (e.g. hydroxychloroqine or chloroquine) during the screening and treatment period, or within 30 days of enrollment.
- Coumadin (warfarin) anticoagulation during treatment period

4.6. Drug dispensing

Study drug can be picked up in person or shipped to the patient directly. If study drug is shipped, the temperature will be monitored during shipment. Study staff will call the patient to ensure that shipment was received in good condition at the patient's home, and instruct patient to keep and return all empty, partially empty, or full bottles/blisters to the site at next visit for drug reconciliation. This call, including verbal confirmation of receipt by the patient, will be properly documented in the medical record. If COVID-19 precautions prevent the return of used/unused study drug supplies to the site, then study staff will review the remaining pills during a telemedicine visit with a photo or video documentation of drug destruction (using a drug disposal pouch) that can be sent to the IND Sponsor (or designee). Undelivered supplies should be returned to the clinical site.

5. Dosing Delays/Dose Modifications

If patients are unable to tolerate 600mg of camostat four times a day, the dose will be reduced to 300mg four times a day. If patients are unable to tolerate 300mg four times a day, treatment will decrease to 200mg three times a day (approved dose in Japan). If patients are unable to tolerate that dose, treatment will be stopped.

If patients are unable to tolerate 150mg of bicalutamide, the daily dose will be reduced to 100mg. If patients are unable to tolerate 100mg, the dose should be reduced to 50mg. If 50mg is unable to be tolerated, treatment should stop.

6. Study Activities

6.1. Screening period

All patients must sign a written informed consent form before any study specific procedures are performed. If the patient meets eligibility and screening requirements, he/she will be randomized to one of two arms. All required treatment study procedures and assessments must be initiated within 72 hours of the baseline screening evaluation.

6.2. Randomization

Once eligibility is confirmed, patients will be randomized to a treatment group in a 1:1 fashion and stratified by gender and by receipt of SOC drugs/vaccine. All patients must commence treatment within 72 hours of randomization.

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should call/email the coordinating center at crocc@jhmi.edu for registration. The Registration Form and Eligibility Worksheet will be supplied to each participating site.

Subjects who sign a consent form, but do not initiate protocol treatment for any reason (e.g., subjects who are screen failures), will be replaced and will not count towards our accrual goal. The Coordinating Center should be notified as soon as possible.

Registration Process

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and emailed to crocc@jhmi.edu and the lead CROCC Study Coordinator:

•Registration Form

•Signed patient consent form

•Eligibility Screening Checklist

•Copies of source documents, as applicable.

Study treatment cannot begin until the patient is registered.

The Research Nurse or Study Coordinator at the participating site will then e-mail (crocc@jhmi.edu and the lead CROCC Study Coordinator) the Coordinating Center to verify eligibility. To complete the registration process, the Coordinating Center will:

•Assign a patient study number

•Register and randomize the patient on the study

•Email the patient study number to the participating site

6.3. Stratification

In this study, patients will be stratified by gender and receipt of SOC drugs/vaccine.

6.4. Baseline studies

1. COVID-19 symptoms
2. COVID-19 NP swab with RT-PCR testing

Optional (pending resource availability):

1. Comprehensive metabolic panel (Na, K, Cl, BUN, Cr, Ca, Tot Protein, Alb, bilirubin, AST, ALT, Alk phos, HCO_3)
2. Complete blood count w/differential
3. Clinical severity markers: ESR, CRP, D-dimer, ferritin, CK
4. Serum ultrasensitive PSA, testosterone (free and total), estradiol, luteinizing hormone, follicle stimulating hormone
5. Research NP swab for quantitative viral load
6. Blood and sputum sample for quantitative viral load (if resources permit) (~20cc of blood)
7. Research blood draw for banking (to be grouped with clinical blood draws) (~10cc of blood)

6.5. Treatment period

Patients will be followed according to the study calendar (Section 10). Patients in all arms will have telemedicine or audio telephone call at day 3, 7, 21, and day 60 to assess toxicity and recovery. If patients are admitted to the hospital during follow up, we will get information from the medical records.

Patients will be instructed to monitor for emergency warning signs. This includes, but is not limited to: trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, bluish lips or face. If any of these occur, patients will be instructed to call 911 or go to her/his local emergency facility for further evaluation.

6.6. End of initial treatment

After 7 days of oral therapy, treatment will stop and patients will be followed as per section 10 (study calendar).

6.7. Assessing the primary outcome

Patients will be followed for admission to the hospital. Electronic medical records, including EPIC at JHH and CRISP (throughout Maryland and surrounding states) will be queried for hospital admission. If patients report a hospital admission outside of these systems, records will be collected from the corresponding hospital.

6.8. End of study

Day 60

6.9. Early discontinuation

The reason for study removal and the date the subject was removed will be documented in the CRF. A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow up portion of the trial for any of the following reasons:

- The subject or legal representative (such as legal guardian) withdraws consent.
- Intercurrent illness that prevents further administration of treatment,
- Patient is hospitalization due to COVID-19,
- Unacceptable toxicity, as listed in section 6.10,
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up,
- Patient becomes pregnant

Patients who discontinue treatment will remain on study unless one of the above reasons for discontinuation from the study are met. The patients who discontinue treatment will continue to be followed as specified in section 10 (study calendar), per study protocol.

6.10. Definition of unacceptable toxicities

Unacceptable toxicities are defined as:

- Any treatment-related ≥ grade 3 AEs possibly related to the agents
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued bicalutamide or camostat dosing.

6.11. Definition of an overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

All occurrences of overdose must be reported as SAEs (see section 7.1.2 and 7.5).

Bicalutamide

A single dose of bicalutamide that results in symptoms of an overdose considered to be life threatening has not been established.

In the management of an overdose with bicalutamide, vomiting may be induced if the patient is alert. Dialysis is not likely to be helpful since bicalutamide is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

Camostat

There is no known information on overdose of camostat.

6.12. Survival

Patient records will be monitored for 60 days for vital status. For patients who have died, date of death will be collected, and overall survival duration will be calculated from randomization to death.

7. Adverse Events

7.1. Definitions

Toxicities will be graded using the NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
In those cases where the NCI criteria do not apply, intensity will be defined as:

- Mild: awareness of symptom or sign, but easily tolerated
- Moderate: discomfort is enough to cause interference with normal activities
- Severe: inability to perform normal daily activities
- Life threatening: immediate risk of death from the reaction as it occurred

7.1.1. Adverse Event

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline

will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (induce clinical signs or symptoms or require corrective therapy), meets the definition of an SAE, or requires the participant to have study drug discontinued or interrupted. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

7.1.2. Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a new cancer
- Is associated with an overdose (as defined in section 5.11)
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events not considered to be SAEs are hospitalizations for:

- Admission for progression of COVID-19-related symptoms
- A visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

7.2. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

7.3. Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered “unexpected”. An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered “expected”, only if it is included in the IB document as a risk.

7.4. Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor or designee will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB or package insert), and related to camostat or bicalutamide. This notification will be in the form of an expedited safety report (ESR) that is to be emailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The

investigator should also comply with the IRB procedures for reporting any other safety information.

7.5. Reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected and reported from the first dose of study drug, throughout the study, and will only be followed for 28 days unless related to the investigational agent.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

7.5.1. SAE Reporting

All SAEs (including deaths) occurring from the first dose of the study drug through 28 days after the last dose of study drug will be collected and recorded on the Adverse Event Case Report Form (CRF).

All SAEs should be reported to the IND Sponsor (DENMESA@jhmi.edu) and Ono Pharmaceutical Co., Ltd (pmsmailbox@ono.co.jp) within 24 hours of becoming aware of the event occurrence using the **SAE Reporting Form**. **Section 12.3** outlines reporting requirements for the DSMB.

SAEs will be reported to the Johns Hopkins Medicine IRB per institutional guidelines.

Adverse events that are serious, unexpected, and assessed by the investigator to be related to the study drug will be reported within 24 hours of becoming aware of the event occurrence to the post-marketing departments of the drug manufacturer.

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

7.5.1.1. Expedited IND Safety Reports to the FDA

All reporting to the FDA will be completed by the IND Sponsor.

7 Calendar-Day Telephone or Fax Report:

The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be submitted to the FDA within 7 calendar days of

first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:

The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

IND Annual Reports:

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

8. Pharmaceutical Information

The IND Sponsor or the IND Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

The IND Sponsor or the IND Sponsor's representative is responsible for keeping accurate records of the clinical supplies, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the IND Sponsor or the IND Sponsor's representative responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.1. Camostat

FOIPAN® tablets 100mg contain 100mg of camostat mesilate. Inactive ingredients include Hydroxypropylcellulose, Carmellose calcium, Magnesium stearate, Polyoxyethylene (105) polyoxypropylene (5) glycol, Lactose hydrate.

TOXICOLOGY
Contraindications: Patients with a history of hypersensitivity to any of the ingredient of this product.

Precautions: Careful Administration (FOIPAN® should be administered with care in the following patients)
Patient with hypersensitivity [In case patients have hypersensitivity, adverse reactions may be induced.]
Important Precautions:
(1) FOIPAN® should not be administered in patients with severe chronic pancreatitis requiring suction of gastric juice, or dietary restrictions such as fasting and abstention from drinking.
(2) This product should not be used for the treatment of postoperative reflux esophagitis due to reflux of gastric juice since the efficacy of this product cannot be expected.
(3) If improvement of symptoms of postoperative reflux esophagitis is not observed, then the therapy with this product should not be continued aimlessly for a long-term period.
Adverse reactions:
<In clinical studies of Remission of acute symptoms of chronic pancreatitis>
83 adverse reactions to FOIPAN®, including abnormal laboratory test values, were observed in 69 (1.8%) of 3,806 patients evaluated in the investigation conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were rash in 15 incidences (0.4%), pruritus in 9 incidences (0.2%), nausea in 10 incidences (0.3%), abdominal discomfort in 7 incidences (0.2%), abdominal fullness in 6 incidences (0.2%), etc. (At the end of the reexamination period)

<In clinical studies of Postoperative reflux esophagitis>
75 adverse reactions to FOIPAN®, including abnormal laboratory test values, were observed in 57 (1.3%) of 4,224 patients evaluated in the investigation conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were hepatic function abnormalities such as increased AST (GOT) · ALT (GPT) in 12 incidences (0.3%), diarrhea in 8 incidences (0.2%), nausea in 5 incidences (0.1%), etc. (At the end of the reexamination period)

(1) Clinically significant adverse reactions
1) Shock or anaphylactoid symptoms: Shock or anaphylactoid symptoms (both incidences unknown*) may occur. Patients should be carefully monitored. If any symptoms such as decreased blood pressure, dyspnea and pruritus are observed, administration should be discontinued and appropriate measures be taken.
2) Thrombocytopenia: Thrombocytopenia (incidence unknown*) may occur rarely. If such symptoms are observed, the dose should be reduced or administration should be discontinued.
3) Hepatic function disorder or jaundice: Hepatic function disorder accompanied by remarkable increase of AST(GOT), ALT(GPT), γ-GTP, Al-P, or jaundice (both incidences unknown*) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate therapeutic measures such as discontinuing the administration should be taken.
4) Hyperkalaemia: Severe hyperkalaemia (incidence unknown*) may occur. Patients should be carefully monitored by conducting serum electrolyte tests. If any abnormalities are observed, administration should be discontinued and appropriate measures be taken.

(2) Other adverse reactions

	0.1- 0.5%	<0.1%	Incidence unknown*
Hematologic		Leukopenia, erythrocytopenia	Eosinophilia
Hypersensitivity	Rash, pruritus, etc		
Gastrointestinal	Nausea, abdominal discomfort, abdominal fullness,	Anorexia, vomiting, dry mouth, heartburn, abdominal pain,	

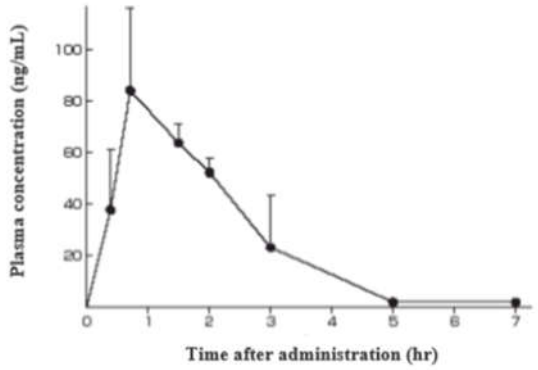
	diarrhea	constipation	
Hepatic	Increased AST (GOT)·ALT(GPT) , etc		
Renal		Increased BUN, increased creatinine	
Other		Edema, hypoglycemia	

*reactions classified as “incidence unknown” are the ones collected from spontaneous reports

PHARMACOLOGY

1. Blood concentration

(1) Healthy adults When a single dose of camostat mesilate at 200 mg was orally administered to 5 healthy adults in the fasted state, the plasma concentration of its active metabolite, 4-(4-guanidinobenzoyloxy) phenylacetate, reached a maximum of 87.1 ng/mL 40 minutes after administration, with a half-life of about 100 minutes (Hiraku S. et al.: Iyakuhin Kenkyu, 13: 756, 1982.).



Plasma concentration of the active metabolite, 4-(4-guani dinobenzoyloxy) phenylacetate

T_{max} (min)	C_{max} (ng/mL)	AUC (ngb min/mL)	$T_{1/2}$ (min)
40	87.1 ± 29.5	10,400 ± 1,400	100 ± 40

Data except T_{max} are shown as mean ± SD.
T_{max} is shown as median

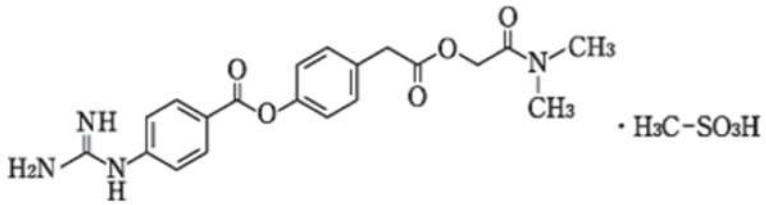
(2) Patients with gastrectomy: When a single dose of camostat mesilate at 100 mg was orally administered to 4 patients with total gastrectomy or subtotal gastrectomy in the fasted state, the maximum plasma concentration was 30 ng/mL, changing at a similar level to healthy volunteers. (Yamamoto T. et al.: Changes in plasma concentration of camostat mesilate in patients with gastrectomy. Internal data of Ono Pharmaceutical Co., Ltd)

2. Metabolism: Carboxylate ester moiety of camostat mesilate is hydrolyzed to an active metabolite 4-(4-guanidinobenzoyloxy) phenylacetate, which is further hydrolyzed to 4-guanidinobenzoic acid. (Ohki S. et al.: Gendai Iryo, 12 (Extra issue): 71, 1980.)) Camostat mesilate is mainly hydrolyzed by carboxyesterase and 4-(4-guanidinobenzoyloxy) phenylacetate by arylesterase (in vitro). (Nemoto H. et al.: The enzymes involved in the metabolism of camostat mesilate. Internal data of Ono Pharmaceutical Co., Ltd.) Camostat mesilate and its metabolite 4-(4-guanidinobenzoyloxy) phenylacetate did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (in vitro). (Matsunaga N. et al.: The effect of camostat mesilate on CYP 450 isozymes. Internal data of Ono Pharmaceutical Co., Ltd)

3. Excretion: When a single dose of camostat mesilate at 200 mg was orally administered to 5 healthy adults in the fasted state, urinary metabolites were accounted for mostly by 4-guanidinobenzoic acid and for only a small proportion, by 4-(4-guanidinobenzoyloxy) phenylacetate. The rates of urinary excretion at 5 - 6 hours after administration were 20% and 0.8%, respectively, and little was further recovered in urine during later periods. (Hiraku S. et al.: Iyakuhin Kenkyu, 13: 756, 1982)

4. Protein binding rate: The protein-binding rate to human serum was 25.8 – 28.2% (in vitro).

PHYSICOCHEMISTRY
Nonproprietary name: Camostat mesilate
Chemical name: Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy) phenylacetate monomethanesulfonate
Molecular formula: $C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$
Molecular weight: 494.52
Structural formula:



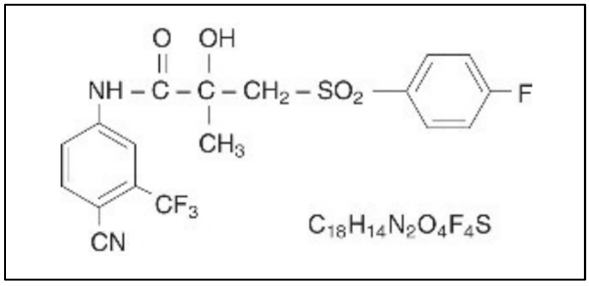
Description: Camostat mesilate occurs as white crystals or a crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (95) and practically insoluble in diethyl ether.
Melting point: 194 - 198°C

PRECAUTIONS FOR HANDLING Dispensing FOIPAN® with olmesartan medoxomil as a “one-dose pack” should be avoided. (In case of storing the one-dose pack containing FOIPAN® and olmesartan medoxomil under conditions of high temperature and high humidity, the discoloration of FOIPAN® tablets may occur.)

PACKAGING FOIPAN® Tablets 100 mg: Boxes of 100, 200, 420, 500, 1,000 and 1,050 tablets in press-through packages and bottles of 500 and 1,000 tablets

8.2. Bicalutamide

Bicalutamide tablets contain 150 mg of bicalutamide, a non-steroidal androgen receptor inhibitor with no other known endocrine activity. The chemical name is propanamide, N [4 cyano-3- (trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+-). The structural and empirical formulas are:



Bicalutamide has a molecular weight of 430.37. The pKa is approximately 12. Bicalutamide is a fine white to off-white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran. CASODEX is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-

enantiomer is essentially inactive. The inactive ingredients of CASODEX tablets are lactose, magnesium stearate, hypromellose, polyethylene glycol, polyvidone, sodium starch glycollate, and titanium dioxide.

Bicalutamide is a non-steroidal androgen receptor inhibitor. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. In clinical trials with bicalutamide as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

TOXICOLOGY

Contraindications: Hypersensitivity CASODEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components. Hypersensitivity reactions including angioneurotic edema and urticaria have been reported. CASODEX can cause fetal harm when administered to a pregnant woman

Warnings and precautions: Hepatitis Cases of death or hospitalization due to severe liver injury (hepatic failure) have been reported postmarketing in association with the use of CASODEX. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of CASODEX patients in controlled clinical trials. Serum transaminase levels should be measured prior to starting treatment with CASODEX, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, CASODEX should be immediately discontinued with close follow-up of liver function.

Hemorrhage with Concomitant Use of Coumarin Anticoagulant In the postmarketing setting, there have been reports of excessive prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) days to weeks after the introduction of CASODEX in patients who were previously stable on coumarin anticoagulants. Some patients had serious bleeding including intracranial, retroperitoneal, and gastrointestinal requiring blood transfusion and/or administration of vitamin K. Closely monitor the PT/INR, and adjust the anticoagulant dose as needed

In clinical trials with CASODEX 150 mg as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving CASODEX in combination with LHRH agonists.

Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response.

Adverse reactions:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. 6.1. Clinical Trials Experience In patients with advanced prostate cancer treated with CASODEX in combination with an LHRH analog, the most frequent adverse reaction was hot flashes (53%). In the multi-

center, double-blind, controlled clinical trial comparing CASODEX 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analog, the following adverse reactions with an incidence of 5% or greater, regardless of causality, have been reported.

Table 1. Incidence of Adverse Reactions (≥ 5% in Either Treatment Group) Regardless of Causality

Body System Adverse Reaction	Treatment Group Number of Patients (%)	
	CASODEX Plus LHRH Analog (n=401)	Flutamide Plus LHRH Analog (n=407)
Body as a Whole		
Pain (General)	142 (35)	127 (31)
Back Pain	102 (25)	105 (26)
Asthenia	89 (22)	87 (21)
Pelvic Pain	85 (21)	70 (17)
Infection	71 (18)	57 (14)
Abdominal Pain	46 (11)	46 (11)
Chest Pain	34 (8)	34 (8)
Headache	29 (7)	27 (7)
Flu Syndrome	28 (7)	30 (7)
Cardiovascular		
Hot Flashes	211 (53)	217 (53)
Hypertension	34 (8)	29 (7)
Digestive		
Constipation	87 (22)	69 (17)
Nausea	62 (15)	58 (14)
Diarrhea	49 (12)	107 (26)
Increased Liver Enzyme Test	30 (7)	46 (11)
Dyspepsia	30 (7)	23 (6)
Flatulence	26 (6)	22 (5)
Anorexia	25 (6)	29 (7)
Vomiting	24 (6)	32 (8)

Body System Adverse Reaction	Treatment Group Number of Patients (%)	
	CASODEX Plus LHRH Analog (n=401)	Flutamide Plus LHRH Analog (n=407)
Hemic and Lymphatic		
Anemia	45 (11)	53 (13)
Metabolic and Nutritional		
Peripheral Edema	53 (13)	42 (10)
Weight Loss	30 (7)	39 (10)
Hyperglycemia	26 (6)	27 (7)
Alkaline Phosphatase Increased	22 (5)	24 (6)
Weight Gain	22 (5)	18 (4)
Musculoskeletal		
Bone Pain	37 (9)	43 (11)
Myasthenia	27 (7)	19 (5)
Arthritis	21 (5)	29 (7)
Pathological Fracture	17 (4)	32 (8)
Nervous System		
Dizziness	41 (10)	35 (9)
Paresthesia	31 (8)	40 (10)
Insomnia	27 (7)	39 (10)
Anxiety	20 (5)	9 (2)
Depression	16 (4)	33 (8)
Respiratory System		
Dyspnea	51 (13)	32 (8)
Cough Increased	33 (8)	24 (6)
Pharyngitis	32 (8)	23 (6)
Bronchitis	24 (6)	22 (3)
Pneumonia	18 (4)	19 (5)
Rhinitis	15 (4)	22 (5)
Skin and Appendages		
Rash	35 (9)	30 (7)
Sweating	25 (6)	20 (5)
Urogenital		
Nocturia	49 (12)	55 (14)
Hematuria	48 (12)	26 (6)
Urinary Tract Infection	35 (9)	36 (9)
Gynecomastia	36 (9)	30 (7)
Impotence	27 (7)	35 (9)
Breast Pain	23 (6)	15 (4)
Urinary Frequency	23 (6)	29 (7)
Urinary Retention	20 (5)	14 (3)
Urinary Impaired	19 (5)	15 (4)
Urinary Incontinence	15 (4)	32 (8)

Other adverse reactions (greater than or equal to 2%, but less than 5%) reported in the CASODEX-LHRH analog treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole: Neoplasm; Neck Pain; Fever; Chills; Sepsis; Hernia; Cyst Cardiovascular: Angina Pectoris; Congestive Heart Failure; Myocardial Infarct; Heart Arrest; Coronary Artery Disorder; Syncope Digestive: Melena; Rectal Hemorrhage; Dry Mouth; Dysphagia; Gastrointestinal Disorder; Periodontal Abscess; Gastrointestinal Carcinoma Metabolic and Nutritional: Edema; BUN Increased; Creatinine Increased; Dehydration; Gout; Hypercholesteremia Musculoskeletal: Myalgia; Leg Cramps Nervous: Hypertonia; Confusion; Somnolence; Libido Decreased; Neuropathy; Nervousness Respiratory: Lung Disorder; Asthma; Epistaxis; Sinusitis Skin and Appendages: Dry Skin; Alopecia; Pruritus; Herpes Zoster; Skin Carcinoma; Skin Disorder Special Senses: Cataract Specified Urogenital: Dysuria; Urinary Urgency; Hydronephrosis; Urinary Tract Disorder Abnormal Laboratory Test Values: Laboratory abnormalities including: elevated AST, ALT, bilirubin, BUN, and

creatinine; and decreased hemoglobin and white cell count, have been reported in both CASODEX-LHRH analog treated and flutamide- LHRH analog treated patients.
The following adverse reactions have been identified during post-approval use of bicalutamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Respiratory disorders: Interstitial lung disease (some fatal) including interstitial pneumonitis and pulmonary fibrosis, most often at doses greater than 50 mg. Hemorrhage: Increased PT/INR due to interaction between coumadin anticoagulants and BICALUTAMIDE. Serious bleeding reported. Skin and subcutaneous tissue disorders: Photosensitivity

PHARMACOLOGY
Pharmacokinetics: Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.
Bicalutamide is highly protein-bound (96%). Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.
Drug interactions: Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogs (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes. In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4 with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Clinical studies have shown that with co-administration of bicalutamide, mean midazolam (a CYP 3A4 substrate) levels may be increased 1.5-fold (for Cmax) and 1.9-fold (for AUC). Hence, caution should be exercised when bicalutamide is co-administered with CYP 3A4 substrates. In vitro protein-binding studies have shown that bicalutamide can displace coumadin anticoagulants from binding sites. PT/INR should be closely monitored in patients concomitantly receiving coumadin anticoagulants and bicalutamide. Adjustment of the anticoagulant dose may be necessary
Females and Males of Reproductive Potential: Antiandrogen therapy may cause morphological changes in spermatozoa. Based on findings in animal reproduction studies and its mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 130 days after the final dose of bicalutamide. Based on animal studies, bicalutamide can lead to inhibition of spermatogenesis and may impair fertility in males of reproductive potential. The long-term effects of bicalutamide on male fertility have not been studied.
Geriatric Use: In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.
Hepatic Impairment: Bicalutamide should be used with caution in patients with moderate-to severe hepatic impairment. Bicalutamide is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of bicalutamide may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for hepatic-impaired patients on long-term therapy. No clinically significant

difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).
Renal Impairment: Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.
Formulation: Bicalutamide is prepared as round, film-coated green or white tablets containing standard excipients and 50 mg of the drug.
Storage and stability: All packages of bicalutamide should be stored securely in a dry place at room temperature.
Route of Administration: Bicalutamide is to be administered in tablet form as a once-daily oral dose. Patients should be instructed to take one 150mg pill once daily.
Supplier: Bicalutamide is commercially available

9. Correlative Studies

Correlative studies obtained will depend on available of Personal protective equipment (PPE) available for research staff and laboratory supplies available for research. Testing will be done according to the study calendar (section 10).

1) Naso/pharyngeal swabs and sputum/blood will be collected, pending available resources. Both investigational drugs are anticipated to disrupt viral replication, leading to a decrease in viral load with a faster time to a negative test/viral clearance. To assess this we will look at viral kinetics with sampling per study calendar (section 10) (nasopharyngeal, sputum, blood).
   a. Viral load (quantitative)
   b. Viral clearance

2) Peripheral Blood (~10cc): Serum and viably frozen PBMC fractions will be prepared from blood draws. We will evaluate:
   a. Serum hormone determination of estradiol, testosterone (free and total), luteinizing hormone and follicle stimulating hormone. We hypothesize that bicalutamide administration will elevate estrogen levels within days of therapy initiation, which can engage pro-repair function in Tregs and other immune cell populations. Although there is robust data on estrogen elevation in patients treated with bicalutamide for prostate cancer, there is no data examining this in an acute timeframe.
   b. Serum antibody titers (and follow-up periods, if available)
   c. Serum measurement of cytokines (Mesoscale MSD)
   d. When sufficient sample available, MANAFEST assay for viral reactive T cell receptors and immunophenotyping
   e. When sufficient sample available, single cell RNA-seq of PBMC
   f. Additional aliquots of serum and PBMCs will be banked

10. Study Calendar

	Day of study									
	Baseline/ screening	Treatment							Follow up (± 3 days)	
	-3 to 0	1	2	3	4	5	6	7[&]	21	60
Eligibility	X									
Consent	X									
Randomization and drug dispensing*	X									
COVID-19 symptoms	X^			X				X	X	X
Follow-up visit (can be in person, via telephone or via telemedicine)**				X				X	X	X
Review of medical record for hospitalization, death, etc[a]		X								
Both arms standard of care		X	X	X	X	X	X	X		
Experimental arm: Bicalutamide + camostat Treatment		X	X	X	X	X	X	X		
Adverse events, con meds (including OTC medications), new infections***				X				X	X	X
COVID-19 nasopharyngeal swab^^	X							X	X	
Clinical and study blood collection (CMP[b], CBC and differential, coagulation, d-dimer, CK, CRP, ESR, ferritin) ^^	X							X	X	
Ultrasensitive PSA + sex hormones[c]^^	X							X	X	
COVID-19 RNA testing (quantitative and qualitative) from blood, oral samples for research)^^	X							X	X	
Additional research blood draw (1 tube)^^	X							X	X	
SARS-CoV-2 antibody analysis^^	X							X	X	

*Study drug may be shipped to the patient. See section 4.6 for information relevant to drug dispensing. Review of remaining pills and Study Drug Patient Diary may be conducted during a telemedicine visit. Copies of the Study Drug Patient Diary may be submitted to study staff by phone, email, fax, or mychart

**If patients are admitted, we will get information from the medical record.

***Any new infection that occurs on study will be recorded. The site of infection and the source of culture (ie BAL, tracheal aspirate, sputum, blood, urine, etc.) will be recorded as well.

[a]The following will be recorded daily (as available) from hospital records: symptoms (see Appendix A), temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, height, weight, oxygen requirements and supplementary oxygen use, procedures (including intubation, renal replacement therapy, vasopressor/inotropic support, ECMO, etc), intermediate care unit duration, intensive care unit duration

[b]CMP: Na, K, Cl, BUN, Cr, Ca, Tot Protein, Alb, bilirubin, AST, ALT, Alk phos, CO_2

[c]Sex hormones: estradiol, free testosterone, total testosterone, FSH, LH

[&] Day 7 labs may be collected +/- 3 days

^ Record the number of days between the onset of symptoms and initiation of treatment.

^^Optional: depending on availability of supplies and facilities (PPE and laboratory equipment availability for research). If obtained for clinical reasons, will record results.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where

determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

11. Statistical considerations

Our null hypothesis is that 20% of patients will require hospitalization by day 28. This is based on internal data (from Dr. David Thiemann's EPIC analysis team at Johns Hopkins Hospital) that demonstrates an overall hospitalization rate of 14% and a hospitalization rate of 18-20% in patients 60 years old and older. We expect that each of the investigational treatment will reduce it to 2% or lower.

The sample size of 20 in each investigational arm is determined based on the comparison to the control arm. The design gives us 80% power to detect a decrease in hospitalization rate from 20% in the control arm to 2% in the treatment arm, based on a one-sided Fisher's exact test with type I error of 0.25.

If we observe 1 or less patient hospitalized within 28 days since randomization in an investigational arm, we reject the null rate of 20% in favor of 4% or less hospitalization rate with that treatment. **Table 1** lists the 90% confidence intervals for various scenarios of observed proportion of hospitalized patients. **Table 2** shows the probability of observing 1 or less hospitalized patient under various true rates. If the true rate is 20% in Arm B or Arm C, the chance of observing only 1 or less hospitalization is low at 7%; and that chance is greater than 80% if the true hospitalization rate is 4% or lower. Given this is a small study, and the true effect size is unknown, the estimates and safety generated in this trial will be used to inform power calculations of a larger, confirmatory trial.

Table 1. Confidence intervals for various observed proportions of hospitalized patients in each arm.

Observed # of hospitalizations (out of 20)	Observed hospitalization rate	90% CI (Wilson method)
0	0%	[0, 11.9%]
1	5%	[1.1%, 19.6%]
2	10%	[3.4%, 26.2%]
3	15%	[6.2%, 32.2%]
4	20%	[9.3%, 37.8%]
5	25%	[12.7%, 43.2%]
6	30%	[16.4%, 48.4%]
7	35%	[20.2%, 53.3%]
8	40%	[24.2%, 58.1%]

Table 2. True hospitalization rate and probability of observing 1 or less hospitalization for each arm.

True hospitalization rate	Probability of observing 1 or less hospitalization (out of 20 patients)
1%	98%
2%	94%
3%	88%
4%	81%
5%	74%
6%	66%
10%	39%
15%	18%
20%	7%
25%	2%

11.1. Analysis of primary endpoint:

The % of patients admitted to the hospital or died will be estimated for each arm as the proportion of patients who are hospitalized or die by day 28 since randomization along with 95% confidence interval. The secondary analysis of comparison between arms will be conducted using Fisher's exact test.

11.2. Analysis of the secondary and exploratory endpoints

The proportion of people with symptoms will be compared to the proportion of people without symptoms and compared using chi-squared test. Proportions with drug-related adverse events and serious adverse events will be compared using chi-squared test. All-cause mortality at day 60 will be compared using Fisher's exact test and a time to event analysis using Kaplan-Meier methods will be used to compare the two arms.

Descriptive statistics will be used to summarize and compare the exploratory endpoints.

12. Data reporting/Regulatory requirements

The Principal Investigator will comply with all regulated local reporting requirements and regulations, including ICH E6 guidelines for Good Clinical Practices.

12.1. Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto eCRFs. Before or between visits, the Principal Investigator, or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

12.2. Safety Meetings

Scheduled meetings will take place weekly (or as needed based on enrollment) and will include the principal investigator, study coordinator(s), research nurse(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings, matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

12.3. Monitoring

Eligibility for all patients will be monitored by the Principal Investigator. The PI safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation.

There will be a COVID Institutional DSMB, chaired by Dr. Elizabeth Jaffee. Every SAE and every death will be reported to the DSMB. The DSMB chair will determine if the DSMB needs to convene to discuss the event(s), which will occur within 24 hours of the report. The DSMB will meet after the first 10 patients are enrolled for each treatment arm to review the clinically available information, to determine if the study can proceed. The DSMB will also meet every 3 months while the study is open to monitor safety.

12.4. Study Documentation

12.4.1. Informed consent process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The subject will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol. The consent will describe in detail the study interventions/products and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

12.4.2. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators and their staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The results of the research study may be published, but subjects' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with subjects' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded. Subjects' records

will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

12.4.3. Future Use of Stored Specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. There will be no plans to re-contact them for consent or to inform them of results.

Samples would not be shared with investigators other than investigators at JHU unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at JHU. Any use of these specimens not specified in the current protocol will be reviewed by the JHU IRB.

12.4.4. Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents.

No study document should be destroyed without prior approval from the Principal Investigator and IND Sponsor. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

13. Multicenter Guidelines

Protocol Chair

- The Protocol Chair is responsible for performing the following tasks:
- Coordinating, developing, submitting, and obtaining approval for the protocol
- as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

CRO Coordinating Center

The CRO Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

Principal Investigator Responsibilities

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that the correct version of the protocol is used.
- Taking responsibility for the overall conduct of the study and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites.

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Appendix A. Symptom Assessment

Adapted from the World Health Organization (WHO)/International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Case Report Form

https://isaric.tghn.org/COVID-19-CRF/

Date: _____

Day of study: _____

Symptom	Yes	If, yes: Severity (mild, moderate, severe)	No	Unknown
Fever				
Sore throat				
Runny nose				
Wheezing				
Shortness of breath				
Cough				
Lower chest wall retraction (goes in when taking a breath)				
Chest pain				
Conjunctivitis (redness of eyes)				
Lymphadenopathy (swelling of lymph nodes)				
Headache				
Loss of smell				
Loss of taste				
Seizures				
Fatigue/malaise				
Anorexia (not eating)				
Altered consciousness/ confusion				
Muscle aches (myalgia)				
Joint pain (arthralgia)				
Inability to walk				
Abdominal pain				
Diarrhea				
Vomiting				
Nausea				
Skin rash				
Bleeding (if yes, specify sites)				
Other symptoms: (if yes, specify)				