Hormonal Intervention for the Treatment in Veterans with COVID 19 Requiring Hospitalization

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HITCH Protocol

Hormonal Intervention for the Treatment in Veterans with COVID-19 Requiring Hospitalization (HITCH): A Multicenter, Phase 2 Randomized Controlled Trial of Best Supportive Care (BSC) vs BSC plus Degarelix

STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
BSC	best supportive care
CBC	complete blood count
CDMS	clinical data management system
CFR	code of federal regulations
CRF	case report form
CSPCC	Cooperative Studies Program Coordinating Center
CT	computed tomography
DMC	data monitoring committee
eCRF	electronic case report form
eDC	electronic data capture
FDA	Food and Drug Administration
Hgb	hemoglobin
ICF	informed consent form
IL-6	interleukin-6
LAR	legally authorized representative
IRB	institutional review board
LDH	lactate dehydrogenase
LFTs	liver function tests
LHRH	luteinizing hormone releasing hormone
MRI	magnetic resonance imaging
PaO_2	partial pressure of oxygen
QT	QT = electrocardiogram interval from onset of the QRS complex to the end of the T wave representing duration of repolarization
QT_CF	electrocardiogram interval for QT interval corrected by the Fridericia correction formula
PI	principal investigator
SAE	serious adverse event
SaO_2	oxygen saturation
SAP	Statistical Analysis Plan
SQ	subcutaneously

1.0 SUMMARY

The overall goal of the proposed study is to determine whether if temporary androgen suppression improves the clinical outcomes of Veterans who are hospitalized to an acute care ward due to COVID-19. This study will compare degarelix + best supportive care (BSC) to placebo + BSC for the participants' clinical improvement. The study will randomize 198 patients from four participating VA sites (another four backup sites) over a 90-day recruitment period. The primary end point of the study is a composite endpoint of mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) at 15 days after the randomization. The study hypothesis is that the degarelix treatment group will reduce the event rate of the composite primary endpoint. Secondary objectives of this study include: 1). the composite endpoint of mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) at 30 days after the randomization.2). time to clinical improvement as defined by a decline of 2 categories or more from the baseline on the modified 7-category ordinal scale of clinical status of hospitalized influenza patients (influenza scale, see Appendix 5.1) or hospital discharge[1], 3). inpatient mortality, 4). duration of hospitalization, 5). duration of intubation for mechanical ventilation, 6). time to normal temperature (T < 37.5℃ for ≥ 48 hours), and 7). maximum severity of COVID-19 illness based on the influenza severity scale.

This statistical analysis plan (SAP) is drafted after review of the current HITCH study protocol and case report forms (CRFs), but before any analysis of the data has begun. Detailed information is given to aid in the production of the statistical output and the statistical section of the final study report, and potential manuscripts for publication. This document provides background of the study based on the protocol and describes the populations that will be analyzed. All participant characteristics and the efficacy and safety parameters that will be evaluated, along with the specific statistical methods, are described. The SAP is an independent statistical document in accordance to the updated version of the study protocol and it serves the guideline for the statistical analyses of the data collected during the study.

2.0 INTRODUCTION

2.1 Background

A novel coronavirus, now termed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), arose late in 2019[2]. The first confirmed cases occurred in December in Wuhan, Hubei province, China. It now infects people on six continents, spreading person to person. The World Health Organization (WHO) classified it as a global pandemic on March 11, 2020. As of April 6, 2020, there are more than 1.2 million confirmed cases and more than 70,000 deaths attributed to this virus. Every person on Earth, as well as every United States Veteran, is at risk. This is the emergent public health threat of our time.

SARS-CoV-2 is a singled stranded RNA virus[3] related to severe acute respiratory syndrome-related coronavirus (SARS-CoV-1).[4] SARS-CoV-2 is thought to be transmissible largely by respiratory droplets or direct contact,[5] but might also be transmitted through aerosolization.[6] SARS-CoV-2 disease severity ranges from no to minimal symptoms, mildly symptomatic with cough and dyspnea, to severe respiratory distress with multi-organ failure requiring admission to an intensive care unit and emergent ventilator support.[7] Although data are evolving, the severity of illness varies with age, co-existing comorbidities, and biological sex, with older age, people with pre-existing cardiovascular disease, and males manifesting greater disease severity.[8]

A worldwide effort is in place to contain and suppress human-to-human transmission.[9] These public-health strategies aim to slow the rate of spread and reduce the burden on critical care infrastructure. However, we also need effective therapeutics. Vaccine trials are underway but potential approvals are at least a year away.[10] Development of new drugs de novo to treat SARS2-CoV-2 will likely take even longer. Thus, the most expedient therapeutic strategy to confront this pandemic will repurpose existing FDA-approved therapeutics. One potential strategy targets viral components directly, using existing antivirals and anti-infectives currently used for other diseases. Such efforts include trials of hydroxychloroquine, remdesivir, and ribavirin.[11,12] Another

strategy involves targeting the human proteins, rather than viral proteins, required for SARS CoV-2 entry and replication.

SARS-CoV-2 recognizes host cell membrane proteins and relies upon their enzymatic activity to infect host cells. Like SARS-CoV-1, SARS-CoV-2 has four structural proteins: E (envelop), M (membrane), N (nucleocapsid), and S (spike).[13] The S protein recognizes and binds the ACE2 receptor expressed on target cells. Binding of S protein to ACE2 facilitates attachment of the virus to the host cell. However, entry of the virus into the host cell requires catalytic cleavage of the S protein (a process termed S protein priming) by the host cell membrane protein TMPRSS2.14 Thus, TMPRSS2 is required for viral entry and infection. This mechanism is similar to that used by SARS-CoV-1.14 SARS-CoV-2 and SARS-CoV-1 can also use the host membrane protein cathepsin B and L (CatB/L) for S protein priming in vitro. However, TMPRSS2 appears to be required for SARS-CoV priming in the infected host whereas CatB/L is not.[14,15] TMPRSS2 is expressed in the aero-digestive tract. TMPRSS2 is expressed within the nasal mucosa, respiratory sinuses, buccal mucosa, tracheal epithelia, bronchial epithelia, lung type 2 pneumocytes, and alveolar macrophages.[16–18] In addition to the aero-digestive tract, TMPRSS2 is highly expressed on prostate, kidney, and pancreatic epithelia.[18]

Inhibition of TMPRSS2 reduces SARS-CoV-2 entry into target cells. Camostat mesylate is a small molecule inhibitor of TMPRSS2 currently approved in Japan for pancreatitis. Pharmacologic inhibition of TMPRSS2 with camostat mesylate prevented SARS-CoV-2 entry into cultured human lung cells.[14] Importantly, effective abrogation of SARS-CoV-2 entry did not require co-targeting of CatB/L, supporting the notion that targeting TMPRSS2 alone is sufficient to block SARS-CoV-2. This is consistent with prior investigations that demonstrated pharmacologic inhibition of TMPRSS2 was sufficient to eliminate lethal SARS-CoV-1 infection in murine models, whereas pharmacologic inhibition of CatB/L was not.[15] Moreover, murine models deficient in TMPRSS2 (tmprss2 knockout mice) were more resistant to SARS-CoV-1 infection than wildtype controls, exhibited reduced viral replication within lung tissue, and profoundly reduced lung immunopathology after infection, suggesting that loss of the TMPRSS2

gene in humans may be protective against SARS-CoV-2 infection.19 The TMPRSS2 knockout mice appeared normal, indicating loss of tmprss2 by itself is not pathogenic.[19] Camostat mesylate is currently being evaluated in a randomized, double-blind study for hospitalized SARS-CoV-2+ patients (NCT04321096) in Denmark. In an entirely separate line of investigation, a chemical library screen of small molecule inhibitors of TMPRSS2 for an entirely unrelated purpose identified the drug bromhexine.20 Bromhexine demonstrated submicromolar inhibition of TMPRSS2 and suppressed TMPRSS2 driven metastatic progression in murine models.[20] The mechanism of bromhexine is not entirely clear, but it is sold over the counter in other countries, available both by mouth and via inhalation for respiratory disorders. In contrast, ACE2 is considered loss-of-function intolerant in humans.[21] In addition, SARS-CoV-mediated down-regulation of ACE2 is thought to contribute to the severity of lung pathologies, indicating that down-regulation of ACE2 may further harm the lungs of infected patients.[22] For all of the aforementioned reasons, it seems that transcriptional regulation of TMPRSS2 is the highest priority for clinical evaluation.

Transcriptional regulation of TMPRSS2. The transcriptional regulation of the TMPRSS2 gene has been extensively characterized, most rigorously within the prostate. The TMPRSS2 gene is located on chromosome [21] and is under the control of the androgen receptor (AR). Binding of androgens (e.g. testosterone or dihydrotestosterone) to the AR results in homodimerization and translocation of the AR to the nucleus, where it binds to its cognate androgen response element in the regulatory regions of its target genes, and thereby regulates gene expression.[23,24] It is firmly established that suppression of AR transcriptional activity through reduction in circulating androgens or direct antagonism of AR-androgen binding using AR competitive antagonists reduces expression and protein levels of TMPRSS2 within the prostate, as well as prostate cancers.[25] Remarkably, expression of TMPRSS2 also appears to be hormonally regulated within the lung and bronchial cells. Notably, the AR is expressed in type II pneumocytes and the bronchial epithelium.[26] Androgens enrich AR binding at the TMPRSS2 enhancer and upregulate expression of TMPRSS2 in human lung cells, in a fashion similarly to that found in the prostate.[26]

In addition, our query of publicly available gene expression databases demonstrated that TMPRSS2 appears to have a high variability of expression amongst individuals.[27] To identify the most promising therapeutic opportunities, we performed a literature-wide screen of RNA-seq datasets in the NCBI Sequence Read Archive (SRA) that incorporated keywords relating to drug treatments. We identified differentially expressed genes from 3,089 distinct case-control comparisons featuring a drug treatment. Notably, anti-androgenic compounds and estrogens were among the strongest and most consistent down-regulators of TMPRSS2 expression, while androgens consistently led to up-regulated TMPRSS2 gene expression.[27] In other words, these studies suggest that the AR induces TMPRSS2 expression, whereas ER transcriptional activity is associated with suppression of TMPRSS2 expression. However, there was an initial surge in TMPRSS2 expression after estrogen treatments, followed by a gradual decrease in TMPRSS2 expression. Moreover, the highly variable expression pattern of TMPRSS2 suggests a provocative and plausible, although unproven, explanation for the wide range in disease severity for patients infected by SARS-Cov-2, as well as the higher rate of severe infections among males and the reduced rate and severity of infection in pre-pubertal children. A link between TMPRSS2 expression and susceptibility to viral infection was discovered by a recent genome wide association study that identified genetic variants with higher TMPRSS2 expression also had more severe H1N1 and H7N9 influenza.[28] Notably, H1N1 and H7N9 influenza, but not all influenza subtypes, require TMPRSS2 for priming.[29,30]

Identification of drugs that suppress TMPRSS2 expression. Based on the aforementioned data that TMPRSS2 is hormonally regulated in the lung by the AR and estrogen receptor (ER), it is hypothesized that drugs that interfere with AR driven transcription or enhance ER driven transcription will reduce TMPRSS2 expression. An informatics analysis of publicly available gene expression data to identify drugs that affect TMPRSS2 expression levels identified several existing FDA approved drugs.[27] Unsurprisingly, these included antagonists of the AR an agonist of the ER. A possible protective effect from estrogenic agonism in the context of another coronavirus was suggested from murine models whereby female mice exhibited reduced susceptibility

and mortality to SARS-CoV-1 infection as compared to males. Furthermore, anti-estrogen treatments of the female mice increased their susceptibility and mortality to SARS-CoV-1.[31]

Thus, either suppression of AR or activation of ER may reduce expression of TMPRSS2. We chose to focus on suppression of AR, rather than activation of ER, because we are concerned that a potential initial estrogen-induced surge in TMPRSS2 expression could acutely worsen viral infections. Fortuitously, a wealth of FDA approved drugs block AR signaling. These include the GnRH analogs that reduce pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby potently suppressing testosterone production, and anti-androgens that interfere with binding of androgens to the AR. These drugs are predominantly used in the treatment of prostate cancer, have well known and generally tolerable side effect profiles, and exhibit reversibility of their biologic effects. As such, we contend that androgen suppression will reduce TMPRSS2 expression in the target cells of SARS-CoV-2 and reduce the severity of illness.

2.2 Objective

The goal of the proposed study is to determine if temporary androgen suppression improves the clinical outcomes of Veterans who are hospitalized to an acute care ward due to COVID-19 as defined by an influenza severity scale or time to discharge.

2.3 Study Design

This study is a parallel, double-blind, placebo controlled, superiority trial in which participants will be randomized to the degarelix + BSC treatment group or to the placebo + BSC control group. The study will randomize 198 Veterans at four VA Medical Centers at a 2:1 treatment assignment ratio, i.e. 132 participants in the degarelix group and 66 participants in the placebo group. The total recruitment period will be approximately 90 days with an approximately follow-up period of 60 days. The

duration of the study will be approximately five months. Informed consent for the study will be obtained prior to participants' enrollemnt eligibility screening. Randomization will be performed via an Interactive Web Response System (IWRS), a computerized system that will allow authorized study personnel to randomize patients and obtain study treatment assignments using a stratified random block method once a participant has eligible to the study. Study drug treatment will be given according to the randomization assignment within 48 hours after randomization. BSC consists of supplemental oxygen, antibiotics, vasopressor support, peritoneal or hemodialysis, antibiotics, intravenous fluids, etc. The participants will be followed up till their discharge. The study flow is shown in Appendix 5.2. Both the participants and the treating physicians/nurses as well site investigators/coordinators will be blinded of the treatment assignment.

Participants will be followed until death or discharge, whichever comes first. If a patient dies or refuses to continue participation, he will be terminated. A termination form will be used to record the termination information for these patients. If a patient remains hospitalized beyond day 30, the patient will continue to be followed for clinical endpoints, but no additional research labs will be obtained.

Study treatment drug, degarelix (as the acetate) is formulated as a sterile lyophilized powder for injection. Degarelix forms a depot upon subcutaneous administration, from which it is released to the circulation. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the depot formed at the injection site(s). The 240 mg dosage is achieved by the administration of two 120 mg SQ doses in the deep abdominal subcutaneous tissue. Participants will be randomly assigned to receive a one-time dose of degarelix 240 mg SQ or matching placebo on randomization day (day 1). The matching placebo will contain equal volume 0.9% saline by following the 60 minute rule after the drug reconstitution. No dose modifications are allowed for degarelix.

Scheduled follow up forms will be filled out weekly after randomization upon till discharge after the randomization and Unschedued follow-up form will be filled out on the time whenever the event occurs during the follow-up time (see Appendix 5.3.1).

2.4 Study Outcome Variables

2.4.1 Primary Outcome Variable

The primary outcome is defined as a composite endpoint of mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) at 15 days after the randomization.

2.4.2 Secondary Outcome Variables

There are five secondary outcome measures

1. The composite endpoint of mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) at 30 days after the randomization.
2. The time to clinical improvement as defined by a decline of 2 categories or more from the baseline on the modified 7-category ordinal scale of clinical status of hospitalized influenza patients (influenza scale, see Appendix 5.1) or hospital discharge, whichever comes first.
3. Inpatient mortality
4. Length of hospital stay
5. Duration of intubation for mechanical ventilation
6. Time to normal temperature (< 37.5℃ for ≥ 48 hours)
7. The maximum severity of COVID-19 illness based on the influenza severity scale (see Appendix 5.1)

2.4.3 Exploratory Outcome Variables

Prognostic factors associated with clinical outcomes

Clinical Factors: Age, use of angiotensin converting enzyme inhibitors, the duration of pre-hospitalization symptoms, or the presence or absence of hypertension, cardiovascular disease, asthma, diabetes mellitus, or COPD

Laboratory Factors D-dimer, IL-6, LDH, ferritin, total WBC, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), or testosterone

Treatment effect on viral load and cytokines (GLA site only)

Viral load NP epithelial cells, PBMC

Serum cytokines TNF-α, IL-1β, IL-6

Other TMPRSS2 expression, anti-viral Ab, genomic factors

2.4.4 Safety Outcome Variables

Safety measures include study-related adverse events (AE) and serious adverse events (SAE), and AE with special interest in the drug toxicity.

2.5 Study Assessments Used in the Analysis

2.5.1. Baseline Assessment

Participants' demographics, medical history, vital signs, and concomitant medication use are collected at the baseline time point. Other baseline assessments will be collected the time between identification of an eligible participant and the randomization including medical history, laboratory measurements of D-dimer, IL-6, LDH, ferritin, total WBC, ANC, ALC, testosterone, and participant clinical status. Data collected during this period is used primarily for the participants' baseline characteristics used for the statistical analysis, monitoring recruitment, and randomization status. We will maintain the information of all identified potential participants. This will be accomplished by completing the screening form for every participant presenting to the clinical site for eligible operations including those who are excluded from the study for any reason.

2.5.2. Follow-up Assessment

Follow-up assessments will be collected after participants' randomization and treatment at day 1, 8, 15, 22, 30, and 60 for the scheduled follow-up assessments of concomitant medications, medical status, laboratory measurements, and clinical assessment. The follow-up assessments also include those unscheduled protocol deviations, AEs and SAEs, and participants' disposition status. The data collection schedule as shown in Appendix 5.3.2.

2.5.3. Safety Assessment

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence. This contributes to patient safety,

regulatory compliance and improvements in study design or procedures. In addition, close attention to AEs provides valuable information about the safety and tolerability of study drugs. This study specific safety plan is designed to collect information on the safety and tolerability of the study medications; thus, reporting will be conducted in accordance with the requirements of GCP and other regulatory requirements governing clinical research in the US. In HITCH, patients will receive a regimen of FDA approved commercially available degarelix for injection (Firmagon ®) 240 mg for subcutaneous use or matching placebo. Local Study Investigators, with assistance from their local SC, are responsible for collecting AE and SAE information regarding the patients at their sites. Non-serious AEs and SAEs will be collected from the time of randomization until 30 days after the last dose of study medication. Throughout the specified duration of AE and SAE collection, data will be collected through spontaneous local SC/LSI/Co-I contact, during in-person study visits, and gathered during telephone contacts and medical record reviews when performed (see Table of Scheduled Events). AEs will be collected based on a review of the electronic medical record. Adverse events that are open will require follow-up reports (if necessary) every 30 days until resolved or until the end of the trial. Adverse events reported to study staff and deemed related to the study drug(s) and all SAEs will be recorded on an AE or SAE form (respectively) and documented in source records (e.g., the electronic VA medical record and/or the patient's study record).

Severity of an Adverse Event The following categories are used to convey the severity of an adverse event:

• Grade 1 Mild; – Events require minimal or no treatment and do not interfere with the patient’s daily activities

• Grade 2 Moderate; – Events result in a low level of inconvenience or concern with the therapeutic measures. Interferes with normal daily activities to some extent

• Grade 3 Severe; – Events interrupt a patient’s usual daily activity and may require systemic drug therapy or other treatment. May severely interfere with or prevent normal daily activities

• Grade 4 Life-threatening consequences; – Events requiring urgent intervention

• Grade 5 Death related to AE.

Serious Adverse Event (SAEs) An AE is considered an SAE if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

• Death

• A life-threatening AE

• Inpatient hospitalization or prolongation of existing hospitalization

• A persistent, significant, or permanent incapacity or substantial disruption in the patient's body function/structure, physical activities and/or quality of life

• Congenital anomaly/birth defect; or

• Important medical events that may not be immediately life-threatening, result in death, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Such events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse

Relatedness Relatedness involves an assessment of the degree of causality (attributability) between the study intervention and the event.

• Definitely Related: The event is clearly related to the study intervention – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the patient’s clinical state.

• Possibly Related: An event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

• Not Related: The event is clearly not related to the investigational agent/procedure. - i.e. another cause of the event is most plausible; and/or a clinically

plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Unanticipated Adverse Event An AE that is new or greater than previously known, in terms of nature, severity, or frequency of occurrence, or any other unanticipated serious problem associated with the investigation that relates to the rights, safety, or welfare of participants, as documented in the protocol or other materials approved by the IRB of record or the characteristics of the study population.

Adverse Events of Special Interest Cardiac arrhythmias and thromboembolic events will be considered AEs of special interest. Any cardiac arrhythmia or thromboembolic event of grade 3-5 according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0; see Appendix 5.4) will be reported in a manner similar to SAEs, whereby the event will be reported to the HITCH reporting system within 3 calendar days of the Study Site Personnel becoming aware of the event.

All adverse events that are related to the study intervention or procedures are recorded at each research assessment visit (description, severity, relationship to study intervention, date onset, date resolution).

2.6 Sample Size Consideration

In a recent antiviral drug trial to treat adults hospitalized with severe COVID-19 published in the New England Journal of Medicine (NEJM) on March 18, 2020[32], the results showed that a mortality rate of 17%, hospital stay rate of 50%, and ECMO or mechanical intubation rate of 11% among the patients managed with BSC after two-week follow-up. In the current study, we propose a composite endpoint of mortality, ongoing need for hospitalization, and ECMO or mechanical intubation at 15 days after randomization. We are expecting to reduce the composite endpoint rate to 35% after the degarelix treatment plus BSC from 60% for patients treated placebo plus BSC.

The sample size estimation and power analysis shown in Table 2 are based on the hypothesis testing of the primary endpoint, which is the composite endpoint of mortality, hospital stay rate, and ECMO or mechanical intubation at 15 days after

randomization (Day 15). According to the composite endpoint outlined in the previous section, we assume that an effect size for the primary endpoint of 42% can be anticipated in the degarelix group. The other assumptions include a three-month accrual time and one-month follow-up time, and 2:1 sample allocation of degarelix: placebo treatment group. The sample size for the study is estimated based on a superiority trial design. To have 90% power of detecting the expected 42% reduction using a two-sided two proportion test with a significance level of 0.05 in the degarelix compared to the placebo group will require 186 evaluable patients total (i.e. 124 evaluable patients in the degarelix group and 62 evaluable patients in the placebo group). Based on an assumed 5% attrition rate, 198 patients will be required (i.e. 132 in the degarelix group and 66 in the placebo group) to achieve actual statistical significance at alpha level of 0.05 and power of 90% (Appendix 5.5).

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Missing Data and Imputations

Every effort will be made to minimize the occurrence of missing data, particularly for the primary and the secondary endpoints. In the event of a potential drop out, every effort will be made to capture missed data from the patient record and VA databases. For patients who drop out during the study the missing values for the primary endpoint analysis will be considered as failures. However multiple imputation (MI) method may be used for certain secondary endpoint analyses. Multiple imputations will be performed using SAS PROC MI under missing at random assumption. If the assumption does not hold, then imputations will be performed. Sensitivity analysis will be performed to compare the results from the various imputation scenarios.

3.1.2 Analysis Conventions

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the

specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- All statistical tests will use a significance level of $\alpha = 0.05$. Two-tailed tests will be performed for all analyses that use statistical testing.
- All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value ≤ α will be considered statistically significant.
- Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The decimal of the percentage may be dropped due to space constraints when creating a table.
- All listings will be sorted for presentation in order of treatment group, site number, participant number, and date of procedure or event.
- All analysis and summary tables will have the population sample size for each treatment group in the column heading.
- Calculating change from baseline to a visit will be done as follows: change = visit –baseline.
- Baseline is defined as the last data point before the first treatment is administered. If baseline data are not available, screening data will be used.
- Version 9.4 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.
- Updated version of MedDRA will be used for adverse event and pre-treatment coding.

- The current version of the World Health Organization (WHO) drug dictionary will be used for the coding of medications.

3.2 Participant Disposition

Participant disposition will be summarized for the ITT population.

- The number and percentage of participants who completed or discontinued prematurely from the study by treatment group will be tabulated and tested using Pearson χ^2 test (Table 3.2.1). The number and percentage of participants who completed or discontinued prematurely in each treatment group will also be displayed graphically (Figure 3.2.1).
- The number and percentage of participants who discontinued for each reason will be presented by treatment group (Table 3.2.2).
- A listing of participants that discontinued prematurely from the study will be presented. The listing will include information about treatment, study center, participant number, age, race, number of days, and reason for discontinuation (Table 3.2.3).
- The number and percentage of participants who completed or discontinued prematurely from the study by study center will be tabulated and tested using Pearson χ^2 test (Table 3.2.4). The number and percentage of participants who completed or discontinued prematurely in each treatment group will also be displayed graphically (Figure 3.2.1).

3.3 Analysis Populations

Intent-to-Treat (ITT) – This population includes all participants randomized to either of the treatment groups – degarelix or placebo. The patients will be categorized (in terms of their treatment assignment) based on their initial randomized group and will be included in analyses irrespective of their status – completer or drop out of the study before completion. The testing power for the primary endpoint is estimated as 90% in this population.

Safety – This population includes all participants randomized to either of the treatment groups – degarelix or placebo.

The number of participants in each population will be summarized for each treatment group and for all participants (Table 3.3.1).

3.4 Study Protocol Adherence

Study treatments and adherence will be summarized by treatment group and overall for the ITT population. The number and percentages of participants will be presented for each treatment group and overall (Table 3.4.1). The number and percentage of non-adherence participants will be summarized by the treatment groups and tested using Pearson χ^2 test. The following information will be presented for each treatment group and overall for adherence:

- Summary of protocol non-adherence (Table 3.4.2)
- Summary statistics (number of participants, mean, median, SD, minimum, and maximum) for study adherence (Table 3.4.3)

3.5 Participant Demographics and Characteristics

The patient demographics and pre-treatment baseline characteristics and medical history will be summarized for each treatment group and overall for the ITT population. For continuous variables, the sample size, mean, median, SD, minimum, and maximum value will be calculated and tested either by Student t or Wilcoxon test depending on data distributions using SAS PROC TTEST and SAS PROC NPAR1WAY, respectively. For categorical variables, the number and percentage of patients by the treatment group will be tabulated and tested based on Pearson χ^2 test using SAS PROC FREQ.

3.5.1 Demographics

The summary of demographics at baseline will include age, race, gender, ethnicity, marital status, military history, location of military service, branch of service, and pre-admission residence (Tables 3.5.1).

3.5.2 Baseline Characteristics

Baseline comparability among the treatment groups will be evaluated by providing a summary of baseline test results (D-dimer, IL-6, LDH, ferritin, total WBC, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin, hematocrit, platelet counts, and testosterone) and baseline medical status (fever, oxygen needs, and days symptoms started prior to hospitalization) (Tables 3.5.2).

3.5.3 Medical History

The number and percentage of participants reporting a medical history will be summarized by the following medical conditions: COPD, hypertension, cardiovascular disease, asthma, diabetes, use of angiotensin converting enzyme inhibitors within last 30 days prior to hospitalization, and use of supplemental oxygen prior to hospitalization (Tables 3.5.3).

3.6 Concomitant Medications

Summaries for prior and concomitant medications will be done for the ITT population. Concomitant medications will be reported at screening, day 8,15,22, and 30. Each summary below will be done for each treatment group and for all participants:

- Prior medications – medications taken prior to the study drug administration
- Concomitant medications –medications taken on or after the study drug administration

All medications recorded on the CRF will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) drug classifications. The current version of the WHO drug dictionary will be used for the coding of medications.

The number and percentage of participants who take medications that are coded to each generic drug name and therapeutic drug class will be tabulated by the treatment group and tested based on Pearson χ^2 test using SAS PROC FREQ (Tables 3.6.1-2). If there are significant differences between the two treatment groups for certain study related drugs, these concomitant medication use will be adjusted for the endpoint efficacy analyses when it is necessary.

3.7 Efficacy Analyses

The primary analysis of the study will be performed on the primary endpoint on the ITT population. The secondary analyses will be performed on the ITT population and available data. Both the primary and secondary endpoints analyses will be performed for the hypothesis testing. While the exploratory endpoints will be analyzed to generate new hypothesis unless otherwise specified. Potential difficulties of convergence of model fit, which arise in efficacy analyses that include covariates, will be handled using the method described in section 3.7.1. The analysis plan is summarized in the Appendix 5.6.

3.7.1. Primary Endpoint Analysis

The primary study endpoint will be the composite outcome of mortality, ongoing need for hospitalization, and ECMO or mechanical intubation at 15 days after randomization. This outcome will be compared according to assigned treatment groups, using Pearson χ^2 test. The test for differences between the treatment groups in the primary outcome will be conducted at an overall α-level of 0.05 (i.e. α = 0.006 for mid-term interim analysis, α = 0.044 for the final analysis). If a participant drops out from the study, then he will be considered as a failure. Additional analyses will be conducted using logistic models to adjust for other clinical factors, such as age, hypertension, and COPD. Logistic regression will be used for the primary endpoint (y = 1 if a composite outcome, otherwise y = 0) analysis with the treatment group as the testing factor (x). The following covariates will be included in the model: age (z1), hypertension (z2), and COPD (z3). Given the composite outcome probability $p = p\ (y = 1|x, z_1, z_2, z_3)$, the basic model is defined as follows:

$$Logit(p) = ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x + \beta_2 z_1 + \beta_3 z_2 + \beta_4 z_3$$

Odds ratio and 95% confidence interval (CI) will be presented using SAS PROC GENMOD or PROC LOGSTIC. If the coefficient for treatment effect is significant, then the null hypothesis will be rejected. Logistic models will be tested for goodness of fit. We will assess goodness-of-fit using the statistic -2 log likelihood, which has a χ^2

distribution under the null hypothesis that all the explanatory variables in the model are zero. We will also consider the Akaike Information Criterion statistic and the Schwartz Criterion statistic, both of which adjust the -2-log likelihood for the number of items in the model. Models that show lack of fit will be reconsidered for the inclusion of additional variables or use of alternate models with assumptions that are better met by the study data. One alternate model if model fit is poor for logistic regression is a log-linear model. The number and percentage of participants with the composite endpoint at the 15 day after the randomization will be summarized and compared using Pearson χ^2 test (Table 3.7.1a). For logistic regression analysis, if the coefficient for treatment effect is significant (i.e., the confidence interval for the odds ratio does not include 1), then the null hypothesis will be rejected. The significant level for each covariate coefficient in the model will best determined by Wald test (Table 3.7.1b). Meanwhile, Cochran Mantel-Haenszel test will be used to adjust for three randomization stratification factors (Age: <65 vs. ≥65, History of hypertension: yes vs. no, and Influenza severity scale: 3 vs 4/5) using SAS PROC FREQ as one of the sensitivity analyses (Table 3.7.1c).

3.7.2 Secondary Endpoint Analyses

Secondary endpoints included in the data analysis are the composite outcome of mortality, ongoing need for hospitalization, and ECMO or mechanical intubation at 30 days after randomization, time to clinical improvement, inpatient mortality, length of hospital stay, length of intubation for mechanical ventilation, time to normal temperature, and the maximum severity of COVID-19 illness, which are defined in the endpoint section. The secondary endpoint analyses will be adjusted for multiplicity with a α-level of 0.0071 for each endpoint.

The composite outcome of mortality, ongoing need for hospitalization, and ECMO or mechanical intubation at 30 days after randomization as a secondary endpoint will be analyzed using the methods described in the primary endpoint analysis (Tables 3.7.2.1a-c).

For the time to clinical improvement as defined by a decline of 2 categories or more from the baseline on the modified 7-category ordinal scale of clinical status of

hospitalized influenza patients (influenza scale, see Appendix 5.1) or hospital discharge (see section 2 for definition of discharge) whichever comes first, survival analysis techniques will be used to analyze the time-to-event data for this endpoint. Participants whose condition worsened, who died, or who withdrew from the study without clinical improvement will be censored. Kaplan-Meier analysis will be used to compare the two curves of the time to the clinical improvement over the patient follow-up time between the two treatment groups and a log-rank statistic will be used to test the equality of the survival function estimates of the two treatment groups using SAS PROC LIFETEST. Kaplan-Meier curves will be created (Figure 3.7.2.1). Additional analysis will be conducted using the Cox's Proportional Hazards model to test the treatment efficacy of the treatment on the time until endpoint events adjusted for three prognostic factors: age, hypertension, and COPD. The hazard ratio and 95% confidence interval (CI) will be presented using SAS PROC PHREG (Table 3.7.2.2). If the coefficient for treatment effect is significant, then the null hypothesis will be rejected. The regression model will be checked for the model assumption, adequacy, and the goodness of fit. If the model shows lack of fit, then alternate models with assumptions that are better met by the study data will be considered.

For mortality endpoint data analysis, the treatment effect will be analyzed initially with a Pearson χ^2 test (Table 3.7.2.3a) and then logistic regression will be performed using SAS PROC LOGISTIC by taking account of prognostic factors described in the primary endpoint analysis (Table 3.7.2.3b).

For the length of hospital stay data analysis, medians (interquartile ranges) will be presented and Wilcoxon tests, a nonparametric method, will be performed to compare the medians of the length of hospital stay between the two treatment groups using SAS PROC NPAR1WAY (Table 3.7.2.4a). In addition, a quantile regression will be used to test the effect of the treatment on the time until the clinical event adjusted for prognostic factors described in the primary endpoint analysis using a SAS PROC QUANTREG (Table 3.7.2.4b).

For the length of intubation for mechanical ventilation data analysis, medians (interquartile ranges) will be presented and Wilcoxon tests, a nonparametric method,

will be performed to compare the medians of the length of hospital stay between the two treatment groups using SAS PROC NPAR1WAY (Table 3.7.2.5a). In addition, a quantile regression will be used to test the effect of the treatment on the time until the clinical event adjusted for prognostic factors described in length of hospital stay data analysis using SAS PROC QUANTREG (Table 3.7.2.5b).

For time to normal temperature data analysis, survival analysis techniques will be used to analyze the time-to-event data for this endpoint. Participants whose temperature remains abnormal will be censored. Kaplan-Meier analysis will be used to compare the two curves of the time to the clinical improvement over the patient follow-up time between the two treatment groups and a log-rank statistic will be used to test the equality of the survival function estimates of the two treatment groups using SAS PROC LIFETEST. Kaplan-Meier curves will be created (Figure 3.7.2.2). Additional analysis will be conducted using the Cox's Proportional Hazards model to test the treatment efficacy of the treatment on the time until endpoint events adjusted for three prognostic factors: age, hypertension, and COPD. The hazard ratio and 95% confidence interval (CI) will be presented using SAS PROC PHREG (Table 3.7.2.6). If the coefficient for treatment effect is significant, then the null hypothesis will be rejected. The regression model will be checked for the model assumption, adequacy, and the goodness of fit. If the model shows lack of fit, then alternate models with assumptions that are better met by the study data will be considered.

For the maximum severity of COVID-19 illness data analysis, Pearson χ^2 test will be performed for this categorical endpoint using SAS PROC FREQ initially. Given the endpoint is also an ordinal variable, Cochran–Armitage test will be performed to test the ordinal trend tendency using SAS PROC FREQ (Table 3.7.2.7a). in addition to the frequency analysis, proportional odds logistic regression will also be performed (Table 3.7.2.7b) using SAS PROC LOGISTIC by taking account of the factors of age, hypertension, COPD, and the baseline influenza scale (see Appendix 5.1).

3.7.3 Exploratory Endpoint Analyses

Clinical and Laboratory Prognostic Factors

Exploratory analyses will be performed to identify the impact of clinical and laboratory prognostic factors on the primary endpoint or any secondary endpoint. Clinical factors include age, presence or absence of COPD, hypertension, or cardiovascular disease, or use of angiotensin converting enzyme inhibitors. Laboratory measurements including D-dimer, IL-6, LDH, ferritin, total WBC, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin, hematocrit, platelet counts, and testosterone are measured during the patient's hospital stay. Further germline genomic factors will also be analyzed if feasible as prognostic factors for the study outcomes for part of the patients.

For continuous variables, the sample size, mean, SD, median, minimum, and maximum values for each treatment will be presented for each parameter at each data collection time point and tested using SAS PROC TTEST between the treatment groups. If a variable is not normally distributed the non-parametric method will be applied using SAS PROC NPAR1WAY (Table 3.7.3.1). For categorical variables, the number and percentage of participants by the treatment group will be tabulated and tested based on Pearson χ^2 test using SAS PROC FREQ (Table 3.7.3.2).

Univariate correlation with the primary endpoint or any categorical secondary endpoint will be assessed for each clinical and laboratory factor based on logistic regressions using SAS PROC LOGISTIC (Table 3.7.3.3). For the secondary endpoints of time to events data, univariate analysis will be performed based on Cox regressions using SAS PROC PHREG (Table 3.7.3.4). For the secondary endpoints of length of hospital stay and length of intubation for mechanical ventilation, nonparametric univariate analysis will be performed based on Spearman correlation method using SAS PROC CORR for the continuous prognostic factors, whereas Mann–Whitney U or Wilcoxon rank-sum test will be performed for the categorical prognostic factors using SAS PROC NPAR1WAY(Table 3.7.3.5). For those prognostic factors significantly associated with the primary and secondary outcomes from the univariate analyses, multiple regressions will be performed by adjusting some other prognostic factors identified from the univariate analyses. The multiple regressions will be performed as

described in the primary analysis and each corresponding secondary endpoint analysis (Table 3.7.3.6).

Viral Load, Cytokines Levels, and TMPRSS2 Expression

To explore the mechanisms that underlie treatment effect, nasopharyngeal (NP) epithelial or peripheral blood mononuclear cell (PBMC) TMPRSS2 expression, NP and plasma viral load, or serum cytokine (TNF-α, IL-1β, IL-6) levels will be tested among the participants from the Great Los Angeles site only.

Viral load kinetics in the two treatment groups over participants' critical period will be monitored from baseline to day 30. The viral load in plasma will be assessed by the viral RNA measured by a reverse-transcriptase–polymerase chain--reaction (RT-PCR) assay and quantified as log_{10} copies/ml. Mean change from baseline in SARS-CoV-2 viral RNA load across each sample collection time point will be compared by the treatment groups. The mean value for log_{10} copies/ml for each week will be calculated and summarized. Log_{10} copies/ml changes from baseline to each week will be summarized. For each week, the sample size, mean, SD, median, minimum, and maximum values for each treatment will be presented. A mixed-effect model of repeated measure (MMRM) for overall changes across all the time point between the two treatment groups using SAS PROC MIXED (Table 3.7.3.7). A longitudinal graph of Log_{10} copies/ml will be created and presented by 95% confidence intervals of the means (Figure 3.7.3.1).

Serum cytokines TNF-α, IL-1β, and IL-6, as well as TMPRSS2 expression and antiviral antibodies will be tested by immunoassays. Mean change from baseline in the cytokine and TMPRSS2 levels, and antibody titers across each sample collection time point will be compared by the treatment groups. The mean value for each week will be calculated and summarized. Mean changes from baseline to each week will be summarized. For each week, the sample size, mean, SD, median, minimum, and maximum values for each treatment will be presented (Table 3.7.3.8). A mixed-effect model of repeated measure (MMRM) for overall changes across all the time point between the two treatment groups using SAS PROC MIXED. A longitudinal graph of each measurement level will be created and presented by 95% confidence intervals of

the means (Table 3.7.3.9). If a measurement level is not normally distributed, then a non-parametric method will be used as an alternative analysis approach.

The exploratory analyses will not be adjusted for multiplicity.

3.7.4 Site Effect Analysis

Site effect will be evaluated for four participating sites. Balances of the treatment of assignment and the primary and secondary outcomes will be assessed among the four sites (Table 3.7.4.1). If there are significant associations between the site and treatment assignment and a study outcome at significance level of 0.05 without multiplicity adjustment, the site effect will be adjusted in the corresponding the primary or any secondary outcome along with the other prognostic factors described in the primary and secondary analyses.

3.7.5 Long Term Effect Analysis

The long-term analysis will be based on the data collected by following the randomized participants up to 60 days after randomization, which will include mortality, readmission to hospital, and oxygen use.

For mortality analysis, the treatment effect will be analyzed initially with a Pearson χ^2 test (Table 3.7.5.1a) and then logistic regression will be performed using SAS PROC LOGISTIC by taking account of prognostic factors described in the primary endpoint analysis (Table 3.7.5.1b).

For hospital readmission rate analysis, the treatment effect will be analyzed initially with a Pearson χ^2 test (Table 3.7.5.2a) and then logistic regression will be performed using SAS PROC LOGISTIC by taking account of prognostic factors described in the primary endpoint analysis (Table 3.7.5.2b). Further, time to hospital readmission will also be analyzed based on survival analysis techniques using log-rank test and Kaplan-Meier curves (Figure 3.7.5.1) by PROC LIFETEST, and Cox regression model adjusted for the covariates as described in the secondary endpoint analyses (Tables 3.7.5.3a-b).

For the oxygen use analysis, Pearson χ^2 test will be performed for this categorical endpoint using SAS PROC FREQ initially. Given the endpoint is also an ordinal variable, Cochran–Armitage test will be performed to test the ordinal trend

tendency using SAS PROC FREQ (Table 3.7.5.4a). in addition to the frequency analysis, proportional odds logistic regression will also be performed (Table 3.7.5.4b) using SAS PROC LOGISTIC by taking account of the factors of age, hypertension, COPD, and the baseline influenza scale (see Appendix 5.1).

The long-term analyses will not be adjusted for multiplicity.

3.8 Safety Analyses

All safety analyses will be done for the safety population and reported in tabular forms. These analyses include serious adverse events (SAE), study related to adverse events (AE), and AE with special interests to monitor drug toxicity.

3.8.1 AE and SAE analyses

Adverse events (AE) and serious adverse events (SAEs) are defined by the ICH for Clinical Safety Data Management (ICH-E2A), the Food and Drug administration as described in the section 9. Incidence of AE/SAEs will be summarized for each treatment group by body system and MedDRA term. The number and percentage of participants with each body system and MedDRA term will be presented for each group. Pearson χ^2 test and/or Fisher Exact test were used to compare the frequency difference of AE and SAE between the treatment groups in System of Body (SOC) and Preferred Terms (PT) levels. Tables to summarize the incidence rates will be created for each of the following groups: Total AE and SAE, AE and SAE by relationship to study treatment, AE and SAE leading to premature discontinuation, AE and SAE presented in descending order of frequency by MedDRA term (no body systems shown). AE and SAE that led to premature discontinuation from the study will be listed. These listings will contain details about the SAEs such as outcome and relationship to study treatments. Other supportive data, such as the participant's age, will be given. All AE and SAE will be coded with MedDRA (updated version) and listed by participant. Tables to summarize the incidence rates will be created for each of the following groups:

- AE and SAE (Table 3.8.1a-b)
- AE and SAE by relationship to study treatment (Tables 3.8.2a-b)

- AE and SAE leading to premature discontinuation (Table 3.8.3a-b)
- AE and SAE presented in descending order of frequency by MedDRA term (no body systems shown) (Table 3.8.4a-b)

AE and SAE that led to premature discontinuation from the study will be listed. These listings will contain details about the AE/SAEs such as outcome and relationship to study treatment. Other supportive data, such as the participant's age, will be given. All AE/SAEs will be coded with MedDRA (updated version) and listed by subject (Table 3.8.5).

3.8.2. Drug Toxicity Analysis

The drug toxicity will be closely monitored and analyzed. Cardiac arrythmia and thromboembolic complications are adverse events of special interest (grade 3 and above) that will be monitored closely and graded according to on CTCAE 5.0. Once the toxicity markers reach a threshold of 25%[33], a statistical analysis of the toxicity will be performed. The treatment difference will be analyzed initially with a Pearson χ^2 test using SAS PROC FREQ (Table 3.8.2.1) and logistic regression will also be performed using SAS PROC LOGISTIC by taking account of prognostic factors described in the primary endpoint analysis (Table 3.8.2.2). If the experimental (degarelix) group has a significant higher toxicity compared to the placebo group at an α-level of 0.01, then results will be reported to the DMC for a recommendation for trial termination.

3.9 Interim Analyses

A mid-term interim analysis of the primary endpoint will be performed when half of the participants (99 randomized participants) complete or are terminated from the study. If the mid-term analysis of the primary endpoint indicates that the null hypothesis can be rejected with a boundary value of 2.77 (standardized Z > 2.77 or < - 2.77) at an α-level of 0.006 or accepted with a boundary value of 0.44 (- 0.44 ≤ standardized Z ≤ 0.44) based on O'Brien and Fleming criteria, the study will be recommended for trial termination for efficacy and futility reasons (shown in Appendix 5.7). The number and percentage of participants with the composite endpoint at day 15 will be summarized and compared using Pearson χ^2 test (Table 3.9.1a) using SAS PROC FREQ. For

logistic regression analysis, if the coefficient for treatment effect is significant (i.e., the confidence interval for the odds ratio does not include 1), then the null hypothesis will be rejected. The significant level for each covariate coefficient in the model will best determined by Wald test (Table 3.9.1b) using SAS RPOC LOGISTIC. The analysis will be done in the ITT population. The detailed analysis is described in the primary endpoint analysis in the section 3.7.1.

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5.0 APPENDICES

APPENDIX 5.1 7-category Ordinal Scale of Clinical Status of Hospitalized Influenza Patients

1: Not hospitalized with resumption of normal activities.

2: Not hospitalized, but unable to resume normal activities,

3: Hospitalization, not requiring supplemental oxygen.

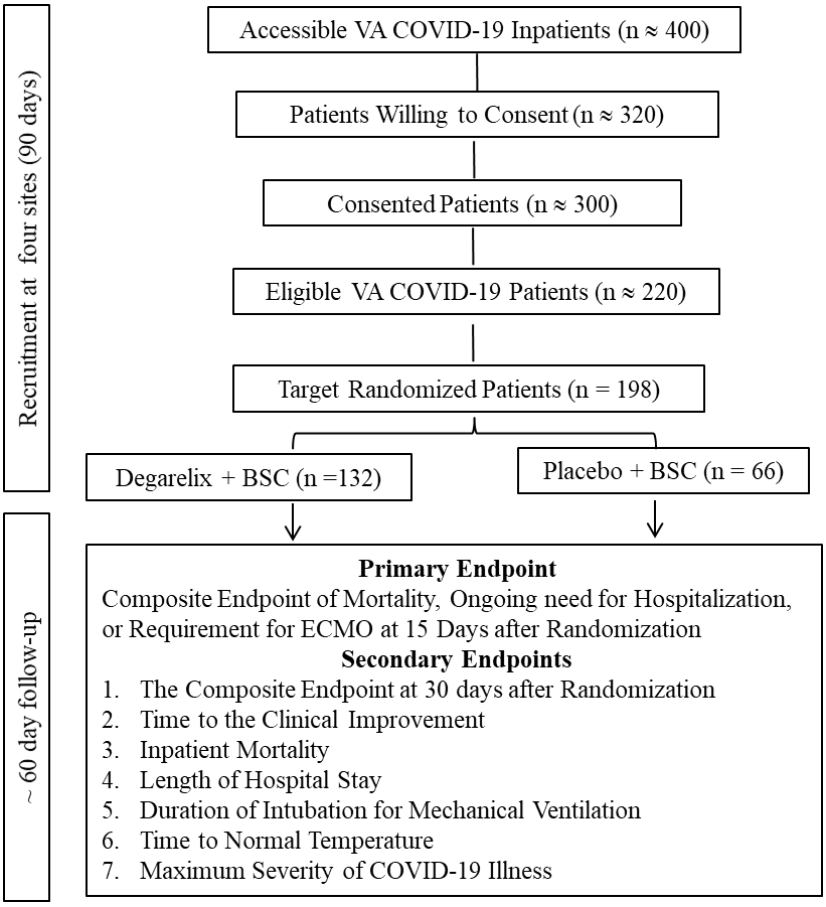
4: Hospitalization, requiring supplemental oxygen.

5: Hospitalization, requiring nasal high-flow oxygen therapy and/or noninvasive mechanical ventilation.

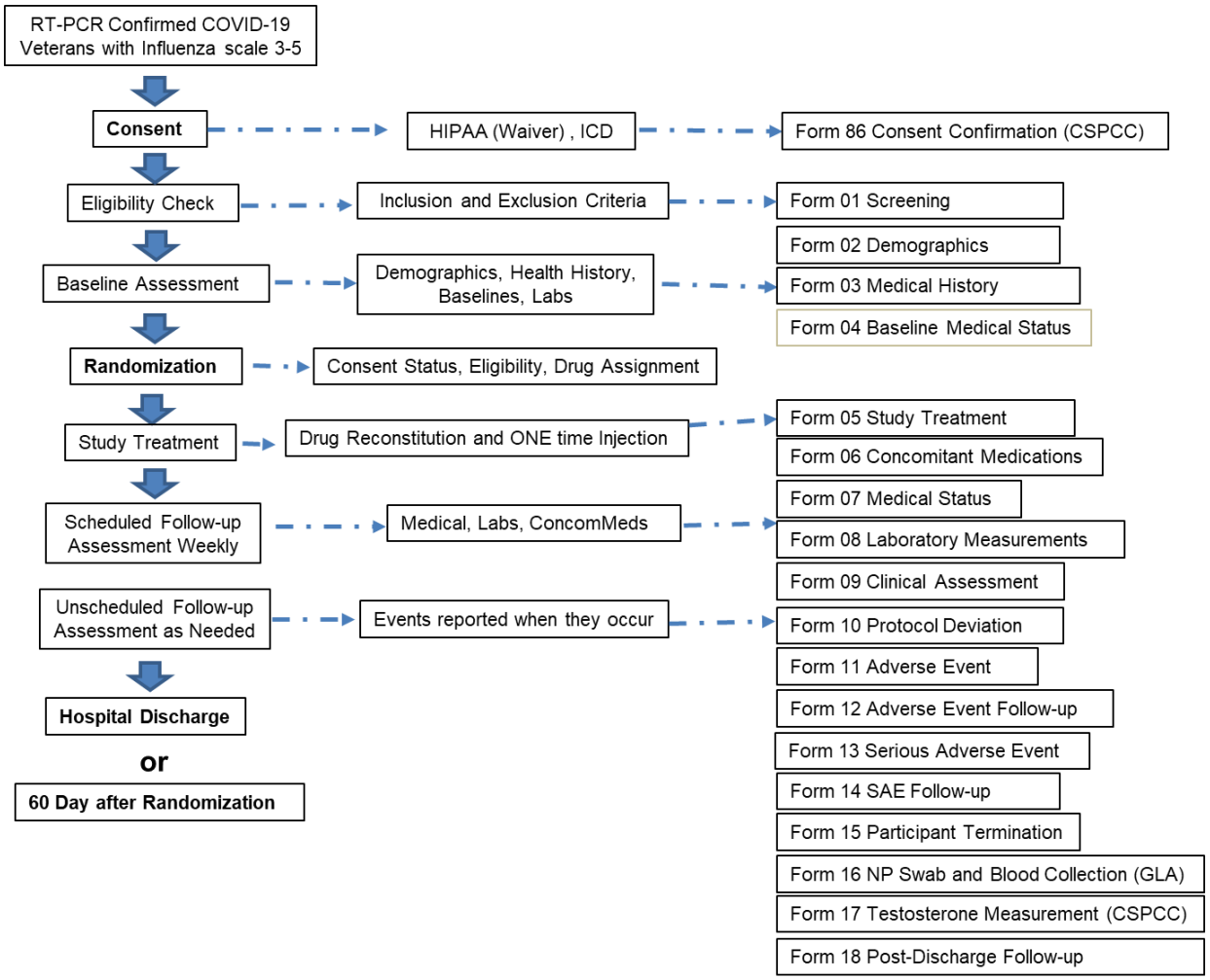
6: Hospitalization, requiring extracorporeal membrane oxygenation and/or invasive mechanical ventilation.

7: Death.

Appendix 5.2 Study Flow



Appendix 5.3.1 Data Collection Schema



Appendix 5.3.2 Data Collection Schedule

Form #	Form Name	Visit 00 (Screening / Baseline)	Visit 01 (Randomization / Day 1)	Visit 01 (Assessments 02 07)	Visit 02 (Day 8)	Visit 02 (Assessments 02-07)	Visit 03 (Day 15)	Visit 03 (Assessments 02-07)	Visit 04 (Day 22)	Visit 04 (Assessments 02-07)	Visit 05 (Day 30)	Visit 06 (Day 37)	Visit 07 (Day 44)	Visit 08 (Day 51)	Visit 09 (Day 60)	Visit 10-17 (if patient is still hospitalized complete weekly until discharge)
1	Screening and Randomization	R														
2	Demographics	R														
3	Medical History	R														
4	Baseline Medical Status	R														
5	Study Treatment		R													
6	Concomitant Medication Log	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
7	Medical Status				R		RH		RH		RH	RH	RH	RH	RH	RH
8	Laboratory Measures	R	R		R		RH		RH		RH					
9	Ordinal Scale of Clinical Status**	R	R	A	R	A	RH	A	RH	A	RH	RH	RH	RH	RH	RH
10	Protocol Deviation	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
11	Adverse Event	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
12	AE Follow-up	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
13	Serious Adverse Event	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
14	SAE Follow-up	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
15	Participant Termination		A	A	A	A	A	A	A	A	A	A	A	A	A	A
16	Research Blood and Nasal Swab Collection (GLA)										RH					
17	Total Testosterone Measurement (CSP completion)										R					
18	Post Discharge Follow-up										RD				RD	

R = Required

RH=Required if patient is still hospitalized (i.e. until discharge is noted on Form 07).

RD=Required if patient was discharged

A = As needed

**Ordinal Scale of Clinical Status will be completed at screening, day 1 and whenever a status change occurs in the patient, but no less than 1x week.

APPENDIX 5.4 CTCAE v5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 5.5 Power Analysis

Effect Size	Treatment Arms	Testing Power		
		80 %	85 %	90 %
30 %	Degarelix + BSC	186	210	244
	Placebo + BSC	93	105	122
	Total	279	315	366
42%	Degarelix + BSC	96	108	124
	Placebo + BSC	48	54	62
	Total	144	162	186
50%	Degarelix + BSC	64	72	84
	Placebo + BSC	32	36	42
	Total	96	108	126

Sample Size: 186 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease 42% of the composite endpoint in the degarelix treatment group compared to the placebo treatment group. Assume 5% attrition rate, then the sample size would be 198 (i.e. 132 in the treatment group, 66 in the control group) to maintain 90% testing power

Appendix 5.6 Efficacy Analysis Schema

Endpoint Analyses	Statistical Methods	SAS Procedures
Primary Endpoint A composite endpoint of mortality, hospital stay rate, and ECMO or mechanical intubation at 15 days after randomization	Pearson Chi-square tests or Fisher exact tests Logistic regression adjusted for Age, Hypertension, and COPD	. PROC FREQ PROC LOGISTC
Secondary Endpoints 1. A composite endpoint of mortality, hospital stay rate, and ECMO or mechanical intubation at 30 days after randomization 2. Time to the clinical improvement 3. Inpatient Mortality 4. Length of Hospital Stay 5. Duration of Intubation for Mechanical Ventilation 6. Time to Normal Temperature 7. Maximum Severity of COVID-19 Illness	1. Pearson Chi-square tests or Fisher exact tests Logistic regression adjusted for Age, Hypertension, and COPD 2. Log-rank test, Kaplan-Meier curves Cox regression adjusted for Age, Hypertension, and COPD 3. Pearson Chi-square tests or Fisher exact tests Logistic regression adjusted for Age, Hypertension, and COPD 4. Wilcoxon test; quantile regression 5. Wilcoxon test; Quantile regression 6. Log-rank test, Kaplan-Meier curves Cox regression adjusted for Age, Hypertension, and COPD 7. Pearson Chi-square test; Cochran–Armitage trend test Proportional odds logistic regression	1. PROC FREQ PROC LOGISTC 2. PROC LIFETEST PROC PHREG 3. PROC FREQ PROC GENMOD 4.5.PROC NPAR1WAY PROC QUANTREG 6. PROC LIFETEST PROC PHREG 7. PROC FREQ PROC LOGISTC
Exploratory Analyses Clinical Prognostic Factors Laboratory Prognostic Factors Viral Load Cytokines Levels and TMPRSS2 Expression Germline genomic factors	1. Time to event data Log-rank tests, Kaplan-Meier curves and Cox regressions 2. Categorical data Pearson Chi-square tests and Logistic regression 3. Interval data Student t / Wilcoxon tests, linear or quantile regressions 4. Longitudinal data Mixed-effect model repeated measure	1. PROC LIFETEST PROC PHREG 2. PROC FREQ PROC LOGISTC 3. PROC TTEST PROC NPAR1WAY 4. PROC Mixed
AE/SAE Analyses 1. Incidence of AE/SAE 2. Frequency Difference of AE and SAE 3. AE /SAE by Relationship to the Treatment 4. AE/SAE leading to premature discontinuation	For All AE/SAE Incidence rate estimation and testing Pearson Chi-square tests or Fisher exact tests	 PROC FREQ SAS Macros
Other Analyses 1. Demographics and Baseline Characteristics 2. Disposition Status 3. Study Protocol Adherence 4. Site Effect	1. Student t or Wilcoxon tests, Pearson Chi-square or Fisher Exact Tests 2. Pearson Chi-square Tests 3. Pearson Chi-square Tests 4. Pearson Chi-square Tests, Student t or Wilcoxon tests, log-rank test	1. PROC TTEST, PROC FREQ, PROC NPAR1WAY 2. PROC FREQ 3. PROC FREQ 4. PROC FREQ PROC LIFETEST PROC NPAR1WAY

Appendix 5.7 Interim Analysis Boundary