Phase 2/3 Study of Upamostat, a Serine Protease Inhibitor, or Placebo for Treatment of COVID-19 Disease

Protocol RHB-107-01

NCT number 04723537

Amendment 4: 15 June 2021

Phase 2/3 Study of Upamostat, a Serine Protease Inhibitor, or Placebo for Treatment of COVID-19 Disease

Protocol RHB-107-01

Sponsor: RedHill Biopharma Ltd.
21 Ha'arba'a St.
Tel-Aviv 64739, Israel
Tel: +972 (0)3 541 3131
Fax: +972 (0)3 541 3144

EudraCT number 2021-002036-22

Original Protocol Date: 13 October 2020

Current Protocol Version: Amendment 4: 15 June 2021

Previous Versions: Amendment 3: 8 March 2021

Amendment 2: 4 February 2021

Amendment 1: 8 December 2020

Table of Contents

Approvals

Sponsor Representatives

_____ 15 June 2021
Reza Fathi, PhD Date
Senior Vice President, Research and Development
RedHill Biopharma Ltd.

_____ 15 June 2021
Terry Plasse, MD Date
Medical Monitor

Approvals

The investigator agrees to conduct the trial as described in the protocol in accordance with all FDA regulations, and according to current ICH GCP.

By agreement to this protocol, the investigator agrees to allow direct access to all essential documents, including source documents to authorized individuals representing the sponsor (including monitors, auditors and other personnel), to institutional review boards (IRBs) and to regulatory authorities.

Principal Investigator:

_____ _____

Name Date

_____

Signature

Protocol Synopsis

Title: Phase 2/3 Study of Upamostat, a Serine Protease Inhibitor, or Placebo for Treatment of COVID-19 Disease

Study drugs: upamostat (RHB-107)

Comparator: placebo

Brief Summary:

This is a 2-part, multicenter, Phase 2/3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of upamostat in adult patients with COVID-19 disease. The primary objective at the end of part A, after 60 patients have completed the study (defined in Section 4.5), is dose selection. An analysis of part A will be performed by a data safety monitoring board (DSMB) who will determine, based primarily on safety results, if the study should proceed to part B and, if so, which dose to proceed with. For part B, the primary endpoint is time to sustained recovery from illness in the entire study population and the first secondary endpoint is incidence of hospitalization or death during the eight-week study period among the high risk patients. The target sample size in part B will be determined at the end of part A but will be at least 250 patients. An interim analysis for adjustment of criteria for high risk, early termination for futility or increase in sample size (to an additional 50% of the initially planned total) will be performed after approximately half of the initially planned patient population has reached end of study; the timing of the interim analysis may also be adjusted at the end of part A.

Rationale:

COVID-19 is a disease caused by a recently discovered coronavirus, designated SARS-CoV-2. It is highly contagious and generally causes fever and respiratory symptoms in symptomatic individuals; additional symptoms are gastrointestinal, cardiac, taste and smell abnormalities, and neurological. The disease spectrum varies from asymptomatic infection through fatal pneumonia and multiorgan failure. Males, older adults and individuals with significant comorbidities, including respiratory diseases, diabetes, obesity and cancer under treatment, are most severely affected.

One medication, remdesivir, has shown efficacy in treatment of COVID-19 in hospitalized patients with severe illness; several monoclonal antibody combinations have demonstrated preliminary evidence of efficacy in the outpatient setting as well. Based on CDC data (CDC, 2020), fewer than 10% of COVID-19 patients are hospitalized. Therefore, an oral, room temperature stable, easily administered medication for treatment of COVID-19 is a major unmet medical need and can be used for both inpatients and outpatients.

Upamostat, a serine protease inhibitor, is a potent inhibitor of trypsin and trypsin-related enzymes.

Several serine proteases, including TMPRSS isoenzymes, which are related to trypsin, are required for attachment of coronavirus particles to host cells. In

addition, trypsin plays a role in tissue damage due to various types of pneumonia as well as gastrointestinal tract irritation, so inhibition of trypsin may decrease pulmonary damage and gastrointestinal symptomatology caused by infections of various etiologies.

In vitro studies in two systems have demonstrated the activity of upamostat against SARS-CoV-2. Entry of vesicular stomatitis virus (VSV) transfected with SARS-CoV-2 S-protein in Calu-3 cells, which express TMPRSS2, was inhibited by upamostat. An in vitro assessment in an organotypic air-liquid-interface (ALI) culture of human primary bronchial epithelial cells (HBEC; EpiAirway™, MatTek) evaluated whether infection and spread of SARS-CoV-2 could be inhibited by several agents. Upamostat at concentrations below that which is pharmacologically achievable inhibited virus growth by several orders of magnitude, somewhat more than camostat, another serine protease inhibitor which has previously demonstrated in vitro activity against SARS-CoV-2 (data on file for both studies, RedHill Biopharma). Thus, based on two in vitro studies, upamostat appears to be a potent inhibitor of SARS-CoV-2 at nontoxic levels.

Enabling toxicology studies for nononcologic indications have been performed. Upamostat has been administered to 189 individuals, both healthy volunteers and cancer patients, with a very favorable safety profile.

Many agents are being tested in hospitalized patients with SARS-CoV-2 infection. However relatively few studies are currently under way to treat symptomatic outpatients, although these patients constitute the majority of COVID-19 patients, infect others and may progress to pneumonia.

This study will assess the activity of upamostat against placebo for treatment of COVID-19 patients who, in the investigator's judgment, do not require hospitalization.

Objectives:

Primary:

Part A of the study: determination of the safety and tolerability of two dose levels and selection of an upamostat dose for part B.

Part B of the study:

Primary objective:

In the entire patient population: comparison between upamostat and placebo in time to sustained recovery from symptomatic illness. A patient will be considered to have recovered once he or she meets the following criteria:

1) is afebrile (<38.0° C core temperature) for at least 48 hours without use of antipyretics;
2) all symptoms have resolved or returned to pre-illness levels (e.g., if patient had respiratory compromise prior to the onset of COVID-19), except for:

a. fatigue, anosmia, ageusia or dysgeusia, which may be persistent at level similar to that during the acute illness, i.e., the same level per symptom questionnaire;
b. chest pain, cough or dyspnea which if persistent must be at least one grade lower than at the start of treatment and no worse than grade 1 (mild).

Sustained recovery is recovery, per above definition, maintained for at least 14 or 28 days, or through end of study, whichever comes first. The period required to confirm sustained recovery, 14 versus 28 days, will be assessed in part A of the study and a decision reached as to which period to use for definition of sustained recovery in part B.

Symptoms to be followed and their grading are given in Appendix 2, Patient Diary.

Secondary:

Comparison between active treatment group and placebo of:

1) Hospitalization or death from any cause by end of study, i.e, day 57.
2) In part A and at the interim analysis in part B, assessment of the risk of hospitalization or death as a function of the presence, number and severity of concerning conditions will be undertaken. This information may be used to develop a definition of very high risk for calculation of the incidence of hospitalization or death in the high risk/very high risk population in part B.
3) Proportion of patients who are PCR-negative at days 8, 15, 29 and 57 from the start of treatment (landmark analyses);
4) Time to resolution of individual disease-related symptoms present at baseline;
5) Development of new disease-related symptoms and/or pneumonia on study;
6) Changes in laboratory markers of disease severity, i.e., oxygen saturation, CRP, lymphocyte count, cardiac troponin, ferritin and D-dimer levels, from baseline to time points at which these are measured on study;
7) Adverse events.

In addition to analysis within the entire study population, subgroup analyses for secondary endpoints 1, 3-6 will be performed in the high risk population. Analysis for secondary endpoint 1 will focus primarily on the high risk and very high risk subgroups.

Exploratory

1) Percent of patients who report household contacts who have developed symptomatic, PCR- or antigen-confirmed COVID-19 by day 57;
2) Levels of serum IgM and IgG antibodies to SARS-CoV-2 at 57days from the start of treatment.

Population:

Inclusion criteria:

1. Patients with symptomatic, diagnostically confirmed COVID-19, per RT-PCR or antigen assay of respiratory tract sample.
2. Patient must have either become symptomatic or found positive by RT-PCR or antigen assay within 5 days, whichever is greater, of randomization.
3. Patients must have at least two symptoms of at least moderate severity on initial questionnaire. Fatigue, anosmia, ageusia or dysgeusia may not be counted among the symptoms of at least moderate severity qualifying the patient for entry.

   Note: patients should NOT be informed prior to completion of the questionnaire that presence of at least 2 symptoms of at least moderate severity is a criterion for study entry.
4. Males and females ≥age 18 years.
5. Oxygen saturation by pulse oximeter ≥92% on room air.
6. Negative urine or serum pregnancy test (if woman of childbearing potential).
7. Females of childbearing potential and males with female partners of childbearing potential must agree to use acceptable contraceptive methods during the study and for at least two months after the last dose of study medication.
8. Ability to complete the daily diary independently
9. The patient must give informed consent.

Exclusion criteria:

1. Patient is in need of acute hospitalization per clinician assessment.
2. Pregnant or nursing women.
3. Unwillingness or inability to comply with procedures required in this protocol.
4. Patient requires supplemental oxygen.

5. Patient is currently receiving, has received within the past 7 days or is expected to receive during the course of the study remdesivir, or other specific antiviral or anticytokine therapy for COVID-19, other than therapeutic monoclonal antibodies allowed or approved in the region in which the patient lives, or systemic corticosteroid equivalent to ≥20 mg daily prednisone/3 mg dexamethasone daily.
6. Patient is currently receiving or has received within 30 days prior to screening any other investigational agent for any indication, including approved agents given for investigational indications (e.g., anti-cytokine treatments).
7. Patient is currently taking or is expected to start taking warfarin, apixabain (Eliquis), or rivaroxaban (Xarelto). Patients may be taking or start on study dabigatran (Pradaxa), standard or low molecular weight heparin.

Design:

This is a randomized, double-blind, placebo-controlled, parallel group study of upamostat compared to placebo in patients with symptomatic COVID-19 who do not require immediate treatment with specific approved (either fully approved or available under emergency use authorization) antiviral or anticytokine therapy, other than therapeutic monoclonal antibodies. The study uses phase 2/3 operationally seamless design methodology for dose selection (part A) and inferentially independent confirmatory phase 3 study (part B). The phase 3 portion will include an interim analysis for revision of the high risk/very high risk subgroup definition, early termination for futility or increase in sample size, as indicated by initial results.

Methodology:

Part A: After qualification for study, patients will be stratified by age, <65 or ≥65, and randomized to treatment as described below. They will then be randomized 1:1:1 to one of the following treatment groups:

1. Upamostat 200 mg two capsules qd (n=20);
2. Upamostat 200 mg one capsule and matching placebo one capsule qd (n=20)
3. Placebo two capsules qd (n=20).

In order to maintain blinding, patients will be given two bottles of medication and instructed to take one pill from each bottle each day. Both pills are to be taken at the same time.

Medication should be taken with water and may be taken with or without food.

Patients are to take medication for 14 days or until one of the following occurs:

- Adverse events, whether related or unrelated to study medication which, in the judgement of the investigator, necessitate discontinuation of treatment;
- The patient or investigator decides that it is in the patient's best interest to stop treatment.

An analysis will be performed by a data safety monitoring board (DSMB) after a total of 60 patients complete part A of the study.

- If the DSMB determines that safety of both regimens is similar, accrual in part B will proceed with the 400 mg qd dose.
- If safety is more favorable with the 200 mg qd regimen, accrual in part B will proceed with the 200 mg qd dose.

The DSMB process is further defined in the body of the protocol and will be detailed in a separate DSMB charter. While the DSMB will perform the evaluation at the end of part A independent of the Sponsor, the results will be provided when available in open label fashion to the Sponsor.

Part B: Based on safety results from part A, either a 200 mg or 400 mg (i.e., one or two 200 mg capsules) treatment regimen will be selected. Patients enrolled in part B will be stratified by

- Presence of one or more high risk characteristics:
  - Age ≥65
  - Hypertension
  - Chronic lung disease (for example, chronic obstructive pulmonary disease, moderate-severe asthma, interstitial lung disease, cystic fibrosis and pulmonary hypertension)
  - Diabetes
  - Obesity (BMI≥30)
  - Cardiovascular disease (including congenital heart disease, coronary artery disease, history of thrombotic events, including stroke and transient ischemic attacks [TIA])
  - Chronic renal disease
  - Immunosuppressive disease or immunosuppressive treatment
  - Sickle cell disease
  - Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
  - Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))
- Planned receipt of therapeutic monoclonal antibody treatment for COVID-19 (whether or not patient has already received the antibody infusion);
- Region in which they are treated; and
- Whether or not the patient is at least 14 days after his or her last dose of COVID-19 vaccine

They will then be randomized 3:2 to active drug or placebo at the schedule selected based on part A. A total of at least 250 patients will be enrolled in part B of the study, at least 150 receiving active drug and at least 100 receiving placebo. Thus, combining both parts of the study, at least 170 patients will receive active drug at the dose selected in part A and at least 120 will receive placebo. However, analyses will be performed independently for parts A and B.

Based on analyses of outcomes at the end of part A and an interim analysis during part B, the risk categories may be adjusted, and the requirements for enrollment may be modified, e.g., a certain percentage of patients may be required to have at least one risk factor and/or some specific combination or number of risk factors.

Patients will complete questionnaires about symptoms, including adverse events, vital signs, including temperature and pulse oximetry, and a log of medications taken, according to the schedule in Table 1. Viral swabs and bloods for safety laboratory and pharmacodynamic markers (where available) will be obtained at home or clinic visits by medical personnel per the schedule in Table 1.

After completion of treatment, patients will be followed through day 57 from the start of treatment.

Study evaluations are shown in Table 1, below.

Endpoints:

Efficacy:

The primary objective of part A is to determine which treatment regimen to carry into part B, which will be based on safety rather than efficacy. However, all parameters to be followed in part B will also be followed in part A. Time to sustained recovery and the proportion of patients who are hospitalized or die will be calculated, although given the small sample size and expected variability of outcome, clinically meaningful differences are unlikely.

The primary endpoint of part B of the study is, for all patients, time to sustained recovery from COVID-19 illness, as defined in the primary objective, above.

The first secondary endpoint is hospitalization or death from any cause by end of study. Analysis of this endpoint will focus primarily on the high risk or very high risk subgroups.

Additional secondary endpoints include:

1) Proportion of patients with PCR-negative viral swabs at the times tested, i.e., days 8, 15, 29 and 57 from the start of treatment;
2) Time to resolution of individual disease-related symptoms present at baseline;
3) Development of new disease-related symptoms or pneumonia on study;
4) Changes in laboratory markers of disease severity, e.g., oxygen saturation, CRP, lymphocyte count and D-dimer levels, from baseline to time points at which these are measured on study;

Exploratory endpoints

1) Percent of patients who have household contacts who have developed symptomatic, PCR-confirmed COVID-19 by day 57;
2) Levels of anti-SARS-CoV-2 serum IgM and IgG at day 57.

Safety:

Patients will be followed for adverse events, including both clinical and laboratory events, throughout the course of the study.

In particular, toxicities resulting in dose reductions or discontinuation of therapy will be followed and tabulated.

Statistics:

In part A of this study, two dose levels of active drug and placebo will be tested. Based on the incidence and severity of toxicities in each active group, overall assessment of safety by the DSMB, a regimen for part B of the study will be selected. In the absence of marked differences in toxicity between the two active

groups, the default choice for continuation into part B will be the 400 mg daily regimen.

Efficacy data from parts A and B will be analyzed separately.

The part B sample size may be expanded and the definition of high risk revised based on interim study results. At the end of part A, along with determination of the dose to take into part B and assessment of risk of various factors, RedHill will make a determination regarding whether to pursue the hospitalization/death endpoint, which is needed for consideration for EUA, or continue the study as originally planned, for consideration for NDA, should results warrant. This decision will be based both on results of part A of the study and the clinical situation at that time.

The sample size currently planned, 250 patients, was determined based on the primary endpoint, time to sustained recovery from COVID-19 illness, as defined in the primary objective. It was calculated that in order to detect an hazard ratio=1.5 comparing an active group to placebo group with 3:2 allocation ratio a total of 201 recovery events are required, to provide 80% power using a log-rank test at a two-sided significance level of 0.05. Assuming 80% sustained recovery rate by end of follow-up (assumed equal follow-up for all enrolled patients), the minimum number of patients enrolled in part B to achieve the primary objective will be 250 in total, 150 in the active arm on the regimen taken into part B of the study and 100 in the placebo arm. If a decision is made to power the study for the hospitalization/death endpoint, the protocol will be amended to include the sample size and the rationale for its determination.

Further information on statistical considerations is provided in section 7 of this protocol and detailed in the statistical analysis plan (SAP).

Schedule of Evaluations

Table 1. Study Procedures and Schedule of Events

Activity	BL	Rx Week 1		Rx Week 2	EOT[a]	Follow-up			EOS[b]
Day/window		1	3+1	8±2	15±2	22±4	29±4	43±4	57±4
Contact[c]	F		T	H/F	H/F	T	H/F	T	F
Initial procedures[d]	X								
Physical examination inc VS[e]	X			X	X		X		X
Temperature[f]		Measure and record temperature three times daily until afebrile for 14 days, then once daily in the evening until afebrile for 28 days							
Pulse oximetry[f]	X	Twice daily through day 15				Thrice weekly through day 29			
Weight	X								X
Questionnaire and diary	X	Every evening days 2-28; days 1, 3, 5 weekly thereafter[g]							
ECG[h]	X			X	X		X		
Nasal mid-turbinate (NMT) swab for SAR-CoV-2 PCR[i]	X			X	X		X		X
CBC, biochem profile[j], D-dimer, INR, PTT	X			X	X		X		X
CRP, D-dimer, troponin, ferritin	X			X	X		X		X
Serum IgG and IgM antibodies to SARS-CoV-2	X							C	X
Alpha-1-antitrypsin and G6PD testing								C[k]	X[k]
Study medication		<----------→							
Adverse events[l]			X	X	X	X	X	X	X
Concomitant medications[l]	X		X	X	X	X	X	X	X

Abbreviations: BL: Baseline; EOS: end of study; EOT: end of treatment

[a]End of treatment visit, regardless of actual study day. Should generally be day 15, the day AFTER last dose of study medication.

[b]End of study visit: generally day 57±4 from start of treatment, regardless of duration of treatment. If patient discontinues study participation prior to then, end of study procedures should be carried out, if possible, at the time of discontinuation from study, even if earlier than day 53.

[c]Type of contact/location: F: in facility: emergency department, clinic, COVID-19 special facility; H: home visit; H/F: option for either home or facility visit; T: televisit, either phone or video. Note: additional televisits may be arranged as needed. If patient returns to medical facility for outpatient visit, if possible, relevant procedures and tests should be performed at that time.

At all clinic and home health visits, temperature, pulse, respiratory rate, blood pressure, pulse oximetry and ECG measurements will be performed. Home health staff will obtain all vital signs independently of patient measurements, to verify that data are being collected accurately.

[d]Within 3 days prior to planned start of treatment: initial procedures include signing informed consent, review of medical history, review of documentation of COVID-19 disease and source/exposure, if available, height (measured or per patient), pregnancy test for women of childbearing potential, as detailed in section 5.2. When feasible, BL and day 1 procedures, i.e., start of treatment, should be completed on the same day.

[e]Physical examination: physical examination of pertinent systems at baseline, then interim examinations on day 1 of week 2, within 72 h of discontinuation of study medication, study day 29 and within last week of follow-up period. Baseline physical is mandatory for study participation. At each physical examination, a full set of vital signs (temperature, pulse, respiratory rate, blood pressure, and oxygen saturation) will be obtained by the examiner. If one or more on-study visits is not feasible, document in CRF.

[f]The patient will be provided with an electronic thermometer and instructed to measure and record temperature three times daily until afebrile (<38.0°C) for 14 days. Temperature should be measured within an hour of getting up in the morning, between 4-7 pm and within an hour of bedtime each day. Additional temperature readings may be taken at patient initiative or at the instruction of the investigator.

Oxygen saturation will be measured by patients twice daily for the first 2 weeks of study and then three times weekly for the next two weeks. During the first two weeks of study, oxygen saturation should be measured within an hour of arising and within an hour of bedtime, in coordination with the morning and evening temperature readings. After that, oxygen saturation should be measured in the evening, at the time of the evening temperature reading if temperature is still being measured or at the time the patient completes the symptom questionnaire. Additional pulse oximetry readings may be performed at the request of the investigator.

[g]When baseline day = day 1, the patient should not repeat the questionnaire in the evening that day. After day 28 of the study, if a patient does not complete the questionnaire on an assigned day (days 1, 3 and 5 of each week), he or she should complete it during the usual timeframe, 7:00-11:59 pm, on the following day.

[h]Electrocardiogram: full 12-lead ECG at baseline visit. At baseline visit and additional days noted, 6-lead ECG is to be performed, either by clinic or home health staff.

[i]Swab at baseline (confirmatory of pre-study test, if a prior swab obtained). At baseline, a rapid PCR or antigen test for diagnosis will be performed on site (if PCR or antigen has not been obtained within 5 days of planned start of treatment), and a quantitative PCR, the same as will be used on other study days, also taken and sent to the central laboratory. Then days 8, 15, 29 and 57. Procedure shown in Appendix 1. The baseline specimen will also be sequenced.

[i]Biochemistry profile to include, at a minimum, albumin, alkaline phosphatase, ALT, AST, bilirubin (total). Bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, sodium, and total protein.

[k]Tests for serum alpha-1-antitrypsin level and whole blood glucose-6-phosphate dehydrogenase (G6PD) deficiency, both to be taken at the day 57 visit only, are optional and will require a separate consent (C), which should be obtained at the day 43 telemedicine visit.

[l]Adverse events and concomitant medications will be recorded by the patient or caregiver daily (first 4 weeks) or d1, 3 and 5 each week (weeks 5-8) in their diary. These will be reviewed at each home or clinic visit or televisit and entered by study staff in the appropriate eCRF forms.

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BL	Baseline
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CBC	Complete Blood Count
CC50	Cytotoxic Concentration of 50%
CDC	United States Centers for Disease Control
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRP	C-reactive protein
CXR	Chest X-ray
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC50	50% Effective (Virus-Inhibitory)
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G6PD	Glucose 6-Phosphate Dehydrogenase
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board
K_i	Inhibitory Constant
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Authorities
mITT	modified Intent-to-Treat

NDA	New Drug Application
PA	Posterior Anterior
PCR	Polymerase Chain Reaction
PP	Per Protocol
PTT	Partial Thromboplastin Time
QD	Quaque Die (Latin), once a day
RT-PCR	Reverse Transcription Polymerase Chain Reaction
S-Protein	Spike Protein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARA-Cov-19	Severe Acute Respiratory Syndrome Coronavirus 2
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SUSAR	suspected unexpected serious adverse reaction
TMPRSS	Transmembrane protease, serine
TMPRSS2	Transmembrane protease, serine 2
ubSSR	Unblinded Comparative Size Re-Estimation
ULN	Upper Limit of Normal
VSV	vesicular stomatitis virus
WHO	World Health Organization

1. Background and Rationale

1.1 COVID-19 Disease

COVID-19 is a disease caused by a coronavirus, SARS-CoV-2. The disease was first noted in December 2019, in Wuhan, China, and subsequently attributed to a virus similar to the SARS coronavirus and now designated SARS-CoV-2. The clinical spectrum of SAR-CoV-2 infection ranges from asymptomatic infection to fatal pneumonia and multiorgan failure (Zhou et al, 2020). Many organ systems, including prominently gastrointestinal and neurological, as well as cardiorespiratory, may be affected. Infected individuals may be infectious for one to three days before onset of symptoms; up to half of new cases may be transmitted during that asymptomatic period (Gandhi et al, 2020). Common symptoms, with their incidence on presentation in the 191 patients in the initially reported severe Wuhan cohort were fever (94%), cough (79%), sputum production and fatigue (each 23%) and myalgia (15%). Bilateral pulmonary infiltrates were noted in 75% of patients on chest X-ray. In many patients, the illness is quite mild, with only a mild sore throat or upper respiratory tract symptoms, without fever.

In a large series from China, 81% of patients diagnosed with COVID-19 disease had mild cases (Wu and McGoogan, 2020). Over the past year, information on milder COVID-19 disease has been obtained (Ghandi et al, 2020; Han et al, 2020). Han and colleagues noted in particular that a large group of patients with mild COVID-19 disease has only gastrointestinal symptoms or a combination of gastrointestinal and mild pulmonary symptoms. Thus, the majority of patients have mild disease, and the spectrum of abnormalities appears to be different from that of severe COVID-19. Data from the Centers for Disease Control (CDC) show that as of mid-September, 2020, the overall incidence of confirmed or probable SARS-CoV-2 infection was approximately 2,000 per 100,000 population in the US; the overall incidence of hospitalization was 170 per 100,000. Thus, the hospitalization rate is under 10% of all confirmed and probable cases, i.e., the vast majority of COVID-19 patients are not hospitalized (CDC COVID Data Tracker).

People over age 65 and those with significant comorbidities, such as diabetes, obesity, or pulmonary disease, are more susceptible to severe infection, require hospitalization and have a higher mortality rate than do younger, otherwise healthy individuals. Men have an approximately 60% higher hospitalization or death rate than women (Williamson et al, 2020; van Gerwen et al, 2021)

For most people, the disease is self-limited. Many patients with relatively mild-moderate symptoms have now been diagnosed based on PCR as having SARS-CoV-2 infection. The majority of patients with COVID-19 symptoms are told to self-isolate, rest, and take symptomatic medications. But a major danger of the disease is spread through a generally nonimmune population, with infection of those who are at risk of severe infection. SARS-CoV-2 is highly contagious, with spread by aerosol and surface contact (van Doremalen et al, 2020) and potentially through stool (Wang et al, 2020). As the disease was first noted about a year and a half ago and testing and interpretation of data take some time, the clinical picture is still evolving. To date, no oral medication has demonstrated efficacy against SARS-CoV-2 infection of any severity. Monoclonal antibody combinations directed against the virus have shown preliminary evidence of efficacy in outpatient studies. However, certain SARS-CoV-2 strains have demonstrated resistance to some of the antibodies. In addition, these antibodies are

not available in many areas and, when available, are not always well accepted by patients. Thus, an effective, low toxicity oral medication will fulfill a major unmet medical need.

1.2 Upamostat

Upamostat, WX-671, is an orally bioavailable prodrug of WX-UK1, a serine protease inhibitor which inhibits several proteases in families which are involved in cleavage of the S-protein of coronaviruses. Cleavage of viral S-protein is important for viral binding and subsequent entry into host cells (Abe et al, 2013; Bertram et al, 2011; Zmora et al, 2018). In particular, WX-UK1 inhibits trypsin isoenzymes with Ki's of 19-190 nM, and several other related enzymes with Ki's under 1 μM (Oldenburg et al, 2018). In addition, trypsin and other enzymes are upregulated in inflammatory lung conditions (Tsujimura et al, 2005; Yamada et al, 2006). Inhibiting these serine proteases may, in addition to a direct antiviral effect, also decrease tissue damage from the virus.

Two in vitro studies have demonstrated that upamostat inhibits SARS-CoV-2 infection (data on file, RedHill Biopharma, Ltd).

Upamostat inhibited entry of vesicular stomatitis virus transduced with the SARS-CoV-2 spike protein (VSVpp+SARS-2-S Δ18). When tested against VSVpp+SARS-2-S Δ18 in Calu3 cells, which have surface TMPRSS2, upamostat showed moderate inhibitory activity, though somewhat less than camostat, another serine protease inhibitor. Interestingly, when tested in Vero76 cells, which do not express surface TMPRSS2, moderate activity was still noted; camostat was inactive in this situation. Upamostat also had similar activity in native VSV infecting Calu3 cells as they did against S-protein transfected VSV. Again, in this setting camostat was inactive. All three compounds were inactive against native VSV infection in Vero76 cells. These results demonstrate activity and suggest that the activity may not be due solely to TMPRSS2. Due to the nature of the model, specific extrapolation to actual in vitro or in vivo inhibitory concentrations is not possible.

Upamostat was studied in a tissue culture model of primary human bronchial epithelial cells (HBEC; EpiAirway™ , MatTek). Camostat was included for comparison and remdesivir was included as a positive control (Pruijssers et al., 2020).. A 3-log reduction in TCID50 was noted at the lowest concentration of upamostat tested, 0.12 μg/mL, rising to 4.5-log reduction at 1 μg/mL. Cytopathic effects were noted only at 30 μg/mL. At equal concentrations, the virus inhibitory effect of upamostat was somewhat greater than that of camostat, while the cytopathic effects were similar for both compounds.

Upamostat has been studied in 40 healthy volunteers and 152 cancer patients in phase 1 and phase 2 studies. Once daily dosing with 200 or 400 mg daily upamostat resulted in WX-UK1 tissue levels ≥0.6 μM (0.4 μg/gm tissue) in most patients and ≥1.0 μM (0.67 μg/gm tissue) in 6 of 10 patients studied (Meyer et al, 2008). Several-fold higher levels of WX-UK1 were found in stool after single doses of upamostat, which may be important given the possible fecal excretion of the virus. The drug was very well tolerated as a single agent and in combination with cytotoxic agents. In a multidose phase 1 study in healthy volunteers, upamostat caused some increases in transaminases, but not to a level to be considered problematic per Hy's law, nor were there changes in bilirubin. In addition, there was no dose-response relationship. In randomized phase 2 studies in cancer patients, in which all patients received a standard agent (either capecitabine or

gemcitabine) in combination with upamostat or control/placebo, there was no transaminase safety signal. Grade 3 or 4 anemia was more common at the 400 mg daily dose of upamostat than in patients receiving 200 mg daily or in the control groups. Other than that, there was no safety signal in the adverse event profiles in the phase 2 studies. Interestingly, in the breast cancer study, but not in the pancreatic cancer study, the incidence of grade 3 or 4 vascular events was 10% lower in patients receiving upamostat than in those receiving placebo.

1.3 Study Rationale

Upamostat will be studied for treatment of patients with symptomatic, PCR- or antigen-confirmed COVID-19. Several findings support the use of upamostat for treatment of COVID-19:

- Analysis of the structure of TMPRSS2 as compared to proteases tested for sensitivity to WX-UK1 suggests that the compound would have a Ki against TMPRSS2 in the high nanomolar to low micromolar range (J Jensen, personal communication);
- In vitro data in two experimental systems demonstrate that upamostat inhibits SARS-CoV-2 at noncytotoxic concentrations, concentrations well below that which are achievable clinically;
- The potent trypsin inhibitory effect of upamostat may decrease pulmonary tissue damage and gastrointestinal symptomatology due to infection;
- Decrease in circulating D-dimer by upamostat, demonstrated in experimental systems, may indicate a systematic anticoagulant effect, which may decrease the incidence or severity of thrombotic events in COVID-19 patients.

The primary endpoint of this study is time to sustained recovery from acute COVID-19 disease for all patients. For high-risk patients, the first secondary endpoint is hospitalization or death. In addition, patients will be followed using multiple additional clinical and laboratory assessments over time. Viral shedding is a secondary endpoint. This is of importance in itself, as continuation of viral shedding increases the risk of spread of disease and impacts quality of life as the patient must spend longer in isolation. Decreasing the duration of viral shedding will safely allow patients to resume normal activities earlier than otherwise possible.

Because a) no oral therapy has demonstrated efficacy in treatment of COVID-19, and b) the existing treatments approved for outpatient use under EUA are antibody combinations indicated only for high risk patients and which require availability of facility for infusion therapy, use of a placebo comparator appears justified in the outpatient population in areas in which the antibodies are not available. In addition, many patients opt not to receive antibody infusions despite their availability. Therefore, patients in part B of the study will be stratified and outcomes will be analyzed according to antibody use. Two thirds of patients entered in part A of the study will receive active drug, and in part B, 60% will receive active drug. Randomization 3:2 in part B will provide an incentive for participation in the study: patients will have a 50% greater probability of receiving active drug than placebo. This also provides a larger sample size for evaluation of safety than a 1:1 randomization. Yet the shift from 1:1 to 3:2 randomization increases the overall sample size by less than 10%.

In part A of the study, upamostat will be administered at a dose of either 200 or 400 mg daily. While both dose levels have been tolerated well in oncology studies, it appears

prudent to test two dose levels in this new population. If both are tolerated similarly, the higher dose will be used in part B of the study. If there are differences in tolerability, absent clinically significant differences in efficacy, the lower dose will be used in part B.

As an early indication of pharmacologic activity, six parameters found to be associated with severity and outcome of COVID-19 disease will be assessed at multiple time points during the study: oxygen saturation, C-reactive protein, lymphocyte counts, D-dimer, troponin and ferritin levels. The primarily pharmacodynamic parameters, CRP, troponin and ferritin, will be followed only in territories in which they are readily available through a central lab which can standardize the results across sites. Those analytes which are also safety parameters, oxygen saturation, D-dimer and lymphocyte counts, will be followed in all patients.

Under this amendment, the study procedures have been modified taking into account experience with the first patients entered into the study, as well as reasons patients have declined to participate. To date, symptoms have resolved in one to under three weeks. Patients have been resistant to the heavy monitoring and questioning in the original protocol, resulting in reluctance to participate in the study, withdrawal of several patients and poor compliance with study procedures. In order to enhance acceptability, accrual and compliance with the protocol, the duration of intensive vital sign monitoring is being reduced. In addition, the definition of sustained recovery is modified to take into account the patient compliance issue and experience to date with those patients who have recovered. If a substantial proportion of patients withdraws prior to the end of study *because* they feel better and the burden of study procedures is excessive, their efficacy results will be censored and those patients will be declared nonresponders. Temperature will be followed through 28 days after resolution of fever, if the patient is febrile, but with lower frequency from day 15 onward after resolution of fever.

Hospitalization or death has been moved to become the first secondary endpoint. FDA views this endpoint as that for which potential emergency use authorization is justified.

2. Objectives

Primary

Part A of the study: determination of the safety and tolerability of two dose levels and selection of an upamostat dose for part B. Part B of the study:

Primary objective: in the entire patient population, comparison between upamostat and placebo in time to sustained recovery from symptomatic illness in all patients. A patient will be considered to have recovered once he or she meets the following criteria:

1) is afebrile (<38.0° C core temperature) for at least 48 hours without use of antipyretics;
2) all symptoms have resolved or returned to pre-illness levels (e.g., if patient had respiratory compromise prior to the onset of COVID-19), except for:
    i. fatigue, anosmia, ageusia or dysgeusia, which may be persistent at a level similar to that during the acute illness, i.e., the same level per symptom questionnaire;
    ii. chest pain, cough or dyspnea, which if persistent must be at least one grade lower than at the start of treatment and no worse than grade 1 (mild).

Sustained recovery is recovery, per above definition, maintained for at least 14 or 28 days, or through end of study, whichever comes first. The period required to confirm sustained recovery, 14 versus 28 days, will be assessed in part A of the study and a decision reached as to which period to use for definition of sustained recovery in part B.

Symptoms to be followed and their grading are given in Appendix 2, Patient Diary.

Secondary:

Comparison between active and placebo of:

1) Hospitalization or death from any cause by end of study, i.e, day 57. The definition of high risk may be adjusted after part A and at the interim analysis in part B based on the incidence of hospitalization or death found in patients initially entered in the placebo group.
2) In part A and at the interim analysis in part B, assessment of the risk of hospitalization or death as a function of the presence, number and severity of concerning conditions will be undertaken. This information may be used to develop a definition of very high risk for calculation of the incidence of hospitalization or death in part B.
3) Proportion of patients who are PCR-negative at days 8, 15, 29 and 57 from the start of treatment (landmark analyses)
4) Time to resolution of individual disease-related symptoms present at baseline;
5) Development of new disease-related symptoms and/or pneumonia on study;
6) Changes in laboratory markers of disease severity, i.e., oxygen saturation, CRP, lymphocyte count, cardiac troponin, and D-dimer levels, from baseline to time points at which these are measured on study;
7) Adverse events.

In addition to analysis within the entire study population, subgroup analyses for secondary endpoints 1, 3-6 will be performed in the high risk population. Analysis for secondary endpoint 1 will focus primarily on the high risk and very high risk subgroups.

Exploratory

1) Percent of patients who have household contacts who have developed symptomatic, PCR or antigen-confirmed COVID-19 by day 57;
2) Levels of serum IgM and IgG antibodies to SARS-CoV-2 at 57 days from the start of treatment.

3. Study Population

A total of approximately 310-435 patients will be entered in this study.

3.1 Inclusion Criteria

1. Patients with symptomatic, diagnostically confirmed COVID-19, per RT-PCR or antigen assay of respiratory tract sample.
2. Patient must have either become symptomatic or found positive by RT-PCR or antigen assay within 5 days, whichever is greater, of randomization.
3. Patients must have at least two symptoms of at least moderate severity on initial questionnaire. Fatigue, anosmia, ageusia or dysgeusia may not be counted among the symptoms of at least moderate severity qualifying the patient for entry,

Note: patients should NOT be informed prior to completion of the questionnaire that presence of at least 2 symptoms of moderate severity is a criterion for study entry.

4. Males and females ≥age 18 years.
5. Oxygen saturation by pulse oximeter ≥92% on room air.
6. Negative urine or serum pregnancy test (if woman of childbearing potential).
7. Females of childbearing potential and males with female partners of childbearing potential must agree to use acceptable contraceptive methods during the study and for at least two months after the last dose of study medication.
8. The patient must be able to complete the diary independently at baseline.
9. The patient give informed consent based on an IRB-approved consent form.

3.2 Exclusion Criteria

1. Patient is in need of acute hospitalization per clinician assessment.
2. Pregnant or nursing women.
3. Unwillingness or inability to comply with procedures required in this protocol.
4. Patient requires supplemental oxygen.
5. Patient is currently receiving, has received within the past 7 days or is expected to receive during the course of the study remdesivir, or other specific antiviral or anticytokine therapy for COVID-19, other than therapeutic monoclonal antibodies allowed or approved in the region in which the patient lives, or systemic corticosteroid equivalent to ≥20 mg daily prednisone/3 mg dexamethasone daily.
6. Patient is currently receiving or has received within 30 days prior to screening any other investigational agent for any indication, including approved agents given for investigational indications (e.g., anti-cytokine treatments).
7. Patient is currently taking or is expected to start taking warfarin, apixaban (Eliquis), or rivaroxaban (Xarelto). Patients may be taking or start on study dabigatran (Pradaxa), standard or low molecular weight heparin.

4. Study Design

4.1 Overview

This is a randomized, parallel-group double blind study of upamostat compared to placebo in patients with symptomatic COVID-19 who do not require immediate treatment with specific antiviral or anticytokine therapy. The study uses phase 2/3 operationally seamless design methodology for dose selection in phase 2 (part A) and inferentially independent confirmatory phase 3 study (part B). The phase 3 portion will include interim analysis for early termination for futility or increase in sample size, as indicated by initial results.

In both parts of the study, patients who have a positive PCR or rapid antigen test for SARS-CoV-2 and meet inclusion and exclusion criteria will be stratified by age (≥65 vs <65 years). In part B, they will also be stratified based on presence of one or more concerning medical conditions and the additional factors shown below and then randomized to treatment with upamostat or placebo, according to randomization ratios specified below. Concerning medical conditions are the following:

- Age ≥65 years on date of randomization
- Hypertension
- Chronic lung disease (for example, chronic obstructive pulmonary disease, moderate-severe asthma, interstitial lung disease, cystic fibrosis and pulmonary hypertension) Diabetes
- Obesity (BMI≥30)
- Cardiovascular disease (including congenital heart disease, coronary artery disease, history of thrombotic events, including stroke and transient ischemic attacks [TIA])
- Chronic renal disease
- Immunosuppressive disease or immunosuppressive treatment
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

All patients who live in regions in which one or more therapeutic monoclonal antibody combinations for outpatient treatment of COVID-19 are available will either be offered antibody, if provided at that facility, or given information as to where they can receive the antibodies. The patient may decide whether or not to take the antibody combination; receipt or refusal of antibody therapy will not affect the patient's participation in this trial. If used, the antibody may be administered before or after the patient starts study medication. However, the patient may not start study medication more than 5 days after onset of symptoms or receipt of laboratory diagnosis of COVID-19, whichever is longer.

In part B, patients will be stratified based on

1. The presence of none versus one or more of the above factors,
2. Planned receipt vs nonreceipt of therapeutic monoclonal antibodies for COVID-19,
3. Region in which patient is treated,

4. Whether the patient is at least 14 days after his or her last dose of COVID-19 vaccine,

and randomized to treatment as described below.

Initially in part B, the proportion of patients in the low risk group, i.e., with no concerning conditions, will be limited to 30%. This number and the definition of high risk, in terms of number and types of risk factors, may be revised at the time of the part A analysis and, in order to enroll a very high risk cohort, again at the interim analysis in part B.

Part A

Initially, a total of 60 patients will be randomized to one of three treatment groups, as follows:

1. Upamostat 200 mg two capsules qd (n=20);
2. Upamostat 200 mg one capsule and matching placebo one capsule qd (n=20)
3. Placebo two capsules qd (n=20).

In order to maintain blinding, patients will be given two bottles of medication and instructed to take one pill from each bottle each day. Both pills are to be taken at the same time.

Part B

After all part A subjects complete the study, further randomization into the study will be held until the part B dose regimen is selected and the high risk or very high risk population is further defined. Analysis of part A will be performed by a data and safety monitoring board (DSMB). Assuming that there are no substantive negative safety signals to continuing with at least one dose level, a decision will be made regarding continuing with the current design and sample size or increasing the number of patients in part B to enable detection of a significant improvement in the incidence of hospitalization or death in the upamostat group as compared to placebo.

If the decision is to continue as originally planned, an additional total of 250 patients, will be treated with the dose selected in part A or placebo. If the decision is to power for detection of a significant effect on hospitalization or death, the sample size will be increased in accordance with the power calculations to be performed at that time.

The DSMB decision-making process is further defined in section 4.7 of the protocol, below, and will be detailed in a separate DSMB charter. As the results of part A will not be combined with those of part B, the analyses may be shared with the sponsor and study team.

Based on results from part A, a dose for part B, either 200 mg (one capsule) or 400 mg (two capsules) daily will be selected. Patients will then be randomized 3:2 to active drug or placebo at the schedule selected based on part A. If the study is powered for the symptom resolution endpoint, part B will have an event-driven design, requiring total of 201 endpoint-events (details in Section 7.1) The target sample size for this part is 250 patients, 150 receiving active drug and 100 receiving placebo. An interim analysis for early termination for futility or increase in sample size (up to maximum total 375), as indicated by comparative interim results will be performed after 50% of the primary endpoint recovery events are realized (details in section 4.8 and section 7.6). This interim analysis is estimated to occur when about 50% (125) of part B subjects have been enrolled and treated.

If the study is repowered to demonstrate a significant reduction in hospitalization or death, the timing of the part B interim analysis may be revised. At the interim analysis, the incidence of hospitalization or death as a function of presence of concerning conditions will be assessed and the stratification or covariate weighting for the final analysis may be modified based on this analysis. In addition, the sample size may be increased by 50% depending on results of the interim analysis.

4.2 Study Drug Administration

4.2.1 Upamostat

Upamostat will be administered as one or two 200 mg capsules once daily for 14 days, preferably at approximately the same time each day. Medication should be administered with water and may be administered with or without food.

4.2.2 Placebo

Placebo will be administered as described above.

4.2.3 Dose modifications

Toxicity is an adverse event judged by the investigator to be possibly, probably or definitely related to study medication. All grade 1 toxicities and adverse events and tolerable unrelated grade 2 adverse events can be treated according to standard clinical practice guidelines, without dose modification.

See Table 2 for the Dose Modification Plan for patients experiencing ≥grade 2 toxicities.

Table 2. Dose Modification Plan for Treatment-Related Toxicities

NCI CTC 5.0 Criteria	Dose Modification Instructions
Symptomatic toxicity (e.g., nausea, vomiting or diarrhea) or laboratory abnormalities (e.g, hypokalemia) ≥grade 3 which can be reduced to ≤grade 1 within 48 h with standard supportive measures	No dose modification.
Any *intolerable* grade 2 toxicity	The investigator should consult the study sponsor regarding grade 2 toxicities that are considered intolerable by the patient or physician. A dose reduction may occur with prior consultation with and approval by the study sponsor.
Any toxicity ≥grade 3 other than the above	Hold study drug. Assess patient at least every 3 days. If the toxicity improves to ≤ baseline within a week, restart study drug and reduce dose by one dose level (Table 3). If toxicity does not improve to ≤ baseline within one week, discontinue study drug. Omitted doses are not made up.

Patients may undergo two step-wise dose reductions, as shown in Table 3. Only two dose reductions are allowed. If the patient still has significant toxicity, as described in Table 2, after two dose reductions, treatment is to be stopped.

Table 3. Dose Levels

Dose Level		
Starting dose	1 cap daily	2 caps qd
Reduction 1	1 cap q2 days	1 cap qd
Reduction 2	Discontinue	1 cap q2 days

In part A of the study, patients may get two bottles of capsules with the same drug (active or placebo) or one bottle of each, active and placebo. In order to dose reduce in that situation, the patient will be told to take one capsule from alternate bottles on alternate days, stopping at day 15, regardless of how many capsules are left. Generally, one capsule should remain at the end of the study, unless a capsule was accidentally damaged or lost.

4.3 Randomization and Blinding

In part A of the study, patients will be stratified by age, <65 or ≥65, and randomized.

In part B, they will be stratified by multiple factors, as described in section 4.1, above, and then randomized as described above. Patients will be randomized using a centralized, automated randomization system, which will assign a blinded treatment kit to each patient.

In part A, randomization will be done in a 1:1:1 ratio among each dose level and placebo with all patients receiving a kit that comprises 2 bottles of medication (active or placebo) and will be instructed to take one pill daily from each. In part B, patients will be randomized 3:2 to active versus placebo. They will receive one bottle of study medication. Depending on whether the dose for part B is 200 or 400 mg daily, patient will be instructed to take either one or two capsules daily.

4.4 Concomitant Therapy

All medications taken during the following periods are to be recorded in the case report form:

- For 28 days prior to the signing of consent;
- While the patient is on study medication and for 42 days thereafter.

Patients should not take other antiviral treatments, other than monoclonal antibody infusions allowed under either EUA, NDA or similar mechanisms in countries outside the US, or any investigational agent for any indication while participating in the study.

Patients may take other medications as necessary for concomitant conditions or for treatment of study therapy adverse effects. In addition, patients whose condition worsens substantially at any time during the course of the study may receive treatment for COVID-19 per current local standard of care, including specific antiviral and anticytokine therapy.

In vitro studies with upamostat and WX-UK1 have suggested a potential for drug interactions with concomitantly administered drugs that are either substrates or inhibitors of CYP3A4. Clinical data concerning potential CYP3A4-mediated drug interactions are not available. Therefore, as a safety precaution, patients that receive strong CYP3A4 inhibitors, sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic range together with upamostat should be carefully monitored concerning potential side effects arising from increased exposure to upamostat or to concomitant medication. Lists of strong CYP3A4 inhibitors and sensitive CYP3A4 substrates can be found in Appendix 3 of the protocol. These lists are based on the FDA website table:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1

In particular, patients should not take warfarin, apixaban (Eliquis), or rivaroxaban (Xarelto). Patients may use dabigatran (Pradaxa), standard or low molecular weight heparin, as these drugs are not metabolized through CYP mechanisms.

If several patients require symptomatic treatment of presumed upamostat-related toxicity, subsequent patients may receive prophylactic treatment. If clinically necessary, routine use of prophylactic medications may be discussed with the sponsor.

4.5 Duration and Discontinuation of Treatment

Treatment will continue for 14 days or

a) the patient or physician decides that it is not in the patient's best interest to continue, due to either deteriorating clinical condition or adverse event, whether or not due to study medication.

b) the patient decides for any reason to discontinue therapy and/or withdraw from the study.

If the patient is still virus positive at 14 days, treatment will be stopped, but follow-up will continue for 42 days. The patient will still be included in analysis for recovery and all other study endpoints. All patients will be followed through day 57 from the start of treatment, regardless of the duration of treatment.

4.6 Replacement of Patients

Patients who are randomized but not treated will be replaced. Replacement patients will be given new randomization assignments; they will not receive the assignment of the replaced patient.

Patients who receive any study medication but discontinue with or without subsequent collection of data will not be replaced.

4.7 Discontinuation of Study

All serious adverse events and grade 4 or 5 adverse events will be reviewed by the sponsor and the DSMB on an ongoing basis. Treatment will be unblinded to the DSMB for all grade 5 adverse events regardless of putative causation, and the DSMB may recommend to the Sponsor unblinding treatment of additional patients reviewed. The DSMB may request unblinding for grade 4 adverse events if, in their judgment, they may be related to study medication and the toxicity poses a risk to subsequent patients.

Based on review of serious, grade 4, and grade 5 adverse events, the DSMB may at any point in the study recommend termination or revision of the study if they feel that toxicity poses a risk to subsequent patients.

4.8 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be convened for oversight of the study. A DSMB charter will be written as a separate document.

Preliminary review: The DSMB will be informed by the Sponsor on an ongoing basis of each patient whose study medication dose is reduced or discontinued due to toxicity. DSMB members may request an early review of all patients if warranted by the type, severity or frequency of toxicities resulting in dose reduction or drug discontinuation.

Initial full review: The DSMB will review data after the 60 patients have completed treatment (part A), with regard to the following:

a) Adverse events requiring dose modification or discontinuation of treatment overall and those considered at least possibly related to study medication;
b) Serious adverse events deemed at least possibly related to study medication;
c) Serious adverse events of any cause;
d) Exacerbation of COVID-19 disease, including hospitalization or death;
e) Effect of treatment on oxygen saturation, C-reactive protein, lymphocyte count and D-dimer (pharmacodynamic markers);
f) Additional efficacy parameters available at that time, including time to sustained recovery
g) Correlations between comorbidities and hospitalization or death.

A statistically significant difference in any of these parameters is unlikely with a limited early data set. However, the DSMB in conjunction with the sponsor will determine using their clinical judgement if, based on the safety profile of the two active arms, the tolerability is substantially lower at 400 mg as compared to 200 mg daily.

A. If the DSMB determines that safety of both dose levels is similar, accrual in part B will proceed with the 400 mg daily schedule.

B. If safety is more favorable with the 200 mg daily regimen, accrual in part B will proceed with the 200 mg daily schedule.

Efficacy will be analyzed in part A but, unless there is a marked difference between the two active dose levels, will not be used to decide on dosing in part B. Similarly, pharmacodynamic parameters will be analyzed but not used to decide on dosing.

At the end of part A, incidence of hospitalization or death will be analyzed as a function of the presence of one or more concerning conditions. The definition of high risk for purposes of the hospitalization/mortality endpoint in part B may be adjusted based on findings in part A.

Interim analysis in part B: If the study proceeds as originally powered, the DSMB will again be convened after approximately half the required information on the primary endpoint has been observed, i.e., 101 recovery events out of a total planned 201 events.

The DSMB will review the same parameters as were reviewed at the first meeting and also the primary efficacy endpoint.

The DSMB will make a recommendation to continue to the planned target number of events, stop the study for futility, or enlarge the study if efficacy results fall in the predefined promising zone.

Classification of primary endpoint result at interim	**Description**	**DSMB recommendation**	**Comment**
Futility zone	Results indicate definite futility if the study proceeds to the planned size	Stop the trial	Statistical futility rule is not binding.
Unfavorable zone	Results do not meet the futility criteria above; however result is still disappointing	Continue the study to planned end	As long as tolerability is reasonable
Promising zone	Result show a trend toward clinical benefit, but initially planned sample size does not provide enough power to demonstrate statistical superiority.	Increase study size up to 50% larger than planned.	
Favorable zone	Interim results sufficiently favorable that the trial continues to the planned end without the need to increase the trial size	Continue the study to planned end	

Early stopping for superior efficacy is not planned.

If the study is repowered for the hospitalization or death endpoint, the timing of the part B interim analysis may be revised. The definition of high risk for purposes of the hospitalization/mortality endpoint may again be adjusted based on the part B interim analysis in order to achieve an expected 15% or greater incidence of hospitalization or death among the high risk or very high risk control group. Other assessments will be conducted as shown in the table above, focusing on the hospitalization or death endpoint.

5. Study Evaluations

5.1 Schedule of Evaluations

Study procedures are shown in Table 1, after the synopsis, and further described in the notes to that table on the following page.

Patients are to be screened and started on treatment within 5 days of onset of symptoms or demonstration of positive PCR or rapid antigen test, whichever is longer.

5.2 Description of Study Procedures

Most study procedures are standard clinical and clinical laboratory procedures.

SARS-CoV-2 Testing

Two baseline SARS-CoV-2 tests will be obtained at the start of the study: a test performed locally to determine eligibility, and an RT-PCR test run in a central laboratory and which allows quantification.

If the patient has a positive result from a PCR or antigen test performed within 5 days of the planned start of treatment (not just screening day if treatment is to start a day or more after screening), a repeat PCR/antigen assay need not be performed. The results must be on an official laboratory report, not word of mouth or doctor's note. A copy of the outside PCR report must be retained by the site as a source document.

If at screening, the patient has not had a positive PCR or antigen test, a rapid test (PCR or antigen) may be performed at the site to determine eligibility. After consent, a second specimen must be taken for shipment to a central laboratory for quantitative PCR and sequencing.

Once a patient has qualified for the study (positive local test for COVID-19 PCR or antigen, determined by the questionnaire to have sufficient symptomatology, and the patient meets all other inclusion/exclusion criteria), the patient is randomized to treatment and the telemetry devices set up.

- Optimally, the screening, randomization and set-up of devices will all occur the same day in the clinic or ER.
- If all procedures cannot be completed the same day, medication can be provided and devices set up the following day, either by visit of study personnel to the patient's home or a return visit by the patient to the facility.

In the event of discrepant results between the rapid PCR/antigen test and standard PCR, results of the rapid PCR/antigen test will determine eligibility, i.e., a patient will not be declared ineligible if the central laboratory PCR is subsequently found to be negative.

Instructions for obtaining and handling samples for SARS-CoV-2 PCR testing are found in Appendix 1 of the protocol.

Study Medication

Study medication will usually be provided to the patient on the initial day of evaluation. In a situation where final eligibility is not determined prior to the patient's leaving the clinic or on the first day of hospitalization, study medication may be provided after the baseline visit, either by the home health staff member who will be seeing the patient or at a return visit to the facility.

Therapeutic monoclonal antibody combinations

In regions in which these are available, they will either be administered at the investigative site or patients will be informed as to where they can receive the antibodies. Use of the antibodies will be discussed with each patient in regions in which they are available. It is the patient's decision whether or not to receive the antibody combination.

Other Tests and Procedures

Patients will complete a smartphone-based diary at baseline and daily from day 2 (the second treatment day) through day 28 and days 1, 3 and 5 each subsequent week during the study. This will collect symptom information, adverse events, and study and concomitant medication administration. A patient who is unable to enter the diary data independently at baseline should not be enrolled in this study. If, however, the patient becomes physically unable to complete the diary during the course of the study, he or she may dictate responses to a caregiver or other companion; that the caregiver is completing the diary should be noted. If the patient is unable to respond to the questions during the course of the study, that should be so noted. A caregiver or companion should *not* complete the diary using assumed responses. The patient will be deemed not to have recovered on any day when he or she is unable to provide responses to the diary questions. If difficulties in use of the smartphone-based diary system occur, paper forms may be substituted for individual patients or in regions in which the smartphone-based system does not function properly.

If the baseline diary is completed on treatment day 1, rather than prior to treatment day 1, the patient should not complete the diary again that evening. The information to be collected is shown in Appendix 2.

At the baseline visit, patients will receive a kit which contains devices for remote patient monitoring. The kit includes:

- Electronic thermometer
- Pulse oximeter
- 6-lead ECG

The ECG device may be kept by the site personnel or by the patient, depending on convenience and logistics at each site.

All devices are FDA-cleared (i.e., approved via 510K pathway).

Patients and caregivers will be trained on use of all devices at their baseline visit and will be given additional documentation at the time of the baseline visit.

In addition, home health or clinic staff will obtain all vital signs independently of patient measurements, to verify that data are being collected accurately. ECGs are scheduled only for days when home health or clinic visits occur, and will be conducted by medical personnel, not by the patient.

Home visits will be conducted on days 8, 15 (or end of treatment if prior to day 15), and 29 of the study. Alternatively, at the mutual convenience of study staff and patients, one or more of the visits for days 8, 15 and 29 may be conducted in the facility. Televisits, either audio or audio and video, will be conducted on days 3, 22 and 43. On day 3, in addition to collecting general information about the patient's condition, use of the devices provided will be reviewed.

At the day 57 clinic visit, consenting patients will undergo testing for serum alpha-1-antitrypsin level and whole blood glucose-6-phosphate dehydrogenase (G6PD) deficiency. Consent may be obtained by the investigator either at the day 43 televisit or the day 57 clinic visit.

This is a multinational study. In some locations, performance of certain pharmacology and other specialty tests, e.g., troponin and ferritin levels may not be feasible due to logistic constraints. In addition, obtaining multiple consents for genetic testing (alpha-1-antitrypsin, G6PD) may be problematic and their performance logistically difficult. Accordingly, these tests may not be obtained in all regions.

Visit windows, in relation to day 1 (first treatment day):

Day 3: every attempt should be made to conduct the visit on that day. If impossible due to communication or logistic issues, it may be conducted up to one day later, i.e., on day 4.

Days 8 and 15: ±2 days

Days 22, 29, 43 and 57: ±4 days

5.3 Unscheduled Visit

If, in the Investigator's opinion, a patient should be seen outside of the proposed visit schedule, then an unscheduled visit may be performed. Additional eCRFs will be provided to accommodate such visits. Venue of and activities at these visits will depend upon the investigator's concerns. The investigator will record the reason(s) for the unscheduled visit as well as the information gathered at that visit.

6. Safety Reporting

All subjects will be assessed regularly for potential adverse events (AEs) occurring from the time the subject receives the first dose of study medication, through study day 57. .

6.1 Terminology

An *Adverse Event (AE)* is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (may also be referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product and from any route of administration, formulation, or dose, including an overdose. Worsening of baseline signs, symptoms or concomitant illnesses are also considered adverse events.

Exacerbation of COVID-19-related signs and symptoms are considered lack of efficacy, rather than adverse events. All signs and symptoms will be followed, but will be analyzed as part of the efficacy rather than safety analyses.

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at <u>any dose results in any of the following outcomes</u>:

death;

is a life-threatening adverse event (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 that hypothetically might have caused death if it were more severe);

requires in-patient hospitalization or causes prolongation of existing hospitalization;

a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

a congenital anomaly/birth defect;

is an important medical event. This is defined as a medical event 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 and may require medical or surgical intervention 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.

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and be evaluated by the Sponsor for expedited reporting.

A *suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

A suspected adverse reaction is considered *unexpected* if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

6.2 Assessment of Causal Relationship

The following categories and definitions for assessing the causal relationship of an event to the investigational product(s) are provided as a guide for evaluating adverse events reported in this study to determine “suspected adverse reactions” that require expedited reported to regulatory agencies if they are unexpected, i.e., SUSARs, suspected unexpected serious adverse reactions. In addition to the assessment below, the aggregate number of occurrences will be considered to decide whether the event is a reportable event and requires an IND safety report.

Table 4. Relationship of Study Medication to Adverse Events

Unrelated	The study drug almost certainly (or certainly) did not cause the event. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another obvious etiology.
Probably not related	It is more likely that the event is due to another etiology than due to the study drug. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another more likely etiology.
Possibly related	It is approximately equally likely that the event is due to the study drug as it is due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The drug seems as likely as other etiologies to have caused the effect
Probably related	It is more likely that the event is due to the study drug than due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event may be consistent with a known pattern of drug (or drug class) effects; The drug seems more likely than other etiologies to cause the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; and/or The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)
Definitely related	The evidence is compelling that the study drug caused the adverse event. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event is consistent with a known pattern of drug (or drug class) effects; The drug is far more likely than other etiologies to have caused the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)
Unknown	The data are inadequate to assign any of the above causal relationship categories to the study drug.

6.3 Adverse Event Grading and Coding

AEs will be coded, grouped and tabulated by MedDRA preferred terms by body system organ class. The MedDRA version current at study initiation will be used for the entire study.

Adverse events will be graded according to US National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0. The following are the general criteria for severity grading:

Grade	Description
1	Mild
2	Moderate
3	Severe
4	Life-threatening or disabling
5	Fatal

The NCI CTCAE v5.0 can be downloaded in pdf format at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

6.4 Handling of Serious Adverse Events

Adverse events classified as serious must be recorded on the AE page of the CRF and require expeditious handling and reporting to the sponsor to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All SAEs must be reported using the Serious Adverse Event Report form. To the extent possible, the descriptive terminologies and other SAE attributes entered on the SAE report form should approximate similar information in the CRF. The completed SAE report form with supporting documentation must be provided to the sponsor within 24 hours of the study site personnel's initial notification/awareness of the event. All telephone communication regarding SAE must be followed by a written report. Duly authorized study site personnel may sign completed SAE report forms; however, it is recommended that the investigator sign each final SAE report.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries, additional lab and test results, autopsy reports, etc.), should be collected subsequently, if not available at the time of the initial report, and immediately sent to sponsor using the same procedure as the initial SAE report. Information on the SAE must be in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

For ease of analysis, worldwide standardization, and regulatory reporting, the sponsor will code each reported adverse event or symptom to its corresponding preferred term and body system/organ class in the MedDRA dictionary version adopted for the study. The principal investigator will be responsible for assessing severity based on the intensity of the event as it presented using the criteria listed in section 6.3, above.

All SAE reports must be sent to the study medical monitor and the sponsor's regulatory/clinical affairs contact:

Medical Monitor:	Terry Plasse, MD Mobile phone: +972-50-588-7376 or +1-917-913-7315 e-mail: terry@redhillbio.com
Pharmacovigilance officer:	Sanan Smith Email: sasmith@fhiclinical.com Phone: + 1 919 544 7040 x1234 Additional pharmacovigilance contacts will be provided for ex-US sites

As required, all investigators will be notified of all AE reports that are determined to be serious, unexpected, and related (by the reporting investigator or sponsor) to the investigational product. The notification will be in the form of a Safety Update (Dear Doctor Letter).

The notification is considered an addendum to the current Investigator's Brochure; therefore, upon receiving such notices, the investigator must review and immediately submit a copy to the IRB according to local regulations. The notification must be retained within the Investigator's Brochure. The investigator and IRB will determine if the informed consent requires revision.

6.5 Laboratory Test Abnormalities

All new abnormal laboratory findings and those abnormal at baseline which change significantly (i.e., by at least one toxicity grade as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) are considered AEs. Laboratory AEs for which there is no clinical intervention will be recorded only on the laboratory data pages of the eCRF. Laboratory AEs not listed in the NCI CTCAE v5.0 will be considered as grade 1 (mild) if there is no clinical effect or intervention. Laboratory values outside the normal range for certain parameters will not be considered AEs if they are generally not considered as indicating an abnormality; this includes such parameters as liver enzymes which are below the normal range. If there is a clinical sequela or intervention, the laboratory abnormality is to be graded according to the criteria used for clinical AEs, described above.

The NCI CTCAE v5.0 can be downloaded in pdf format at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

6.6 Other Safety Considerations

Patients will be followed for a total of 8 weeks from the start of study medication. After the enrolment visit until the end of study visit, direct contacts between study personnel and patients may be entirely by home and televisits. Alternatively, at the mutual convenience of patients and study staff, one or more of the interim visits may be held at the investigative site In some instances, in particular for significant exacerbations of disease or adverse events regardless of relationship to study medication, the patient will come to the medical facility for an in-person assessment.

All AEs must be recorded and followed until resolution or for at least 28 days after discontinuation of study medication, whichever comes first.

Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the AE page of the CRF.

7. Data Analysis and Statistical Considerations

This section of the protocol describes the statistical analysis as it is foreseen at the time of planning the study. A fully detailed Statistical Analysis Plan (SAP) will be produced and finalized after finalizing the protocol and before breaking the blind of the study for interim analysis.

The SAP will be reviewed after analysis of data from part A. Modifications may be made to the analyses planned for part B based on that review. The revisions will be finalized before reaching the interim analysis point for part B.

7.1 Sample Size Considerations

Part A

In the first part of this study, two different dose levels of upamostat will be tested; randomization will be 1:1:1 to the two upamostat dose levels and placebo.

The objective of this part is to evaluate the tolerability of two dosing levels of upamostat in order to select the dose level that will be evaluated in the confirmatory Part B of the study.

The sample size for part A, consisting of 20 subjects per each arm (placebo, upamostat 200 mg qd, upamostat 400 mg qd) was not chosen for statistical power consideration, as there are no formal statistical inferences planned. The size of this part is judged adequate for the tolerability assessment.

Part B

After accrual to the first part of the study is completed and a determination as to which active arm to continue into the next part of the study is made, accrual will continue at a 3:2 ratio, active:placebo. A minimum total of 250 patients will be accrued to part B, 150 to the active arm using the regimen selected in part A of the study and 100 to placebo.

The sample size currently shown for part B was determined based on the primary endpoint, time to sustained recovery from COVID-19 illness, as defined in the primary objective. It was calculated that in order to detect a hazard ratio for sustained recovery=1.5 comparing the active group to placebo group with 3:2 allocation ratio, a total of 201 recovery events are required, to provide 80% power using a log-rank test at a two-sided significance level of 0.05. Assuming 80% sustained recovery rate in the control arm by end of follow-up (assumed equal follow-up of 57 days for all enrolled patients), it was calculated that in order to achieve the required number of events, the minimum number of patients enrolled will be 250 in total. As this study is defined as an operationally seamless phase 2/3 study, subjects from the part A of the study will not be combined with those in part B for the efficacy analysis. Therefore the target enrollment for part B is the total number of required subjects, namely 250 subjects in total, 150 and 100 for the active and placebo groups, respectively.

The target number of events for this event-based part B portion is 201, taking into account a non-binding futility analysis that will be performed when 50% of the information (primary events) have been realized.

Sample size re-assessment

In light of the limited information currently regarding time to sustained recovery and incidence of hospitalization or death expected in the control arm, and /or to address the

possibility that the magnitude of upamostat effect may be smaller than the relatively large target effect size but is still trending in the right direction and is big enough to be of clinical relevance, sample size re-assessment will be performed.

The sample size of 250 subjects was predicted to be sufficient to provide the required total 201 'recovery' events (assuming 80% sustained recovery rate by study day 57, in the control arm). The study design plan for part B is to continue recruitment until there are at least 201 subjects with a "recovered" status, if more than 250 subjects are needed for this.

If part A results suggest that the initial assumptions above should be altered, an updated target number of events and/or number of subjects will be predefined for part B.

In part B, sample size re-estimation, the results of which will be unblinded only to the DSMB, will take place when about 50% of target primary endpoint recovery or hospitalization or death events have been realized, to allow increasing the target event size by 50% (that is to a maximum of 301), thus requiring an associated increase of the sample by 50% (that is to a maximum of 375 subjects), only in the case that interim results falls within a "promising zone", as strictly defined in Chen et al, 2004, and Mehta and Pocock, 2011. Using this approach, a valid (using the conventional statistic for the final analysis, and the type-1 error not inflated) increase in sample size following an unblinded comparative look is allowed when the observed interim treatment effect, although smaller than hoped for, is still trending in the right direction and is of clinical relevance.

To safeguard study integrity, the pre-specified rules will be documented separately, in the DSMB charter.

If at the end of part A, the study is repowered to achieve statistical significance for the hospitalization or death endpoint, the incidence of this endpoint in the treatment groups in part A as well as literature data will be considered in determining the sample size for part B. This will take into account not only overall results of part A but also results in patients who are defined as high risk. It is understood that these calculations are based on a very small database, which may prove to be very imprecise.

If part B of the study is repowered, the timing of the interim analysis may be adjusted. At the interim analysis, the incidence of hospitalization or death in the high risk group, defined as patients with one or more of the concerning conditions listed in Section 4.1, may be modified. A higher risk group may be defined in order to establish an adequate incidence level of hospitalization or death in a well-defined subgroup to ensure the study is adequately powered for the analysis of this endpoint in a meaningful patient population. This may result in a revised sample size and limiting or redefining recruitment in the different subgroups. Sample size reassessment for the primary endpoint will only be conducted if the revised sample size is lower than the maximum sample size proposed for the primary endpoint as above.

7.2 Analysis Datasets

The primary and most secondary efficacy analyses will be performed on the modified intent to treat (mITT) population, defined as all randomized patients who receive any treatment. A per protocol (PP) analysis will be performed on patients with no major protocol violations and who receive at least one week of study medication or the reason

for stopping medication is worsening COVID-19 or development of AEs. In these analyses patients will be analyzed according to their randomized treatment. Analysis for the first secondary endpoint, hospitalization or death, will be performed primarily on a subset of the mITT population, the high risk or very high risk subset to be defined at the end of part A and redefined at the interim analysis of part B.

Formal efficacy analyses will be performed using part B enrolled subjects, the efficacy data from part A subjects will be descriptively summarized separately.

Safety analyses will be performed on all patients who receive any study medication in parts A and B combined, according to the treatment actually received.

7.3 Study Population and Demographics

Demographic and pretreatment patient characteristics, including disease parameters and comorbidities, will be summarized with appropriate descriptive statistics, by study part, overall and by treatment group. The descriptive statistics will include sample size, mean, standard deviation, median, minimum, and maximum for continuous variables and number and percentages for discrete variables.

7.4 Efficacy Analyses

7.4.1 Analysis of the primary efficacy endpoints

The primary endpoint of the study is time to sustained recovery from COVID-19 illness, as defined in section 2 of the protocol. The first secondary endpoint , incidence of hospitalization or death, will primarily be assessed in the high risk or very high risk population.

Time to sustained recovery is the number of days from first dose of study medication until the day on which patient is recovered and remains recovered for at least 14 days or until end of study, whichever comes first**.** The definition of “sustained” may be modified, as noted above, at the end of part A. First date of recovery will be defined as the **latest** time among the events below:

1) Start date of the period during which the patient is afebrile for at least 48 hours without use of antipyretics;
2) First date when all symptoms have resolved or returned to pre-illness levels (e.g., if patient had baseline respiratory compromise), except for
    a. fatigue, anosmia, ageusia or dysgeusia, which may be persistent at levels similar to the acute illness, or
    b. dyspnea, cough or chest pain, which, if persistent, must be at least one grade lower than baseline and no worse than grade 1 (mild).

Time will include the first day of study medication and the day on which patient is declared to have recovered.

Patients who have reached day 57 from the start of treatment but have not recovered will be censored at day 57. In addition, several situations override the above definition of recovery:

- Patients lost to follow-up during treatment or follow-up (before recovering) will be censored at day 57.

- Patients who recover per the definition above but are subsequently hospitalized for any reason and are in hospital at day 57 will be censored at day 57.
- Patients who die before recovery will be censored at day 57, the end of follow-up, reflecting the most unfavorable possible outcome for this endpoint.

Calculation of time to sustained recovery requires completion of the symptom diary. If a patient is hospitalized, he or she will be considered as not recovered on those days, regardless of the reason for hospitalization.

Supportive analysis will be performed to include recovery from viral shedding in the definition of recovered event. In this analysis time to recovery will be the latest between the two events above and time of first negative nose viral swab.

The comparison of the time to sustained recovery between active and placebo groups will be performed using stratified log-rank test, at 5% significance level. The stratification factors used for randomization will be used. Kaplan-Meier plots of time to sustained recovery will be provided along with median estimates and hazard ratio (HR) will be estimated along with 95% confidence interval using stratified Cox regression model. Estimates of cumulative incidence of sustained recovery at certain time points (for example days 15, 29, 43 or 57) for each group, along with 95% confidence interval will be tabulated.

More details on statistical analyses of the primary endpoint and sensitivity analyses will be provided in the SAP. These will address the following aspects:

- Using the PP population and ITT population
- To account for the possibility of errors in values of stratification factors used for randomization, the primary analysis will supportively be repeated using the correct values.
- Comparison between the treatment and control groups when controlling for possible imbalance in important baseline factors will be analysed by evaluating the HR obtained from estimating a multiple proportional hazards Cox regression model.

Subgroups to be analyzed, such as various risk categories, will be enumerated in the SAP. Handling of missing data will be described in the SAP.

7.4.2 Analysis of the secondary efficacy endpoints

Comparison between active treatment and placebo of the following secondary efficacy endpoints will be performed:

1) Incidence of hospitalization or death: the primary assessment of this endpoint will be among patients in the high risk group. This has been defined preliminarily above. The group may be redefined and recruitment restricted based on analysis at the end of part A and again in the interim analysis of part B. Additional secondary endpoints include:
2) The proportion of patients who are PCR-negative at each time point assessed, days 8, 15, 29 and 57 from the start of treatment (landmark analysis);
3) Time to resolution of individual disease-related symptoms present at baseline;
4) Development of new disease-related symptoms or pneumonia on study;

5) Changes in laboratory markers of disease severity, i.e., oxygen saturation, CRP, lymphocyte count and D-dimer levels, from baseline to time points at which these are measured on study;

The time frame for all endpoints unless otherwise stated is from Day 1 (day of first dose of study medication) through study Day 57. The time to event endpoints will be analyzed using the methods described for the primary endpoint above.

Binary (Yes/No) endpoints (development of pneumonia, hospitalization and mortality) will be summarized using counts and percentages for each group. A 95% confidence interval will be constructed for each proportion. Population-level risk differences will be used to estimate treatment effect. More specific details will be provided in the SAP.

Changes from baseline in continuous variables will be summarized by descriptive statistics and analyzed using repeated-measures model. Data will be log transformed, as needed.

7.4.3 Type 1 error control

The overall type 1 error for the study is 5%, which will be used for the efficacy analysis of the dose level assessed in part B of the study. As data from part A of the study will not be used for the main, part B efficacy analysis, no correction for multiplicity or selection is needed.

The unblinded comparative size re-estimation (ubSSR) at the time of part B interim analysis will follow the rules that increase sample size only if comparative results falls in a pre-defined 'promising zone'. Building on the theoretical work of Chen, DeMets and Lan (2004) and Mehta and Pocock (2011), it has been shown that the 'Promising Zone approach' allow type 1 error to be preserved with the use of conventional final analysis test statistic, that is without need for statistical adjustment. To safeguard study integrity, all details regarding the pre-defined ubSSR rules will be documented separately.

The interim analysis will allow only early stopping for futility (non-binding), and not for efficacy, therefore no inflation of type one error is associated with study early stopping criteria.

To protect the overall 5% type I error arising from secondary endpoint multiplicity, all the secondary endpoints will be interpreted inferentially only if a statistically significant treatment effect (p-value ≤0.05) is detected in the primary endpoint for the study.

The order of the secondary endpoints defines an hierarchy according to which these endpoints will be sequentially tested, where an endpoint can be inferentially interpreted only if the previous endpoint was statistically significant. The hierarchy of endpoints will be finalized after Part A data are available but before unblinding of Part A and will be documented in the SAP.

7.5 Safety Analyses

The safety and tolerability of upamostat will be determined by reported AEs, physical examinations, vital signs, and laboratory tests. Patients who receive any study medication, even a partial dose, or who immediately vomit the study medication are considered evaluable for safety.

As noted above, exacerbation of COVID-19-related signs and symptoms are considered lack of efficacy, rather than adverse events. Therefore, hospitalization or death from COVID-19 will be considered in the efficacy rather than safety analyses, although all hospitalizations and deaths, regardless of cause, will be included in the overall statistics for these events. COVID-19-related events will be followed similarly to serious adverse events, but not counted in the analyses thereof.

In part A of the study, safety data will be analyzed per the outline in section 4.8, above, to determine which treatment regimen to carry into part B of the study.

As possible, summaries will be provided for dose level that will be used in both study parts combining data from both parts. Similarly, placebo safety data will be combined. The unselected dose level data will be presented separately.

7.5.1 Adverse Events

The NCI-CTCAE v5.0 system will be used to grade new or worsening clinical and laboratory abnormalities. New laboratory abnormalities for which there are no CTCAE v5.0 criteria will be assigned grade 1 if there were no clinical effects or interventions, and according to the criteria in section 6.5 if there were clinical effects and/or interventions. AEs will be grouped and tabulated by MedDRA preferred terms by system organ class.

The Medical Dictionary for Regulatory Activities (MedDRA) version current at time of study initiation will be used to classify all AEs with respect to system organ class and preferred term.

Summary tables of AEs and SAEs will be prepared by system organ class, preferred term and severity for each treatment group. AEs that lead to premature discontinuation from the treatment or to death will be listed separately via data listings.

7.5.2 Clinical Safety Laboratory Tests

Laboratory tests and change from baseline at each time point will be tabulated by treatment groups. No inferential testing will be performed to compare the differences between the treatment groups.

7.5.3 Other Parameters

The results from physical examination will be presented in the subject data listings. Vital signs and physical findings will be shown in listings, but no calculations or study report tables will be generated. Findings on physical examination, including vital signs, which constitute clinically significant changes will be listed as adverse events.

Concomitant medications will be summarized and presented, as will be detailed in the SAP.

7.6 Interim Analyses

Once treatment and follow-up of the first 60 patients (part A) is completed, data will be reviewed by the DSMB for safety, as described in section 4.8, above, and a decision made regarding which regimen to continue into part B of the study. As the study is defined as ‘operationally seamless’ such that efficacy data from part A will not be used both for the dose selection and the confirmatory analysis, the Sponsor may take part in that decision and be exposed to the comparative part A data.

At that time, the parameters being studied and the analysis plan will be reviewed and may be adjusted based on findings in part A before initiating part B.

A second analysis and DSMB review will be conducted in part B, at one of the time points described above, depending on whether the study is powered for the sustained recovery endpoint or the hospitalization or death endpoint.

To safeguard study integrity and to minimize operational bias from the planned interim analysis, the following operational procedures will take place (Mehta and Pocock, 2011; FDA Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics, November 2019):

- The unblinded independent statistician who is not otherwise involved in the study will perform the interim analyses calculations.
- The DSMB charter will describe what the interim analysis report should contain, who may have access to that report, the precise rules for increasing the sample size, and the procedure to be followed in making the sample size recommendation to the sponsor.
- The unblinded sample size increase will use a discretized fixed decision rather than a continuous adaptation decision to limit the option of back-calculation of treatment effect.
- Procedure for notifications to be followed by DSMB if recommendation to stop study or to increase sample size will be specified. For example, if the sample size is increased after an interim analysis, trial sites would not be notified of the specific targeted final sample size.

8. Study Medications

Upamostat will be provided in 200 mg capsules. Patients will receive an adequate supply of medication for 14 days. Medication is to be stored at room temperature, 15-25°C (59-77°F).

Matching placebo for upamostat will also be provided in blinded fashion.

For part A of the study, the two bottles provided will be labeled A and B. Patients will be instructed to take one capsule from each bottle each day. For patients in the 200 mg daily group, i.e., receiving different medications in bottles A and B, active and placebo will be randomized between the two bottles so that A or B will not automatically signify either active or placebo. If dose is reduced, patients will be instructed to take one pill from alternate bottles each day.

9. Investigator Responsibilities

9.1 Compliance with Declaration of Helsinki and Good Clinical Practices

The study will be performed in accordance with the Declaration of Helsinki (1964) as revised, most recently in Seoul (2008), US FDA, as well as regulations in other countries in which patients may be accrued, and the ICH Guideline for Good Clinical Practice, E6(R2). The investigator will ensure that all those concerned with conducting the study (such as pharmacists, research nurses and co-investigators) are provided with copies of the protocol and all safety information prior to the start of the study.

9.2 Institutional Review Board (IRB)/Ethics Committee (EC) Review and Approval

The investigator is responsible for obtaining IRB/EC approval to conduct this study (including IRB/EC approval of the Informed Consent form) and for ensuring continuing review as required by the IRB/EC. Written confirmation of this approval and periodic review must be provided to the sponsor prior to the start of the study and at appropriate intervals.

9.3 Informed Consent

The investigator will inform subjects as to the nature, expected duration and purpose of the study, the administration of the study medication, and the hazards involved, as well as the potential benefits that may come from treatment with this investigational drug. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), and other national regulations, if study is conducted at sites outside the US.

The subject will be informed that his/her medical records will be subject to review by the sponsor and possibly by a representative of the Food and Drug Administration, as well as national regulatory authorities, for patients treated outside the US. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from this study at any time without prejudicing further care. Informed consent must be obtained from every subject prior to study entry. This will be kept by the investigator and will be subject to review by the sponsor; it will also be available to the subject.

9.4 Confidentiality

All information provided to the investigator relevant to the study medication, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the sponsor, except as required by law.

9.5 Source Documentation

The investigator will allow inspections of the study site and documentation by clinical research and audit personnel from the sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to the subjects' medical or clinic records is necessary. The investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the study describing the study number, the drug being evaluated, the study number assigned to that subject and a statement that consent was obtained;
- a note of each subsequent study visit including any concerns about adverse events or abnormal laboratory data and their resolution;
- notes of all concomitant medication taken by the subject including start and stop dates;
- a note of when the subject terminated from the study, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study (thereafter it will be archived with the study file).

9.6 Drug Accountability

The investigator agrees to supervise the maintenance of records of the receipt, dispensing and return or destruction of study material supplied by the sponsor. Destruction of any material must be witnessed and documented in writing. The dispensing record must make it clear which subject received which material.

9.7 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study center one or more times during or after the study for monitoring purposes and to assist the research staff with any queries they may have.

Due to the nature of the illness being treated and the data collected, some or all monitoring at certain sites may be performed remotely.

9.8 Case Report Forms, Investigator's Study File and Record Retention

All case report forms and supporting source documentation must be available to the sponsor during monitoring visits.

Prior to review of the case report forms by the sponsor's representative and forwarding of the case report forms to the sponsor, they should be reviewed for completeness and legibility by the investigator or a member of the research team.

The investigator will maintain all records relating to the study (including copies of case report forms) for at least 2 years after written notification by the sponsor that the investigational drug program has been either completed or terminated, or that a New Drug Application (NDA) has been approved by the FDA. Should the investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the study records, custody must be transferred to a person who will accept that responsibility, and the sponsor must be notified in writing of the name and address of said person.

9.9 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this study without the prior written permission of the subject, the sponsor and the IRB/EC.

10. Sponsor Responsibilities

10.1 General

The sponsor agrees to adhere to US FDA Guidelines on Good Clinical (Research) Practices and with the ICH Guideline for Good Clinical Practice, E6(R2). The sponsor has a legal responsibility to report fully to regulatory authorities the results of this study. It is the sponsor's responsibility to obtain appropriate regulatory approval to perform the study.

10.2 Case Report Forms

Case report forms will be provided by the sponsor or, upon agreement with the sponsor, forms generated by the investigative site may be used. The electronic data collection system used will be compliant with applicable aspects of 21 CRF Part 11, ICH guidelines, GCP and HIPAA.

10.3 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study centers. Due to the nature of the research and the issues surrounding travel at this time, on-site monitoring may not occur until after completion of the study. Case report forms and source documentation will be available for review during monitoring visits to the center. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and good clinical (research) practice obligations, proper maintenance of records including drug accountability records, correct administration of study medications including storage conditions and accurate reporting of adverse events.

10.4 Audit

The sponsor has an obligation to audit a proportion of studies; this is usually undertaken by a department other than the clinical research department. Therefore the sponsor, an independent auditor or a regulatory authority may wish to audit the study site and documentation and these audits may take place as the study is running or up to several years later.

10.5 Confidentiality

The sponsor will not keep any material on file bearing any subject's name, and the subject's confidentiality will be maintained at all times.

11. Protocol Modifications

If necessary during the course of the study, the protocol may be modified by the sponsor in consultation with the investigator. Except in the case of modifications to resolve an imminent safety issue, any protocol modification or revision must be reviewed and approved by the investigator's IRB/EC prior to implementation.

12. Publication

RedHill will provide unblinded data to a publications committee for publication of the results of this study once completed and all data have been cleaned and the blind broken. The publications committee will be constituted according to the guidelines developed by the Company. If deemed necessary by the Company for protection of proprietary information prior to patent filing, the investigators agree to delay for 60 days before any presentation or publication is submitted.

13. References

Abe M, Tahara M, Sakai K, Yamaguchi H, Kanou K, Shirato K, Kawase M, Noda M, Kimura H, Matsuyama S, Fukuhara H, Mizuta K, Maenaka K, Ami Y, Esumi M, Kato A, Takeda M. TMPRSS2 Is an Activating Protease for Respiratory Parainfluenza Viruses. J Virol. 2013 Nov;87(21):11930-5.

Bertram S, Glowacka I, Muller MA, Lavender H, Gnirss K, Nehlmeier I, Niemeyer D, He Y, Simmons G, Drosten C, Soilleux EJ. Jahn O, Steffen I, Pohlmann S. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. J Virol. 2011 Dec;85(24):13363-72.

CDC COVID Data Tracker: https://covid.cdc.gov/covid-data-tracker/#cases_totalcases. Downloaded 9/20/20.

Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med 2004;23:1023–38.

Gandhi RT, Lynch JB, del Rio C. Mild or moderate COVID-19. New Eng J Med 2020; online ahead of print.

Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, Zjang L, Lin R, Liu J, Ding Z, Hou X. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol 2020;115:916-23.

Massarweh A, Eliakim-Raz N, Stemmer A, Levy-Barda A, Yust-Katz S, Benouaich-Amiel A, Ben-Zvi H, Moskovits N, Brenner B, Bishara J, Yahav D, Tadmor B, Zaks T, Stemmer SM. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CV-2 in patients undergoing treatment for cancer. JAMA Oncol 2021 published online.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30: 3267–84

Meyer JE, Brocks C, Graefe H, Mala C, Thans N, Burgle M, Rempel A, Rotter H, Wollenberg B, Lang S. The oral serine protease inhibitor WX-671 – First experience in patients with advanced head and neck carcinoma. Breast Care 2008;3:20-4.

Oguntuyo KY, Stevens CS, Siddiquey MNA, Schilke RM, Woolard D, Zhang H, Acklin JA, Ikegame S, Huang C-T, Lim JK, Cross RW, Geisbert TW, Ivanov SS, Kamil JP, Lee B. In plain sight: the role of alpha-1-antitrypsin in COVID-19 pathogenesis and therapetucs. bioRxiv, 2020.

Oldenburg E, Schar CR, Lange EL, Plasse TF, Abramson DT, Towler EM, Levitt M, Fathi R, Jensen JK. New potential therapeutic applications of WX-UK1, as a specific and potent inhibitor of human trypsin-like proteases. Proc Amer Assn Cancer Res 2018;abstract 784.

Pruijssers AJ, George AS, Schafer A, Leist SR, Gralinski LE, Dinnon KH III, Yount BL, Agostini ML, Stevens LJ, Chapell JD, Lu X, Hughes TM, Gully K, Martinzez DR, Brown AJ, Graham RL, Perry JK, Du Pont V, Pitts J, Ma B, Babusis D, Murakami E, Feng JY, Bilello JP, Porter DP, Cihlar T, Baric RS, Denison MR, Sheahan TP. Remdesivir potently inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. bioRxiv 2020. 32 (3); 107940.

Tsujimura S, Saito K, Nakayamada S, Tanaka Y. Bolus infusion of human urinary trypsin inhibitor improves intractable interstitial pneumonia in patients with connective tissue diseases. Rheumatol 2008;47:907-13.

van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020 Mar 17.

van Gerwen M, Alsen M, Little C, Barlow J, Genden E, Naymagon L, Tremblay D. Risk factors and outcomes of COVID-19 in New York City; a retrospective cohort study. J Med Virol 2021;93:907-15.

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in different types of clinical specimens. J Amer Med Assn 2020;epub ahead of print.

Williamson EJ Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AUS Grieve R Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera F, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-46.

World Health Organization. WHO R&D Blueprint: novel coronavirus. 2020. Downloaded 3/20/20: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf?ua=1

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. J Amer Med Assn 2020;323:1239-42.

Yamada H, Le QT, Kousaka A, Higashi Y, Tsukane M, Kido H. Sendai virus infection up-regulates trypsin I and matrix metalloproteinase-9 triggering viral multiplication and matrix degradation in rat lungs and lung L2 cellls. Arch Virol 2006;151:2529-37.

Yamane D, McGivern DR, Wauthier E, Yi M, Madden VJ, Welsch C, Antes I, Wen Y, Chugh PE, McGee CE, Widman DG, Misumi I, Bandyopadhyay S, Kim S, Shimakami T, Oikawa T, Whitmire JK, Heise MT, Dittmer DP, Kao CC, Pitson SM, Merrill AH Jr, Reid LM, Lemon SM. Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation. Nat Med. 2014 Aug;20(8):927-35.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.

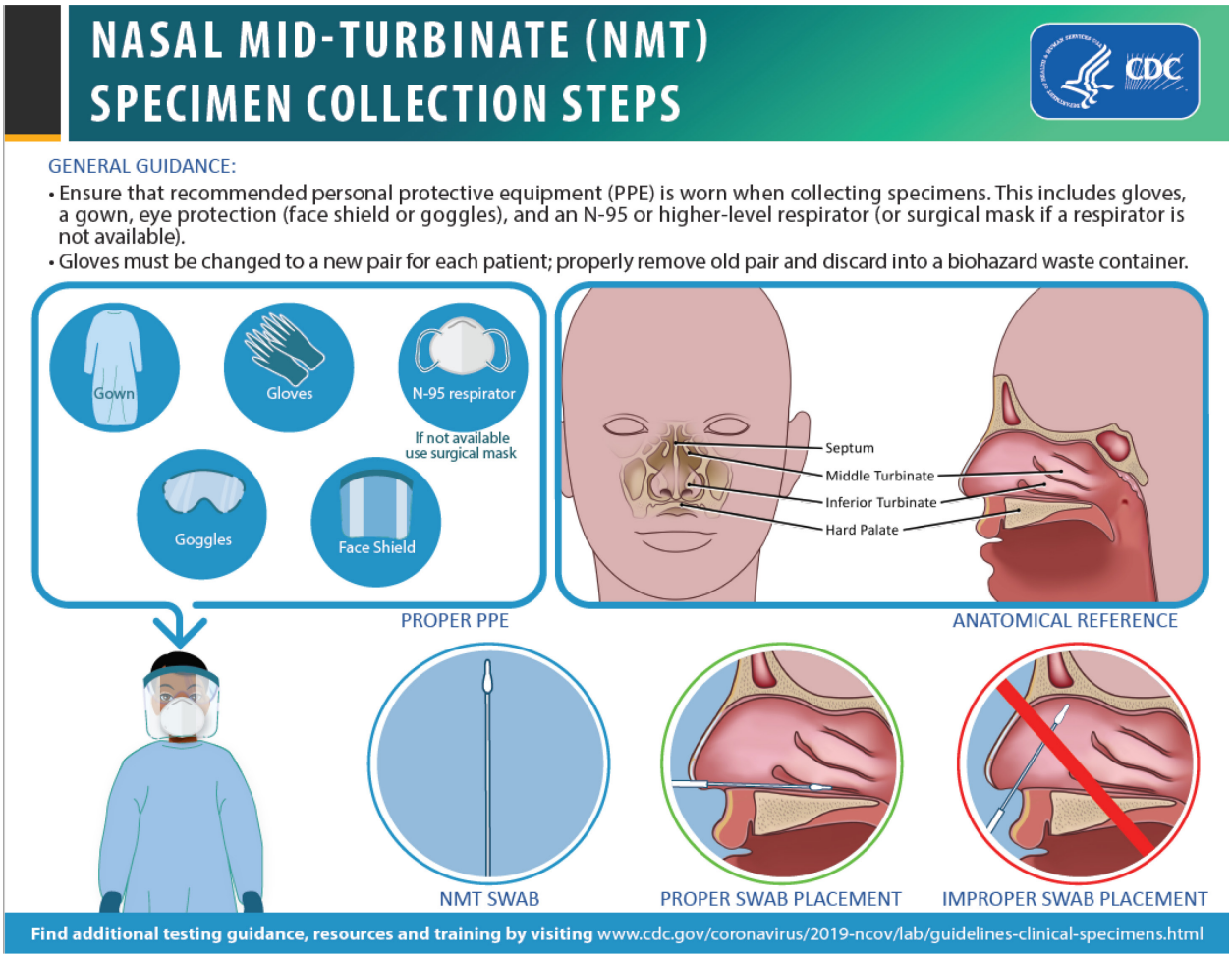
Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet 2020;395:1054-62.

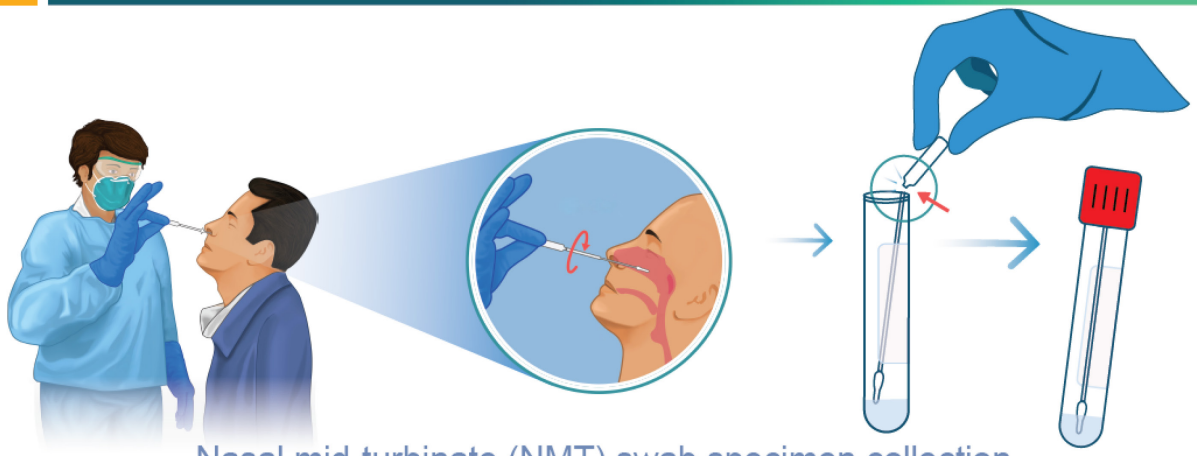
Zmora P, Hoffman M, Kollmus H, Moldenhauer A-S, Danov O, Braun A, Winkler M, Schughart K, Pohlmann S. TMPRSS11A activates the influenza A virus hemagglutinin and the MERS coronavirus spike protein and is insensitive against blockade by HAI-1. J Biol Chem. 2018 Sep 7;293(36):13863-13873.

Appendices

Appendix 1. Nasal Mid-Turbinate (NMT) Specimen Collection

US CDC-recommended procedure on next two pages.





Nasal mid-turbinate (NMT) swab specimen collection

STEP 1

Tilt patient's head back 70 degrees.

Use a flocked tapered swab.

Some swabs come with a stopper, which indicates proper nasal insertion depth.

STEP 2

While gently rotating the swab, insert it less than one inch (about 2 cm) into nostril parallel to the palate until resistance is met at turbinates.

STEP 3

Rotate the swab several times against nasal wall.

Remove swab, insert it into the other nostril and repeat the process.

STEP 4

Place swab, tip first, into the transport tube provided.

Once the tip is near the bottom, break the swab handle at the swab breakpoint by bending back and forth or cut it off with sterile scissors.

The swab should fit in the tube comfortably so that the cap can be screwed on tightly to prevent leakage and contamination.

Find additional testing guidance, resources and training by visiting www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html

Appendix 2. Patient diary

Patient-Reported COVID-19 Sign and Symptom Diary (PRO-COVID-19)

General information (not to be included in the actual questionnaire): Questions and response options are sorted into four separate domains based on affected system including: body/systemic, respiratory, gastrointestinal and nose/mouth/throat.

Instructions

This questionnaire asks about the impact of COVID-19 on your health. Please respond as accurately as possible.

Domain 1: Body/Systemic

1) At their worst, what was the severity of your **CHILLS OR SHIVERING** over the last 24 hours? Chills and shivering are a feeling of coldness or shaking while not in a cold environment.

   ◯ None
   ◯ Mild
   ◯ Moderate
   ◯ Severe

2) At its worst, what was the severity of **FEELING HOT OR FEVERISH** over the last 24 hours?

   ◯ None
   ◯ Mild
   ◯ Moderate
   ◯ Severe

3) At their worst, what was the severity of your **MUSCLE OR BODY ACHES** over the last 24 hours?

   ◯ None
   ◯ Mild
   ◯ Moderate
   ◯ Severe

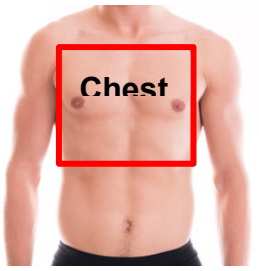
4) At their worst, what was the severity of your **HEADACHES** over the last 24 hours?

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

5) At its worst, what was the severity of your **TIREDNESS OR FEELING OF LOW ENERGY** over the last 24 hours?

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

6) At its worst, what was the severity of your **CHEST PAIN** over the last 24 hours? This picture shows the location of your chest.



- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

Domain 2: Respiratory

7) At its worst, what was the severity of your **DIFFICULTY BREATHING** over the last 24 hours?

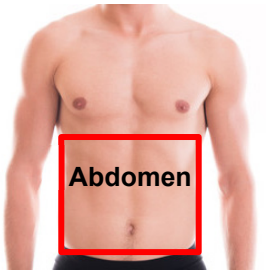
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

8) At its worst, what was the severity of your **COUGH** over the last 24 hours?

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

Domain 3: Gastrointestinal

9) At its worst, what was the severity of your **ABDOMINAL PAIN** over the last 24 hours? This picture shows the location of your abdomen.



- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

10) At its worst, what was the severity of your **NAUSEA** over the last 24 hours? Nausea is the feeling of needing to vomit, commonly referred to as throwing up.

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

11) At its worst, what was the severity of your **LOSS OF APPETITE** over the last 24 hours? Loss of appetite is not wanting to eat or drink.

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

12) How many times did you have **DIARRHEA** in the last 24 hours? Diarrhea is having loose or watery and more frequent bowel movements.

- ◯ I did not have diarrhea at all
- ◯ 1-2 times
- ◯ 3-4 times
- ◯ 5 or more times

13)How many times did you have **VOMIT (THROW UP)** in the last 24 hours? Vomiting is expelling stomach contents through your mouth.

- ◯ I did not vomit at all
- ◯ 1-2 times
- ◯ 3-4 times
- ◯ 5 or more times

Domain 4: Nose & Throat

14)At its worst, what was the severity of your **SORE THROAT** over the last 24 hours? A sore throat may be painful or feel scratchy or irritated.

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

15)At its worst, what was the severity of your **STUFFY OR RUNNY NOSE** over the last 24 hours?

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

16)Rate your **SENSE OF SMELL** in the last 24 hours

- ◯ My sense of smell is the same as usual
- ◯ My sense of smell is less than usual
- ◯ I have no sense of smell

17)Rate your **SENSE OF TASTE** in the last 24 hours

- ◯ My sense of taste is the same as usual
- ◯ My sense of taste is less than usual
- ◯ I have no sense of taste

GLOBAL

1) In the past 24 hours, have you returned to your **USUAL HEALTH** (before your COVID-19 illness)?

   ◯ Yes
   ◯ No

2) In the past 24 hours, have you returned to your **USUAL ACTIVITIES** (before your COVID-19 illness)?

   ◯ Yes
   ◯ No

3) In the past 24 hours, what was the severity of your **OVERALL COVID-19-RELATED SYMPTOMS** at their worst?

   ◯ None
   ◯ Mild
   ◯ Moderate
   ◯ Severe

Additional Health and Medication Assessments

1. **In the past 24 hours, have you experienced any other changes in health that have not already been reported?**

   ◯ **Yes**
   ◯ **No**

   ∗ *Answering "Yes" will trigger a short free-text box to describe issue, and a note to contact study staff if medical assistance is required immediately.*

2. **Please enter each medication (other than the study medication) you have taken for COVID-related symptoms today, including the amount taken over the past 24 hours.**

I didn't take any medication for COVID-19-related symptoms today. ☐
OR
Medication name: _____

Dose per tablet/capsule (of primary ingredient): _____

Number of doses taken over past 24 hours (since you last filled out the questionnaire):

_____

Did you take any additional medications for COVID-19? Yes: ☐ No: ☐

Answering yes will trigger another set of lines to list additional medication, dosage and number of doses.

3. What time did you take your study medication today?

Enter time: HH:MM AM/PM

☐Check this box if study medication was not taken

(If time entered):

3a. How many capsules did you take?

◯ **1 capsule**

◯ **2 capsules**

Appendix 3. CYP3A4 Strong inhibitors and sensitive substrates

Strong inhibitors

boceprevir
clarithromycin
cobicistat
danoprevir and ritonavir
elvitegravir and ritonavir
grapefruit juice
idelalisib
indinavir and ritonavir
itraconazole
ketoconazole
lopinavir and ritonavir
nefazodone
nelfinavir
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir and ritonavir
telaprevir
tipranavir and ritonavir
telithromycin
troleandomycin
voriconazole

Sensitive substrates

alfentanil
avanafil
budesonide
buspirone
conivaptan
darifenacin
darunavir
dasatinib
dronedarone
ebastine
eletriptan
eplerenone
everolimus
felodipine
ibrutinib
indinavir
lomitapide
lovastatin
lurasidone
maraviroc
midazolam
naloxegol
nisoldipine
saquinavir
simvastatin
sirolimus
tacrolimus
tipranavir
triazolam
vardenafil
quetiapine
sildenafil
ticagrelor
tolvaptan

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1 Downloaded 11/23/20.