Appendix C:

A Phase 2 Safety and Efficacy Study of Upamostat for Early Outpatient Treatment of COVID-19

Intervention: Upamostat or Placebo

Industry Supporter – RedHill Biopharma Ltd.

Information/activities described in the Master Protocol (MP) apply to this PSA. Any information/activities in the Master Protocol that do not apply to this Product Specific Appendix (PSA) are indicated by ~~strikethrough~~, while evaluations that have been added to this PSA are indicated by **bold** text. Section numbering aligns with the master protocol. Sections that have no additional information changes from the master protocol are not included.

Version 5.0

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SUMMARY OF CHANGES FROM PREVIOUS VERSION:

Affected Section(s)	Summary of Revisions Made	Rationale
C 1.2 Schedule of Activities, C 9.4.1, C 9.4.2 Screening and Enrollment Visit	Updated order of activities	Updated to clarify that screening activities under the PSA (ECG) cannot be performed until product specific informed consent and Step 1 randomization completed
C 6.3 Lifestyle Considerations	Added caution for alcohol consumption while taking study drug	FDA request
	Added Table of Contents	Added table

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

USG funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of USG-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

SIGNATURE PAGE

The signature below constitutes the approval of this product appendix and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the master protocol and product appendix, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator: _____

Name/Title (Print/Type)

Signed: **Date:**

_____ _____

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C 1 PROTOCOL SUMMARY

C 1.1 Study Synopsis

PSA Title:	A Phase 2 safety and efficacy study of upamostat for early outpatient treatment of COVID-19
Overall Study Description:	This study is a global, multicenter, adaptive, randomized, double blind, platform trial evaluating promising investigational products (IP) for early outpatient treatment of SARS-CoV-2 infection
Objectives:	**Primary:** To determine if early treatment with upamostat can shorten time to sustained symptom alleviation or resolution in participants infected with SARS-CoV-2. **Secondary:** • To determine if early treatment with upamostat can reduce disease severity in participants infected with SARS-CoV-2 • To determine if early treatment with upamostat can decrease the incidence of hospitalization due to COVID-19 • To evaluate virologic efficacy of upamostat compared to placebo • To evaluate the safety and tolerability of upamostat compared to placebo **Exploratory:** • To determine the presence and titer of antibodies to SARS-CoV-2 at baseline, the development of antibodies during study participation, and their association with clinical outcome • To assess the impact of host transmembrane protease polymorphisms on drug efficacy
Endpoints:	**Primary:** Time to sustained alleviation or resolution of COVID-19 symptoms [Timeframe: Day 0 to Day 28]
	Secondary: • Change in overall COVID-19 symptom severity score [Timeframe: Day 0 to Day 28] • Proportion of participants in each treatment group developing new COVID-19 symptoms graded as severe on the symptom score [Timeframe: Day 0 to 28] • Proportion of participants who report: o Return to usual state of health o Return to usual activities [Timeframe: Days 7, 14, 28 Week 8, and Week 12]

	• Proportion of participants hospitalized for COVID-19 [Timeframe: Day 0 to Week 12] • Number and proportion of participants hospitalized (all cause) • Number and proportion of death (all cause) • Comparison of active and placebo treatment groups in time to negative PCR [Timeframe: Day 0 to Week 12] **Safety:** • Incidence of Serious Adverse Events (SAE) • Comparison between active and placebo treatment groups in proportion of all and ≥grade 3 adverse events as assessed by the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017. • Incidence of AEs causing IP discontinuation • Incidence of all-cause IP discontinuation or interruption • Incidence of Adverse Events of Special Interest (AESI) (if applicable to PSA) • Number of participants hospitalized due to adverse events regardless of cause	
	Exploratory: • Assay for anti-SARS-CoV-2 IgM and IgG baseline and Week 8 • Targeted analysis of polymorphism of known host transmembrane proteases which may be involved in viral entry into host cells	
Study Population:	Up to 300 SARS-CoV-2 infected adults	
Description of Sites/Facilities Enrolling Participants:	Ivory Coast	Abidjan: Institute Pasteur Bouake: Institut Pierre Richet / Institut National de Santé Publique
	Republic of South Africa	Bloemfontein: JOSHA Research Institute
	Thailand	Bangkok: Royal Thai Army
	Uganda	Fort Portal Regional Referral Hospital
	United States	Baltimore, MD: Johns Hopkins Hospital Bayview Medical Center

Description of Study Intervention:	Upamostat Oral capsule : 400 mg (2×200 mg) daily for 14 days
Study Duration:	18 Months
Participant Duration:	12 Weeks

C 1.2 Schedule of Activities (SoA)

The SoA provided below includes all activities described in the Master Protocol.

Activities in the Master Protocol that do not apply to participants randomized to the upamostat Appendix C are indicated by ~~strikethrough~~, while activities that have been added are indicated by **bold** text.

STUDY VISIT LOCATION [a]	IN PERSON OR REMOTE [b]	**IN PERSON**		**REMOTE** [b]		IN PERSON			**REMOTE**	IN PERSON OR REMOTE
STUDY PROCEDURES	SCREENING [c]	ENROLLMENT D0	D3	D7	D10	D14	D28	**WEEK 8** [d]	WEEK 12	UNSCHEDULED [e]
VISIT WINDOW (+/- DAYS OR WEEKS)	UP TO 24 HOURS PRIOR TO ENROLLMENT	0	1 DAY	1 DAY	1 DAY	2 DAYS	4 DAYS	**1 WEEK**	2 WEEKS	NOT APPLICABLE
SCREENING & PROCEDURES										
Screening Informed Consent	X									
Demographics	X									
Medical History	X									
SARS-CoV-2 Vaccination History [m, j]	X	X	~~X~~	X		~~X~~	~~X~~		~~X~~	
Vital Signs [f]	X	X								
Physical Exam [g, f]	X	X								
Height and Weight [f]	X	X								
Pregnancy Test [h, f, j]	X	X	When pregnancy is suspected				**X**	When pregnancy is suspected		
Screening Symptom Questionnaire [i, j]	X	X								

Study Visit Location [a]	In Person or Remote [b]	**In Person**		**Remote** [b]		In Person			**Remote**	In Person or Remote
Study Procedures	Screening [c]	Enrollment D0	D3	D7	D10	D14	D28	**Week 8** [d]	Week 12	Unscheduled [e]
Visit Window (+/- days or weeks)	Up to 24 hours prior to Enrollment	0	1 day	1 day	1 day	2 days	4 days	**1 week**	2 weeks	Not Applicable
Diagnostic Test for SARS-CoV-2 [k, j]	X	X								
Concomitant Medication Review [j]		X	X	X	X	X	X	X	X	X
Randomization (Step 1)		X								
Study (IP) Informed Consent		X								
Screening Assessments [i, j]	X	X								
Randomization (Step 2)		X								
Dispense Study Kit		X								
Collect and Update Contacts		X	X	X						
EFFICACY										
Daily Follow Up Symptom Questionnaire			Daily					**X**	X	X
Upper Respiratory Specimen		X	X	X	X	X	X	**X**	X	X
Clinical Outcome Assessment			X	X		X	X	**X**	X	X

STUDY VISIT LOCATION [a]	IN PERSON OR REMOTE [b]	**IN PERSON**		**REMOTE** [b]		IN PERSON			**REMOTE**	IN PERSON OR REMOTE
STUDY PROCEDURES	SCREENING [c]	ENROLLMENT D0	D3	D7	D10	D14	D28	**WEEK 8** [d]	WEEK 12	UNSCHEDULED [e]
VISIT WINDOW (+/- DAYS OR WEEKS)	UP TO 24 HOURS PRIOR TO ENROLLMENT	0	1 DAY	1 DAY	1 DAY	2 DAYS	4 DAYS	**1 WEEK**	2 WEEKS	NOT APPLICABLE
SAFETY										
Vital Signs		X	X			X	X	**X**		X
Physical Exam		X	X			X	X	**X**		X
Venous Blood Sampling										
Hematology		X	X			X	X	**X**		X
Blood Chemistry		X	X			X	X	**X**		X
Coagulation Studies		**X**	**X**			**X**	**X**	**X**		**X**
ECG	**X** [m j]		**X**			**X**				**X**
Adverse Events		Continuous								
UPAMOSTAT or PLACEBO ADMINISTRATION										
Administer Upamostat or Control [m]		**Daily for 14 days (drug dispensed on Day 0)**								
RESEARCH LABS										
Serum Anti-SARS-CoV-2 antibody		**X**						**X**		
Whole Blood, Plasma and Serum Storage for Possible Future Research		**X**	**X**			**X**	**X**	**X**		**X**
Pharmacokinetics [n]		**X**	**X**			**X**				

Study Visit Location [a]	In Person or Remote [b]	**In Person**		**Remote** [b]		In Person			**Remote**	In Person or Remote
Study Procedures	Screening [c]	Enrollment D0	D3	D7	D10	D14	D28	**Week 8** [d]	Week 12	Unscheduled [e]
Visit Window (+/- days or weeks)	Up to 24 hours prior to Enrollment	0	1 day	1 day	1 day	2 days	4 days	**1 week**	2 weeks	Not Applicable
Whole Blood Sample for Host Polymorphism Assessment [o]		**X**								

a. In person visits may include those that take place at the research site, home visits or visits to participants admitted to hospital for social, quarantine or isolation purposes. Remote visits may take place over the phone or by video conferencing.
b. If remote visit not feasible or is not permitted under local regulation, the visit may be conducted in person.
c. If screening visit conducted remotely, SARS-CoV-2 testing (if applicable), ECG, and pregnancy test will be completed at the enrollment visit prior to enrollment visit activities. Screening and enrollment activities may take place on the same day.
d. A Week 8 visit has been added for participants randomized to the upamostat Appendix C
e. For Unscheduled Visits - These procedures may be done according to clinical judgement.
f. These activities may take place at screening or enrollment. Activities completed at screening do not need to be repeated at enrollment
g. Physical exam will be performed by a healthcare professional qualified in the clinical practice of medicine. This may include physicians, nurses, or other allied health professionals who are registered/licensed in the local jurisdiction and the performance of a physical exam is within the current scope of practice. Physical exam may be conducted in person or via a research staff-assisted telehealth physical exam
h. Pregnancy testing will be completed in all females of childbearing potential defined as premenopausal females capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose male sexual partners have been vasectomized or are using contraceptive devices. If screening and enrollment are not conducted on the same day, then pregnancy testing will not be repeated for enrollment. Pregnancy testing may be performed with serum or urine and must be authorized for use by the relevant national authority for the detection of pregnancy in the country where the test is administered.
i. The Screening Symptom Questionnaire may be completed at Screening if performed on same day as Enrollment. If Enrollment does not take place on the same day as Screening, then Screening Symptom Questionnaire will be repeated at Enrollment. Results of the questionnaire will be used to determine final eligibility for enrollment
j. Final eligibility will be determined upon completion of these activities. For activities completed at Screening, results will be reviewed and verified at enrollment to determine eligibility.
k. Diagnostic testing must be an approved molecular or antigen diagnostic test for SARS-CoV-2 from any upper respiratory specimen performed at screening or enrollment or within 5 days of enrollment. The test used must be authorized for use by the relevant national authority for the detection of SARS-CoV-2 in the country where the test is administered. Test kits can be obtained from a locally acquired source. Historical testing results will be acceptable if testing performed within the required window. The local testing result, specimen type, assay type, and date of test will be recorded in the CRF. The test result must be available and reviewed by site PI or study staff to confirm eligibility. At baseline, the specimen will also be tested to determine SARS-CoV-2 variant.

l. Screening assessments will include Screening symptom questionnaire, concomitant medications, pregnancy testing, SARS-CoV-2 diagnostic testing results, SARS-CoV-2 vaccination history, and baseline ECG. Screening assessments may be performed at screening or enrollment but must be reviewed by research staff before determination of final eligibility

m. 1 bottle to be dispensed at D0, with empty bottles and/or remaining capsules to be collected at D14 visit

n. PK sampling will be performed. All participants will have Day 0 sampling prior to administration of study drug and Day 14 sampling approximately 22-26 hours after the last dose of study medication. Participants will then follow one of two schedules for Day 3 sampling (see Section 9.2.6 Pharmacokinetic Testing). Study staff may call participant the day prior to the Day 3 sampling to remind them of timing of upamostat dose and venous blood sampling.

o. A sample of whole blood will be stored for planned future host protease polymorphism assessment

C 3 INTRODUCTION

C 3.1 Study Rationale

There are four main sub-groupings of coronaviruses (classes alpha, beta, gamma, and delta). SARS-CoV-2 is a member of the beta class coronaviruses that also include the close relatives SARS-CoV (the first identified severe acute respiratory syndrome-related coronavirus) and MERS-CoV (Middle East respiratory syndrome-related coronavirus). All three viruses predominantly attack the respiratory system, but can also impact the gastro-intestinal system, heart, kidney, liver, and central nervous system, potentially leading to the failure of multiple organs.

Transmembrane serine proteases are essential for viral fusion with the host cell membrane [Yao 2022]. Upamostat is a first-in-class orally administered potent inhibitor of serine proteases targeting multiple indications. Upamostat was initially studied as an inhibitor of urokinase plasminogen activator targeting oncology indications. Subsequent studies revealed that the compound is a potent inhibitor of other serine proteases, especially trypsins. The presumed mechanism is inhibition of spike protein cleavage necessary for viral entry into host cells. It targets human cell rather than viral factors and as such, is expected to be effective against emerging variants. In vitro, upamostat inhibited the original SARS-CoV-2 virus at a concentration well below that achievable in patients. Preliminary results of testing against SAR-CoV-2 BA.5 variant showed a 3-log decrease in viral titer at the highest dose tested. A pilot outpatient study in symptomatic, SARS-CoV-2 positive patients revealed that the drug was well tolerated at both dose levels tested, 200 and 400 mg daily for 14 days [Plasse 2022]. While the study was not powered for efficacy determination, only one of 41 patients (2.4%) receiving upamostat at either of the two doses used developed new severe symptoms on study, versus 4 of 20 (20%) of placebo recipients. Importantly, no upamostat-treated patient was hospitalized for COVID-19 during the study versus 3 of 20 (15%) of placebo recipients. Pharmacologic parameters (reduction in mean D-dimer levels and increased incidence of minor increases in INR and PTT) demonstrated dose-dependent effects.

C 3.3 Study Hypotheses

That early treatment with upamostat among outpatients infected with SARS-CoV-2 can shorten time to sustained symptom alleviation or resolution as compared to standard treatment.

C 3.4 Risk/Benefit Assessment

C 3.4.1 Known Potential Risks

C.3.4.1.1 Risks Associated with Upamostat

To date, 230 subjects have been treated with upamostat in clinical trials, including 41 in a recently concluded pilot study of upamostat for outpatient treatment of COVID-19.

In randomized clinical trials the only events attributable to upamostat were transient increases in transaminases, rash and, in patients receiving capecitabine, palmar-plantar erythrodysaesthesia syndrome.

In the COVID-19 study, no increase in transaminases was seen at either upamostat dose level as compared to placebo. International Normalized Ratio (INR) or activated partial thromboplastin time (aPTT) were often mildly abnormal at baseline in patients in the COVID-19 study. On-study, 25% of placebo patients, 50% of upamostat 200 mg recipients and 62% of upamostat 400 mg recipients developed increases in either INR or aPTT of at least one grade per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. Almost all increases were Grade 1; no clinical bleeding was noted.

C.3.4.1.2 Steps Taken to Minimize Risks

1. Risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, as well as periodic review of all safety data by an independent data monitoring committee

2. Because upamostat may inhibit CYP3A4, patients receiving anticoagulants metabolized by CYP3A4 (warfarin, apixaban [Eliquis], or rivaroxaban [Xarelto]) may not be entered into the study, nor may these medications be started while a patient is receiving upamostat.

C 3.4.3 Assessment of Potential Risks and Benefits

This study involves potential risks to and potential health benefits for the participant. Potential benefits, along with anticipated vital knowledge the trial is likely to generate, suggest that benefits of the study outweigh the risks.

C 4 OBJECTIVES AND ENDPOINTS

C 4.1 Early Treatment

In addition to those listed in the MP, the following objectives and endpoints will be included:

	Objectives	Endpoints
Secondary	• To determine if early treatment with upamostat can reduce disease severity in participants infected with SARS-CoV-2	• Change in overall COVID-19 symptom severity score [Timeframe: Day 0 to Day 28] • Proportion of participants in each treatment group developing new COVID-19 symptoms rated as severe [Timeframe: Day 0 to 28] • Proportion of participants who report: o Return to usual state of health o Return to usual activities [Timeframe: Days 7, 14, 28 Week 8, and Week 12]
	• To determine if early treatment with upamostat can decrease the incidence of hospitalization due to COVID-19	• Proportion of participants hospitalized for COVID-19 [Timeframe: Day 0 through Week 12]
	• To evaluate the clinical efficacy of upamostat compared to placebo	• Number and proportion of participants hospitalized (all cause) [Timeframe: Day 0 to Day 28] • Number and proportion of participant deaths (all cause) [Timeframe: Day 0 to Day 28]
	• To evaluate virologic efficacy of upamostat compared to placebo	• Comparison of active and placebo treatment groups in time to negative PCR [Baseline through Week 12]

	Objectives	Endpoints
Safety	• To evaluate the safety and tolerability of upamostat compared to placebo	• Incidence of Serious Adverse Events (SAE) • Comparison between active and placebo treatment groups in proportion of all and ≥grade 3 adverse events as assessed by the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017. • Incidence of AEs causing IP discontinuation • Incidence of all-cause IP discontinuation or interruption • Number of participants hospitalized due to adverse events regardless of cause
Exploratory	• Characterize the impact of SARS-CoV-2 genetic variability on primary and secondary outcomes	• Difference in efficacy outcomes among circulating variants of interest (VOI) and variants of concern (VOC) via o Geographic and temporal prevalence o SARS-CoV-2 genome sequencing
	• To determine the presence and titer of antibodies to SARS-CoV-2 at baseline and the development of antibodies during study participation	• Assay for anti-SARS-CoV-2 IgM and IgG at baseline and Week 8
	• To assess the impact of host transmembrane protease polymorphisms on drug efficacy	• Targeted analysis of polymorphism of known host transmembrane proteases which may be involved in viral entry into host cells

C 5 STUDY DESIGN

C 5.1 Overall Design

A Phase 2 adaptive, randomized, double-blind, placebo-controlled platform trial to evaluate the safety and efficacy of upamostat for early outpatient COVID-19 treatment. From the master protocol, following completion of the screening and enrollment requirement, participants who meet the entry criteria for upamostat are eligible for randomization to the upamostat Early Treatment arm of the trial. Probability of randomization to the upamostat arm will be dependent on the number of PSAs enrolling in the Early Treatment indication. For example, if three products are enrolling in the treatment indication at the same time, probability of randomization to the upamostat arm is 1:3.

Once randomized to upamostat, participants will undergo an upamostat specific informed consent. A second, blinded randomization will be to the active agent orplacebo. The probability of the second randomization will also be dependent on the number of products enrolling in the indication at that time. The ratio of assignment to active agent or placebo will be r:1 where r is the number of IPs in the Early Treatment indication that a given participant is eligible to receive.

The total sample size is projected to be 300 (150 upamostat, 150 control). If additional IPs are enrolling in the treatment indication, the sample size will be adjusted based on the ability to share control groups of concurrently enrolled participants.

Interim analyses and saftey monitoring will be conducted and will allow early stoppage for futility, efficacy, or safety described in Section C 10. Adverse Events and Serious Adverse Events and Section C 13. Statistical Considerations.

C 5.3 Scientific Rationale for Study Design

The purpose of this PSA is to evaluate the safety and efficacy of upamostat for early outpatient COVID-19 treatment. The platform trial design will maximize efficiency within the trial to allow for sharing of controls. Interim analysis plans will allow for early stopping for success, futility or if there is a safety signal.

C 5.4 Justification for Dose

Doses of 200 and 400 mg upamostat daily were well tolerated in previous studies. In a healthy volunteer study in which patients were given 100, 200 or 400 mg upamostat or placebo daily for 14 days, no difference in tolerability was noted among the upamostat doses. Similarly, in a pancreatic cancer study in which all patients received standard therapy, gemcitabine, and were randomized to either no additional treatment, 200 or 400 mg upamostat daily, both dose levels of upamostat were well tolerated.

In a pilot study of upamostat for treatment of COVID-19, patients received placebo, 200 or 400 mg upamostat daily for 14 days. Both dose levels were well tolerated, with no increase in clinical adverse events over placebo. Clinical adverse event rates (Grade 1, Grade 2) were 10%, 20% in the placebo group, 25%, 0% in the upamostat 200 mg group and 19%, 10% in the

upamostat 400 mg group. The only laboratory effect noted was an increase in the incidence of Grade 1 increases in INR or aPTT in the upamostat-treated patients as compared to those receiving placebo, noted in 25% of placebo patients, 50% of upamostat 200 mg patients and 65% of upamostat 400 mg patients. Most of these were one grade increases and none was accompanied by any bleeding.

Both dose levels in this small (20-21 patients/group) study appeared to protect patients from new severe symptoms from and hospitalization for COVID-19. Several factors suggest that the 400 mg dose may be more effective than the 200 mg dose. Mean D-dimer levels were stable over the course of the study in the placebo group but decreased by 38% and 48% in the upamostat 200 mg and 400 mg groups, respectively. The only new severe on-study COVID symptom in an upamostat patient occurred in a patient in the 200 mg group. Median time to resolution of all severe symptoms was 8 days in the placebo group, 4 days in the upamostat 200 mg group, and 3 days in the upamostat 400 mg group. In summary, there was no increase in clinically significant adverse events in the 400 mg group as compared to the 200 mg group, and two parameters suggest that there may be some improvement in outcome in the high dose group as compared to the low dose group.

C 6 STUDY POPULATION AND STUDY ENROLLMENT

Population A: Adults seeking care or testing for COVID-19

C 6.1 Inclusion Criteria

Inclusion criteria are specified in the Master Protocol and:

1. **Women of childbearing potential must agree to use an effective contraceptive method upon enrollment in the study through 8 weeks after the last dose of the investigational product. This would include oral contraceptives, implanted contraceptives, intrauterine devices, and barrier methods.**
    - **A woman is considered of childbearing potential unless post-menopausal (subject is at least 50 years old and has history of ≥2 years without menses without other known or suspected cause), or permanently surgically sterilized.**
    - **Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.**

C 6.2 Exclusion Criteria

Exclusion criteria as specified in the Master Protocol and:

1. **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.**
2. **Patients with prolonged QT/QTc interval and/or increased susceptibility to arrythmia defined as the presence of any of the following:**
    - **QTc interval > 450 msec**
    - **Pathological Q-waves (defined as Q-wave > 40 msec or depth > 0.4-0.5 mV)**
    - **Evidence of ventricular pre-excitation**
    - **Electrocardiographic evidence of complete LBBB, RBBB, incomplete LBBB, in complete RBBB**
    - **Evidence of second- or third-degree heart block**
    - **Intraventricular conduction delay with QRS duration > 120 msec**
    - **Bradycardia as defined by sinus rate< 50 bpm**
    - **Personal or family history of long QT syndrome**
    - **Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, except for sinus arrhythmia**
    - **Syncopal episodes or additional risk factors for torsades de points (e.g., heart failure, hypokalemia)**

C 6.3 Lifestyle Considerations

Lifestyle Considerations as specified in the Master Protocol and:

1. **Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives for 8 weeks after investigational agent is administered.**
2. **Participants should refrain from sperm donation for 8 weeks after investigational agent administration.**
3. **Upamostat may increase the sedative effects of alcohol so participants are encouraged to avoid alcohol while taking the study medication.**

C 7 STUDY INTERVENTION

C 7.1.1 Study Intervention Description

Upamostat is designated chemically as ethyl 4-{3-[(E)-amino(hydroxyimino)methyl]-N-[(2,4,6-triisopropylphenyl) sulfonyl]-L-phenylalanyl}-piperazine-1-carboxylate hydrogen sulphate.

C 7.1.2 Dosing and Administration

Upamostat 400 mg will be dosed orally once daily for 14 days.

C 7.2 Preparation/Handling/Storage/Accountability

C 7.2.2 Acquisition

Upamostat and placebo will be provided by RedHill either directly or through a third-party clinical supply distributer.

C 7.2.4 Formulation, Appearance, Packaging, and Labeling

Size 1 oral capsules contain a white to yellowish powder of 200 mg upamostat or placebo and are packaged in round white, 40 cc 33-400 wide-mouth marlex bottles with a white 33mm child resistant polypropylene cap with an induction seal at 30 capsules per bottle.

A standard label will be adhered to each bottle. Participants will be assigned to receive their treatment according to the randomization. For each cohort, randomized subjects will be assigned a unique number.

The unique number will be the only participant identifier used on all sample collections and return of results. The site's blinded pharmacist or qualified designee will provide each participant with study drug and instructions for use; the initial doses for Day 0 will be given at the site.

C 7.2.5 Product Storage and Stability

Investigational drug must be kept in an appropriate, limited-access, secure place at controlled room temperature 15° to 25°C (60° to 77°F) and protected from light until it is used or returned to the industry supporter or designee for destruction. Investigational drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day while the drug is still in the research unit.

C 7.2.6 Preparation

All bottles provided contain 30 capsules of 200 mg upamostat or placebo and are prelabelled according to country specific requirements. 1 bottle will be dispensed to each participant at Day 0.

C 7.4 Measures to Minimize Bias: Randomization and Blinding

C 7.4.1 Randomization

Once randomized to the upamostat early treatment indication, participants will undergo a second, blinded randomization to either upamostat or placebo through the Interactive Voice/Web Response System (IxRS). Probability of randomization will be dependent on the number of products enrolling in the early treatment indication at that time.

The ratio of assignment to upamostat or placebo will be r:1 where r is the number of IPs concurrently enrolling in the early treatment indication that a given participant is eligible to receive. For example, if two products are enrolling in the treatment indication simultaneously, the probability of randomization of an eligible participant to upamostat or placebo will be 2:1. See also Section C 13 Statistical Considerations.

The site research pharmacist(s) will be responsible for maintaining secure access to randomization assignments through the IxRS.

C 7.4.2 Blinding and Unblinding

Both participants and study investigators will be blinded to this second randomization.

Refer to the Master Protocol regarding unblinding.

C 7.6 Concomitant 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 Supplement 1. These lists are based on the US Food and Drug Administration guidance [US Food and Drug Administration, 2022].

Patients may 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.

C 9 STUDY ASSESSMENTS AND PROCEDURES

C 9.2 Clinical and Laboratory Assessments

C 9.2.1 Clinical Assessments

Clinical assessments will be conducted according to the Master Protocol with the following additions and exceptions as presented in Section 1.2 Schedule of Activities.

Clinical assessments include:

Vaccination status

- **Vaccination status collected at baseline and Day 7 only**

Electrocardiogram (ECG)

- **A 12 lead ECG will be performed. ECG will be interpreted by clinicians qualified in ECG interpretation. This may include physicians, nurses, or other allied health professionals who are registered/licensed in the local jurisdiction and the performance and interpretation of ECGs is within the current scope of practice. Remote interpretation will also be permitted.**

C 9.2.1 Lab Assessments

Lab assessments will be conducted according to the Master Protocol with the following additions and exceptions as presented in the Section 1.2 Schedule of Activities.

Additional testing requirments:

- **Coagulation Studies**
  - **International Normalized Ratio (INR)**
  - **Partial Thromboplastin Time (PTT)**
- **Anti-SARS-CoV-2 IgM and IgG**
- **Polymorphisms of relevant host cellular proteases**

C 9.2.3 Screening Assessments

Screening assessments will include the following:

- Screening symptom questionnaire
- SARS-CoV-2 vaccination history
- Concomitant medications
- **ECG**
- Pregnancy test
- SARS-CoV-2 diagnostic test result
    - Diagnostic testing must be an approved molecular or antigen diagnostic test for SARS-CoV-2 from any upper respiratory specimen performed at screening or enrollment or within 5 days of enrollment. The test used must be authorized for use by the relevant national authority for the detection of SARS-CoV-2 in the country where the test is administered. Historical testing results will be acceptable if testing performed within the required window. The test result must be available and reviewed by site PI or study staff to confirm eligibility.

C 9.2.5 Blood Volumes

The maximum volume of blood drawn at any one visit will not exceed 30 mL.

C 9.2.6 Pharmacokinetics

Plasma samples for PK evaluation will be collected at Day 0, Day 3, and Day 14. The analysis will include levels of upamostat and its active metabolite, WXUK1, for each of these time points.

Day 0: all patients will have a specimen drawn prior to first treatment with study medication.

Patients will be randomized to one of two sampling regimens for Day 3:

A) Day 3 specimen within 2 hours prior to dosing;

OR

B) Day 3 specimen 2-4 hours after dosing.

Day 14: all patients will have a specimen drawn 22-26 hours after previous dose.

An attempt will be made to get a specimen 22-26 hours after the last dose from patients who stop treatment early.

C 9.4 Study Visits

Study Visits will be conducted according to the Master Protocol with the following additions and exceptions as presented in Section 1.2 Schedule of Activities.

Activities in the Master Protocol that do not apply to participants randomized to the upamostat Appendix C are indicated by ~~strikethrough~~, while activities that have been added are indicated by **bold** text.

C 9.4.1 Screening Visit – In Person or Remote (Within 24 hours Prior to Enrollment)

Potential participants will be screened for presumptive eligibility for the study according to the procedures described below. All procedures may be completed in a stepwise manner, as suggested below, for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined. For potential participants who participate in the screening visit **remotely** and are found to be presumptively eligible, final eligibility will be confirmed upon completion of screening procedures at the Enrollment Visit scheduled to take place within 24 hours of screening. Screening and enrollment may take place on the same day (Day 0).

- Screening Informed Consent (in person or verbal)
- Demographics
- Medical history
- SARS-CoV-2 vaccination history
- Screening Symptom Questionnaire
- Physical exam
- Height and weight
- Vital signs
- Pregnancy test for women of childbearing potential
- Diagnostic test for SARS-CoV-2 (for eligibility assessment)
- Concomitant medication review

C 9.4.2 Enrollment Visit – In Person (Day 0)

Participants who are found to be presumptively eligible at their Screening Visit will complete the Enrollment visit within 24 hours of the Screening Visit. Participants who completed the screening visit remotely will complete all remaining screening procedures as well as enrollment procedures during the in-person Enrollment Visit. Participants who do not complete an Enrollment Visit within 24 hours of screening must repeat the entire Screening Visit. All participants must complete the screening evaluation prior to study enrollment. For those who meet the study eligibility criteria from the screening procedures, the enrollment procedures below may be undertaken in a stepwise manner, as suggested below, to confirm eligibility. As done with the Screening Visit, procedures will be discontinued if ineligibility is determined at

this visit. The site investigator will determine final eligibility after review of all screening assessments prior to product administration.

NOTE: If the enrollment visit is after the screening visit, the patient must still start therapy within 5 days of initial positive test for SARS-CoV-2 AND within 5 days of onset of initial symptom(s). Presumptively eligible participants who cannot start therapy within that time frame are not permitted to participate in the study, even if they meet all other enrollment qualifications.

- Screening Symptom Questionnaire (repeat if visit not performed on same day as Screening)
- Randomization (Step 1)
- Study (IP) Informed Consent (in person)
- Screening assessments (see Section C 9.2.3 Screening Assessments)
- **ECG**
- Eligibility evaluation (review of all screening and eligibility assessments)
- Randomization (Step 2)
- Upper respiratory specimen collection (prior to administration of upamostat or control) (for efficacy assessment)
- Venous blood sampling (prior to administration of upamostat or control)
  - Hematology (prior to administration of upamostat or control)
  - Chemistry (prior to administration of upamostat or control)
  - **Coagulation Studies**
  - **Anti-SARS-CoV-2 IgM and IgG**
  - **Polymorphisms of relevant host cellular proteases**
  - **Whole Blood, Plasma and Serum Storage for Possible Future Research (prior to administration of upamostat or control)**
  - **Pharmacokinetics**
- **Administration of upamostat or control**
- Collect and update contacts
- Dispense study kit
- Adverse event recording and reporting

C9.4.3 Day 3 Visit – ~~Remote or~~ In Person

This visit is scheduled to take place In Person on Day 3. Every effort should be made to complete the Day 3 visit requirements on Day 3; however, the visit may take place — if necessary +/- 1 days.

- ~~SARS-CoV-2 Vaccination Status~~
- Concomitant medication review
- Collect and update contacts
- Daily Symptom Follow Up Questionnaire (daily until day 28 then at **Weeks 8** and 12)
- Upper respiratory specimen collection
- Clinical outcome assessment
- Vital signs
- Physical exam
- Venous blood sampling (for Pharmacokinetics Group A: venous blood sampling should be collected within 2 hours prior to administration of upamostat or control, for Pharmacokinetics Group B: venous blood sampling should be collected 2-4 hours after administration of upamostat or control)
  - Hematology
  - Chemistry
  - **Coagulation studies**
  - **Whole blood, plasma, and serum storage for possible future research**
  - **Pharmacokinetics**
- **ECG**
- Adverse event recording and reporting

C 9.4.4 Day 7 Visit- Remote ~~or In person~~

This visit is scheduled to take place Remotely on Day 7. Every effort should be made to complete the Day 7 visit requirements on Day 7; however, the visit may take place — if necessary +/- 1 days. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person.

- ~~SARS-CoV-2 Vaccination Status~~
- Concomitant medication review
- Collect and update contacts
- Daily Symptom Follow Up Questionnaire (daily until Day 28 then at **Weeks 8** and 12)
- Upper respiratory specimen collection (self-collection)
- Clinical Outcome Assessment
- Adverse event recording and reporting

C 9.4.5 Day 10 Visit- Remote

This visit is scheduled to take place Remotely on Day 10. Every effort should be made to complete the Day 10 visit requirements on Day 10; however, the visit may take place — if necessary +/- 1 days. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person.

- Daily Symptom Follow Up Questionnaire (daily until Day 28 then at **Weeks 8** and 12)
- Concomitant medication review
- Upper respiratory specimen collection (self-collection)
- Adverse event recording and reporting

C 9.4.6 Day 14 Visit – In Person

This visit is scheduled to take place In Person on Day 14. Every effort should be made to complete the Day 14 visit requirements on Day 14; however, the visit may take place — if necessary +/- 2 days

- ~~SARS-CoV-2 Vaccination Status~~
- Concomitant medication Review
- Daily Symptom Follow Up Questionnaire (daily until Day 28 then at **Weeks 8** and 12)
- Upper respiratory specimen collection
- Clinical outcome assessment
- Vital signs
- Physical exam
- Venous blood sampling (should be collected from all participants 22-26 hours after previous dose of upamostat or control)
  - Hematology
  - Chemistry
  - **Coagulation studies**
  - **Whole blood, plasma, and serum storage for possible future research**
  - **Pharmacokinetics**
- **ECG**
- Adverse Event Recording and Reporting

C 9.4.7 Day 28 Visit – In Person

This visit is scheduled to take place In Person on Day 28. Every effort should be made to complete the Day 28 visit requirements on Day 28; however, the visit may take place — if necessary +/- 4 days.

- ~~SARS-CoV-2 Vaccination Status~~
- Concomitant medication Review
- Daily Symptom Follow Up Questionnaire (daily until Day 28 then at **Weeks 8** and 12)
- Upper respiratory specimen collection
- Clinical outcome assessment
- Vital signs
- Physical exam
- **Pregnancy test**
- Venous blood sampling
  - Hematology
  - Chemistry
  - **Coagulation studies**
  - **Whole blood, plasma, and serum storage for possible future research**
- Adverse Event Recording and Reporting

C 9.4.8 Week 8 Visit – In Person

This visit is scheduled to take place In Person at Week 8. Every effort should be made to complete the Week 8 visit requirements at Week 8; however, the visit may take place — if necessary +/- 1 week.

- **Concomitant medication review**
- **Daily Symptom Follow Up Questionnaire (daily until Day 28 then at Weeks 8 and 12)**
- **Upper respiratory specimen collection**
- **Clinical outcome assessment**
- **Vital signs**
- **Physical exam**
- **Venous blood sampling**
  - **Hematology**
  - **Chemistry**
  - **Coagulation Studies**
  - **Anti-SARS-CoV-2 IgM and IgG**
  - **Whole blood, plasma, and serum storage for possible future research**
- **Adverse event recording and reporting**

C 9.4.9 Week 12 ~~In Person OR~~ Remote

This visit is scheduled to take place Remotely at Week 12. Every effort should be made to complete the Week 12 visit requirements at Week 12; however, the visit may take place — if necessary +/- 2 weeks.

- ~~SARS-CoV-2 vaccination status~~
- Concomitant medication review
- Daily Symptom Follow Up Questionnaire (daily until Day 28 then at **Weeks 8** and 12)
- Upper respiratory specimen collection (self-collection)
- Clinical outcome assessment
- Adverse Event Recording and Reporting

C 9.4.10 Unscheduled Visits – In Person or Remote

An unscheduled visit is defined as any visit to the clinical trial site outside of the protocol evaluation time points, where the participant is seen by a member of the clinical research staff. Participants will be encouraged to report any medical problems or discomfort to the study staff and may be instructed to return to the clinical trial site if they experience new or worsening COVID-19 symptoms or become infected with SARS-CoV-2 any time after enrollment. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person.

In the event of an unscheduled visit these procedures may be done according to clinical judgement:

If conducted remotely the following procedures may be performed:

- SARS-CoV-2 vaccination status
- Concomitant medication review
- Daily Symptom Follow Up Questionnaire
- Upper respiratory specimen collection (self-collection)
- Clinical outcome assessment
- Adverse event recording and reporting

If conducted in person following procedures may be performed:

- SARS-CoV-2 vaccination status
- Concomitant medication review
- Daily Symptom Follow Up Questionnaire
- Upper respiratory specimen collection
- Clinical outcome assessment
- Vital signs
- Physical exam

- Venous blood sampling
  - Hematology
  - Chemistry
  - **Coagulation studies**
  - **Whole blood, plasma, and serum storage for possible future research**
- **ECG**

Depending on the reason for the visit, the participant may have additional assessments or laboratory tests, as clinically indicated, or may be referred to the appropriate service for follow up.

C 10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

C 10.1.9 Pregnancy and Breastfeeding

Since there are no data regarding the use of upamostat in participants who are pregnant or breastfeeding, participants who are pregnant or breastfeeding are not eligible for the study. Participants of childbearing potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in Section C 6.3 Lifestyle Considerations.

If a participant becomes pregnant during the study (post-entry), administration of upamostat will be discontinued (if still taking) and study follow up will continue for the duration of the study. At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

C 12 PAUSE AND STOPPING CRITERIA

C 12.1 Individual Participant Pause and Stopping Criteria

The administration of IP to any participant may be stopped or paused for any SAE, clinically significant AE, severe lab abnormality or any medical condition that may indicate to the Investigators that IP continuation is not in the best interest of the participant. In addition, a subject in the clinical trial may discontinue study drug at their request for any reason. Every effort should be made to encourage subjects to remain in the study for the duration of their planned outcome assessments. Unless the subject withdraws the consent, those who discontinue study drug early will remain in the study. The reason for subject discontinuation will be documented in the case report form.

For an individual participant, the 14-day course of IP can be interrupted or stopped if there is a suspected drug-related event suggestive of QTc interval prolongation, anticoagulant effect, elevated liver enzymes or other, as per investigator or medical monitor discretion if it is deemed to be in the participant's best interest. All participants will receive baseline chemistry, liver enzyme, and coagulation studies as well as a baseline ECG.

The individual pause and stopping criteria will include (but not be limited to) the following:

- The subject worsens and requires treatment for worsening COVID-19 as recommended by the NIH COVID-19 Treatment Guidelines. Upamostat administration will be discontinued. All other study activities will continue, participant will not be withdrawn from the study.
- The subject worsens and requires hospitalization for worsening COVID-19. Upamostat administration will be discontinued. All other study activities will continue, participant will not be withdrawn from the study.
- QTc Interval: QTc increase >60 msec over baseline: repeat ECG within 48 hours and if >60 msec increase over baseline persists, IP will be discontinued. Participant will continue to be participate in follow up visits and, if necessary, until resolution or stabilization of the event.
- INR, PTT: increase over baseline > 2 Grades (per NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) corrected Version 2.1, July 2017): pause therapy. Repeat INR and PTT within 48 hours of initial awareness of the abnormal laboratory value. If repeat testing ≤ 2 Grades above baseline, may resume therapy until total of 14 days from start; missed days will not be made up. If repeat testing > 2 Grades above baseline, IP will be discontinued. Participant will continue to be participate in follow up visits and, if necessary, until resolution or stabilization of the event.
    - If increase over baseline 1 Grade: no additional follow up
    - If increase over baseline 2 Grades: In addition to scheduled PTT/INR testing on Day 3 and Day 14, participant will have coagulation testing on Day 28. If either PTT or INR is increased by ≥ 1 Grade at Day 28, repeat testing will be performed at Week 8. Additionally, participant will be questioned at Day 7, Day 10, Day 14 visits, and

twice weekly from Day 14 until resolution of the coagulation abnormality to ≤ 1 Grade above baseline or Week 8 (whichever comes first), regarding bleeding, bruising or petechiae.

- Transaminases, bilirubin: increase over baseline >1 Grade above baseline: pause therapy. Repeat transaminase and bilirubin levels within 48 hours of initial awareness of the abnormal laboratory value. If repeat testing ≤1 Grade above baseline, may resume therapy until total of 14 days from start; missed days will not be made up. If repeat testing >1 Grade above baseline, IP will be discontinued. Participant will continue to be participate in follow up visits and, if necessary, until resolution or stabilization of the event.

C 12.2 Study and/or PSA Pause and Stopping Criteria

In addition to those listed in the Master Protocol, the study pause criteria listed in Table 1 will apply.

Table 1 Product Specific Criteria for Study Pause

Parameter	Investigational Products Related Adverse Events (AEs)	Action
Prolonged QTc Interval	QTc [a] >500 msec **OR** QTc [a] >60 msec above baseline on repeat ECG within 48 hours	Prompt reporting (within 24 hours of observation or report) Consider pause of the PSA PSRT to monitor for trend
ALT (SGPT), ALP (SGOT), or Total Bilirubin, High	> 1 Grade [c] increase in verified [d] abnormal AST, ALT, and total bilirubin in >2 patients	Prompt reporting (within 24 hours of observation or report) Consider pause of the PSA PSRT to Monitor for trend
PT, PTT, or INR, High (Not on anticoagulation therapy)	> 2 Grade increase in verified PT, PTT or INR >2 patients	Prompt reporting (within 24 hours of observation or report) Consider pause of the PSA PSRT to Monitor for trend

a Corrected QT may be calculated using any standardized formula or automated interpretation. The same methodology for calculating the QT interval should be applied throughout the participants enrollment in the study

c Per NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) corrected Version 2.1, July 2017

d Verified definition: If no evidence of disease is present other than the abnormal laboratory value, the test must be repeated at least one time in order to be considered "verified". The verification period will be a maximum of 48 hours after initial awareness of the abnormal laboratory value. When signs and symptoms are present, repeat test WILL NOT be needed

C 13 STATISTICAL CONSIDERATIONS

C13.1 Statistical Hypotheses

The primary hypothesis is that early treatment with upamostat among outpatients infected with SARS-CoV-2 can shorten time to sustained alleviation or resolution of Targeted COVID-19 symptoms (time to resolution) as compared to standard treatment.

The general statistical approach will compare outcomes among participants randomized to receive the active agent, upamostat, to outcomes among participants who were eligible to have been randomized to upamostat but who were randomized instead to any of the placebo arms enrolling at that time. This ensures that the comparison is limited to concurrently randomized participants eligible to receive upamostat.

C 13.4 Primary Endpoint/Estimand Analysis

The primary objective is to estimate the relative time to sustained alleviation or resolution of symptomatic COVID-19 infection for a participant that receives upamostat compared to a participant that does not receive upamostat.

The estimand of interest is the hazard ratio of a participant that has symptomatic COVID-19 with standard of care background therapy when starting treatment with upamostat compared to no upamostat. A hazard ratio greater than 1 indicates a shorter time to resolution of symptomatic COVID-19 infection.

The primary analysis population for upamostat is the modified intent-to-treat population, with a treatment arm consisting of all participants that were randomized to upamostat active treatment arm and received at least one dose of the active treatment. The control arm consists of all participants eligible to be randomized to upamostat that were randomized to placebo and received at least one dose of the placebo.

The primary analysis model is a Cox proportional hazards model for the time to alleviation or resolution of COVID-19 symptoms, with treatment arm (active upamostat vs placebo) as a covariate. The model estimated hazard ratio will be used as the estimator for the estimand of interest. The estimate and 95% confidence interval for the hazard ratio will be presented.

The primary hypothesis test is that upamostat increases the hazard (decreases time to resolution) of COVID-19 symptoms. A hypothesis test will be conducted for testing whether the upamostat hazard ratio is greater than 1 at a one-sided 2.5% level. One interim analysis will be conducted and a final analysis with type I error control over the two possible interims of 2.5%.

C 13.5 Outcome Measures and Statistical Analyses

C 13.5.1 Early Treatment

C 13.5.1.1 Primary Outcome

- Time to sustained alleviation or resolution of COVID-19 symptoms evaluated from Day 0 through Day 28 assessed via completion of a Daily Follow Up Symptom Questionnaire.

Sustained alleviation or resolution will be defined as the number of days from randomization to the first day the participant reports all symptoms as mild or none (≤ 1 or returning to pre-COVID-19 illness levels) for at least 3 consecutive days (the first day being considered the Event Day). Targeted symptoms will be used for analysis (Supplement 3 of the MP). Any patient that does not have alleviation or resolution of symptoms by Day 28 will be considered censored for alleviation or resolution at Day 28.

The primary efficacy analyses will be conducted using the modified intention to treat (mITT) population. The primary analysis is a Cox proportional hazards model with treatment assignment as a fixed covariate with a proportional effect. A one-sided p-value for the test of a hazards ratio of 1 compared to the alternative of a hazard ratio greater than 1 (upamostat reduces time to resolution of symptoms) will be presented and used for testing superiority. An interim analysis will be conducted when 50% of maximum enrollment has reached 28 days of exposure. A Kim-Demets (with parameter 2) spending function will be utilized for testing for superiority of upamostat at the interim and final analysis. At the interim analysis, futility analyses will be conducted, where enrollment to the upamostat cohort will be stopped if the predictive probability of superiority by the final sample size is less than 5%.

The hazard ratio for the time to resolution of COVID-19 will be presented with 95% confidence intervals. Additional sensitivity analyses for the primary analysis will utilize additional covariate adjustments in the Cox proportional hazards model.

C 13.5.1.2 Secondary Outcome: Clinical

For each analysis, a 5% two-sided significance will be used. 95% confidence intervals will be presented to summarize each effect estimate. Dichotomous outcomes will be summarized with relative proportions. Ordinal outcomes will be summarized with stacked bar plots, cumulative proportion graphs, and percentiles. Kaplan-Meier plots will be used for summarizing time to event outcomes. Continuous measures will be summarized box plots (means, medians, and inter-quartile ranges).

Each of the secondary analyses will be conducted using the modified intention to treat (mITT) population. Each analysis will be repeated using the per protocol population.

- Change in overall COVID-19 symptom severity score from Day 0 through Day 28

The overall symptom severity question on the Daily Symptom Follow Up Questionnaire will be used for this secondary endpoint. A mixed model repeated measure (MMRM) model will be

used to model the symptom severity score at each day using the baseline symptom score, participant, day, and treatment by day as covariates. The treatment effect by day will be summarized.

- Proportion of participants in each treatment group developing new COVID-19 symptoms rated as severe from Day 0 to Day 28

A Cox proportional hazards model will be used to analyze development of new severe symptoms. A new severe symptom is defined as scoring a 0 to 1 on any symptom in the questionnaire and subsequently scoring a 3 for that symptom (or a 2 for change in taste or smell). Treatment arm will be modeled with a proportional hazard effect. The hazard ratio will be summarized.

- Proportion of participants who report a return to usual state of health at Days 7, 14, 28, Week 8, and Week 12.

A Cox proportional hazards model will be used to analyze the time to return to usual state of health. Participants without symptomatic COVID-19 will be considered a 0 for return to usual state of health. Treatment arm will be modeled with a proportional hazard effect. The hazard ratio will be summarized.

- Proportion of participants who report a return to usual activities at Days 7, 14, 28, Week 8, and Week 12.

A Cox proportional hazards model will be used to analyze the time to return to usual activities. Participants without symptomatic COVID-19 will be considered a 0 for return to usual activities. Treatment arm will be modeled with a proportional hazard effect. The hazard ratio will be summarized.

- Proportion of participants in each treatment group hospitalized for COVID-19, as adjudicated prior to study unblinding.
- Number and proportion of participants hospitalized (all cause) from Day 0 to Day 28
- Number and proportion of participant deaths (all cause) from Day 0 to Day 28

Outcomes will be summarized with relative proportions

C 13.5.1.2 Secondary Outcome: Virological

- Comparison of active and placebo treatment groups in time to negative RT-PCR from Day 0 to Week 12

Time to negative RT-PCR will be defined as the time of the first of two consecutive readings below the lower limit of detection. A Cox proportional hazards model will be used to analyze the time to negative PCR.

C 13.5.1.3 Safety and Tolerability

An external DSMB will conduct interim reviews for safety. Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur monthly throughout the study and will be conducted by the DSMB. Only the DSMB is authorized to evaluate unblinded interim efficacy and safety analyses.

Safety analyses will include:

- Incidence of Serious Adverse Events (SAE)
- Comparison between active and placebo treatment groups in proportion of all and ≥grade 3 adverse events as assessed by the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017.
- Incidence of AEs causing IP discontinuation
- Incidence of all-cause IP discontinuation or interruption
- Number of participants hospitalized due to adverse events regardless of cause

All adverse events will be listed by participant and will include:

- Event description
- Treatment group (active agent vs placebo)
- Clinician's assessment of severity and relationship to upamostat
- Outcome

The number and percentage of participants with AEs will be summarized for each treatment group. Overall treatment group differences may be compared using Chi-square tests or Fisher’s exact tests.

Serious AEs, TEAEs, and hypersensitivity reactions will also be summarized. The counts and proportion of participants experiencing these events will be reported for each treatment arm. Treatment groups may be compared by Chi-square tests or Fisher’s exact tests.

Permanent discontinuations or interruptions of upamostat due to AEs will be listed. The count and proportion of discontinuations of the study drug due to AEs will be reported.

Categorical safety measures including hospitalization will be summarized with counts and proportions of participants and may be compared by treatment using either a Chi-square test or a Fisher’s exact test.

C 13.5.1.4 Exploratory

Prevalence and titer of anti-SARS-CoV-2 IgM and IgG antibodies at baseline and at Week 8 will be determined, and the effect of presence and titer of anti-SARS-CoV-2 IgG at baseline on treatment outcome will be assessed.

For participants receiving upamostat, targeted analysis of known host transmembrane protease polymorphisms will be described and compared to time to resolution of symptoms among key subgroups including by sex, race, and ethnicity.

C 13.5.1.5 Sub-Group Analyses

The primary analysis and each of the secondary analyses will be conducted in different patient subgroups of the mITT population for exploration of heterogeneity of treatment effect. The following patient subgroups will be analyzed:

- Age (< 30, 30-50, >50 years old)
- Sex
- Race
- Baseline symptom severity
- SARS-CoV-2 vaccination status
- Location (by continent)

C 13.6 Interim Analysis Plan

An interim analysis will be conducted when 50% (n=150) of participants have reached Day 28 of study. There are prospectively defined criteria for determining superiority of upamostat to its control arm or determining futility on upamostat to its control arm. The DSMB will evaluate safety and need to stop for safety concerns. The detailed rules for declaring superiority/futility are described in C 13.9 Sample Size Determination. Table 2 highlights the interim analysis plans for upamostat.

Table 2 Analysis Schedule and Actions Reviewed at Interim Analysis

Analysis Point	Test for Superiority	Futility Analysis	Safety Analysis
75 randomized to upamostat completing Day 28 post enrollment	Cox Proportional hazards analysis for superiority on the primary outcome; Kim-Demets alpha-spending adjustment	Futility triggered if predictive probability of superiority is less than 5%	DSMB review of safety for continued randomization
150 randomized to upamostat completing Day 28 post enrollment	Final analysis of superiority; Adjusted final nominal alpha		

The interim analyses will be conducted by an unblinded and firewalled external DSMB. The DSMB will provide any recommendations based on the interim efficacy analysis triggers and additionally will review and make recommendations on safety at each interim analysis.

The nominal alpha at the interim analysis will be calculated based on the exact sample size for the interim analysis using the Kim-Demets spending function. As an example, if there are exactly 75 patients on the upamostat arm at the interim analysis then the nominal one-sided alpha at the interim would be 0.00625 with a final analysis nominal alpha of 0.02178.

C 13.7 Final Analysis Plan

Statistical analysis of this PSA will be the responsibility of the IND Sponsor. A statistical analysis plan (SAP) will be finalized prior to the interim analysis and will provide a detailed description of the statistical analyses described in this section.

C 13.9 Sample Size Determination

The maximum sample size for the upamostat arm primary analysis is 300 participants with 1:1 allocation to the upamostat arm and its control arm. The maximum sample size of 300 participants (150 active and 150 controls) and the adaptive design provides 90% power to detect a hazard ratio of 1.50 (a 33% reduction in median time to resolution) and approximately 80% power for a hazard ratio of 1.42 (a 30% reduction in the median time to resolution).

Table 3 presents the likelihood of the trial determining superiority at the interim analysis (50%) and the final analysis for a range of assumed effect sizes for upamostat and a range of placebo median times to resolution. The expected median time to symptom resolution of 9 days for the control arm is based on review of relevant literature [Akaishi 2022, Akavian 2022, Zhang 2022]. The probabilities of determining futility at 50% is reported (5000 simulations pre scenario based operating characteristics in FACTS, 6.4). Simulations use a log-rank test for calculations of power as an approximation to the Cox proportional hazards model.

Table 3 Operating Characteristics for the Adaptive Design Including Superiority and Futility for a Range of Assumed Event (Symptomatic COVID-19) Rates for Upamostat Active Treatment and Upamostat Control Arm

Control Median Time to Resolution	Upamostat Hazard Ratio	Cumulative Proportion Superiority for Upamostat		Proportion Futility
		150 total	300 total	150 total
12 days	1	0.008	0.025	0.610
	1.25	0.109	0.405	0.165
	1.42	0.315	0.786	0.045
	1.50	0.436	0.883	0.021
	1.67	0.678	0.981	0.004
	2	0.939	1.000	0.000
9 days	1	0.008	0.026	0.612
	1.25	0.122	0.434	0.153
	1.42	0.340	0.812	0.035
	1.50	0.464	0.906	0.018
	1.67	0.709	0.986	0.003
	2	0.953	1.000	0.000
6 days	1	0.007	0.024	0.612
	1.25	0.131	0.458	0.138
	1.42	0.363	0.830	0.033
	1.50	0.488	0.916	0.015
	1.67	0.728	0.990	0.002
	2	0.956	1.000	0.000

APPENDIX C ABBREVIATIONS

In addition to those listed in the Master Protocol

aPTT	Activated Partial Thromboplastin Time
CDER	Center for Drug Evaluation and Research
ECG	Electrocardiogram
INR	International Normalized Ratio
ITT	Intention to Treat
IxRS	Interactive Voice/Web Response System
MERS-CoV	Middle East respiratory syndrome-related coronavirus
mITT	Modified ITT
NGS	Next Generation Sequencing
PTT	Partial Thromboplastin Time
TMPRSS2	Transmembrane protease serine 2

APPENDIX C AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
V 1.0	25 Mar 2022	N/A	Initial Protocol
V 2.0	26 Apr 2023	1. Specified that this is a Phase 2 study. 2. Updated formatting and section numbering. 3. Updated study objectives and endpoints. 4. Updated study visits to clarify activities and procedures. 5. Added new information about the effectiveness of upamostat against current SARS-CoV-2 variants and pharmacologic parameters. 6. Updated hypotheses to look at sustained symptom alleviation or resolution. 7. Added clinical adverse event rates and percentages and new information for the 200 mg and 400 mg doses. 8. Removed the exclusion criteria for requires supplemental oxygen. Added exclusion criteria for patients with prolonged QT/QTc interval and/or increased susceptibility to arrythmia with a list of defining criteria. 9. Added a new section with information regarding potential drug interactions and prohibited medications. 10. Specified that vaccination status will only be collected at baseline and Day 7 and that a 12 lead ECG will be performed. 11. Added Polymorphisms of relevant host cellular proteases to additional testing requirements. 12. Added specific screening assessments. 13. Added sample collection and testing information for PK evaluation. 14. Added and updated sections to outline pause and stopping criteria at the individual participant or	1. Clarify study phase. 2. Consistency with Master Protocol. 3. Clarified for clear expectations. 4. Clarified for clear expectations. 5. Updated with current known information. 6. Consistency with Master Protocol. 7. Updated with new information. 8. Updated based off current information. 9. Updated with new information. 10. Clarified for clear expectations. 11. Clarified for clear expectations. 12. Clarified for clear expectations. 13. Clarified for clear expectations. 14. Added per FDA recommendation. 15. Updated with current information. 16. Clarified for clear expectations. 17. Consistency with Master Protocol. 18. Clarify concomitant medications with potential drug interactions.

Version	Date	Description of Change	Brief Rationale
		Study/PSA level. 15. Updated the primary, secondary: virological, safety and tolerability, exploratory, and sub-group analysis outcome analysis information. 16. Updated interim analysis criteria and added information for the DSMB. 17. Added new section with sample size information. 18. Added a list of CYP3A4 Strong inhibitors and sensitive substrates for reference.	
V 3.0	01 Jun 2023	1. Pregnancy test added at D28 visit. 2. Race added as a sub-group for analysis.	1. Added per FDA recommendation. 2. Added per FDA recommendation.
V 4.0	01 Nov 2023	1. Updated storage temperature range to be consistent with pharmacy manual. 2. Changed bullets to numbering. 3. Added clarification that overall symptom severity assessme879nt question on the Dailly Symptom Follow Up Questionnaire will be used for this endpoint. 4. Added upamostat dose to Description of Study Intervention 5. Added study staff may remind participant of Day 3 dose and venous blood draw according to PK regimen assignment. 6. Added reference to recently published upamostat pilot study. 7. Clarified corrected QT requirement and calculation. Moved from Master Protocol to PSA 8. Clarified "women of childbearing potential" definition. 9. Removed FSH requirement. 10. Removed one South Africa site. Added Uganda site	1. Updated for consistency. 2. Data monitoring request 3. DSMB recommendation 4. DSMB recommendation 5. Site feedback and recommendation 6. Updated information 7. Sites may apply different formulas or automated algorithms for recording the corrected QT interval. Clarified that same methodology for the calculation should be applied throughout the participant's study participation. 8. Clarification 9. Removed as most international sites not able to meet this testing requirement. 10. Updated site list

Version	Date	Description of Change	Brief Rationale
V 5.0	26 Jan 2024	1. Updated order of activities 2. Added caution for alcohol consumption while taking study drug 3. Added Table of Contents	1. Updated to clarify that screening activities under the PSA (ECG) cannot be performed until product specific informed consent and Step 1 randomization completed 2. FDA request 3. Added table

APPENDIX C REFERENCES

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C Supplement 1. CYP3A4 Strong Inhibitors and Sensitive Substrates

Strong Inhibitors

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

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

Sensitive Substrates

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

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