PHASE 2/3 STUDY OF UPAMOSTAT, A SERINE PROTEASE INHIBITOR, OR PLACEBO FOR TREATMENT OF COVID-19 DISEASE

Protocol Number: RHB-107-01

IND Number: 151472

Protocol Version: Amendment 4: 15 June 2021

Sponsor Name: RedHill Biopharma

Statistical Analysis Plan for Part A, Version 2.0

SAP Version Date: 13 January 2022

STATISTICAL ANALYSIS PLAN APPROVAL PAGE

Document Information	
Version	2.0
Document Date	13 January 2022
Prepared for	RedHill Biopharma
Prepared by	Mario Chen, FHI 360

Sponsor Approver details	
Name	Terry Plasse, MD
Job Role	Medical Director
Company	RedHill Biopharma
Signature	DocuSigned by Terry F Plasse, MD Terry F Plasse, MD | I approve this document 14-Jan-2022 | 08:18:06 EST 160FE011E0124C30A95CBEBDE0EDA1B0
Date of signature	14-Jan-2022 | 08:18:12 EST

Other Approver details	
Name	Mario Chen
Job Role	Director of Biostatistics and Data Sciences
Company	FHI 360
Signature	DocuSigned by Mario Chen Mario Chen | I approve this document 14-Jan-2022 | 08:38:36 EST CD1A4605A6154A769A07F2E6D22D38CF
Date of signature	14-Jan-2022 | 08:38:48 EST

STUDY SUMMARY

Title:	Phase 2/3 Study of Upamostat, a Serine Protease inhibitor, or Placebo for Treatment of COVID-19 Disease
Design:	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 who do not require inpatient care.
Investigational Drug:	Upamostat (RHB-107)
Reference Treatment:	Matching capsule will be used as placebo treatment
Population:	Patients with positive PCR test for SARS-CoV-2 and symptomatic COVID-19 who do not require inpatient care.
Study Duration:	The enrollment is expected to start in January 2020; each subject is expected to stay in the study for 57 days: 14 days treatment; total 57 days treatment plus follow-up, regardless of duration of treatment.
Primary Objectives:	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: comparison between upamostat and placebo in time to sustained recovery from symptomatic illness.
Primary Endpoints:	Part A: safety and adverse event profile of upamostat at two dose levels compared to placebo Part B: Time to sustained recovery from acute COVID-19 disease

Secondary Objectives: Comparison between active 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, 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.

Where procedures and analyses described in the SAP differ from those in the protocol, those in the SAP take precedence.

This document focuses on analysis of part A of the study. Based on results of part A, study parameters including analysis parameters may be modified for part B. Changes from the current protocol and SAP will be formalized in amendments to the protocol and SAP, respectively.

LIST of ABBREVIATION and SPECIALIST TERM

Abbreviation	Description
AE	Adverse Event
BUN	Blood urea nitrogen
CoV	Coronaviruses
COVID-19	Coronavirus-2019
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HR	Hazard Ratio
INR	International Normalized Ratio
IWRS	Interactive Web-based randomization System
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PP	Per Protocol
RS	Randomization Statistician
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SOC	System Organ Class
ubSSR	Unblinded Sample Size Re-estimation

TABLE OF CONTENTS

1. Introduction

This statistical analysis plan (SAP) expands the summary analysis plan in *Section 7 Data Analysis and Statistical Considerations* of the study protocol "Phase 2/3 Study of Upamostat, a Serine Protease Inhibitor, or Placebo for Treatment of COVID-19 Disease " authored by the sponsor (RedHill Biopharma Ltd.) approved amendment 4 version dated June 15, 2021. This is the first version of the SAP and there are no changes to track from a previous version. This SAP is intended for analysis of part A of the study. ***The SAP for part B will be finalized after analysis of data from part A and an SAP for analysis of part B of the study generated. Modifications may be made to the analyses planned for part B based on that review as allowed in the approved protocol or based on protocol amendments made after Part A analysis. Based on the current protocol, changes that may be made after Part A analysis are highlighted in bold and italicized throughout this SAP.*** The SAP for part A will be approved by the sponsor before unblinding of Part A data. Deviations from this SAP will be documented in the part A analysis report. Changes after approval of version 1.0 of the SAP are summarized in the appendix.

The scope of analysis provided in this part A SAP includes plans for analysis after all subjects enrolled in Part A complete treatment or discontinue early and complete follow-up. The analysis of part A in this SAP is divided into first and second tier analyses. The first-tier analysis is prioritized to allow to proceed to part B expeditiously. Where procedures and analyses described in the SAP differ from those in the protocol, those in the SAP take precedence.

2. Study Objectives

2.1 Primary Objectives

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

2.2 Secondary Objectives

Items 1, 2, 4, 6 and 8, below, are first-tier secondary objectives, to be analyzed initially. Items 3, 5 and 7 are second tier objectives, which may be reported subsequently. Both exploratory objectives are second tier.

Comparison between active treatment group and placebo of

1) Time to sustained recovery from symptomatic illness;
2) Hospitalization or death from any cause by end of study, i.e, day 57;
3) 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.
4) Proportion of patients who are PCR-negative at days 8, 15, 29 and 57 from the start of treatment (landmark analyses);
5) Time to resolution of individual disease-related symptoms present at baseline;
6) Development of new disease-related symptoms and/or pneumonia on study;
7) 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;
8) Adverse events.

2.3 Exploratory

1) Percent of patients who report 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 57 days from the start of treatment.

3. Study Design and Procedures

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 pre-study 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.

In part B, the proportion of patients in the low risk group, i.e., with no concerning conditions, may 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 in order to enroll a sufficiently high risk cohort in Part B.

In Part A, a total of approximately 60 patients meeting the criteria for per protocol analysis 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 part A, 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.

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 reviewed 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 or to revise in order to have adequate power to detect a difference in time to sustained recovery based on the data from part A, 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 7 below and 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 and the sample size is unchanged from that currently in the protocol, 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 below). 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. General Analytic Considerations

4.1 Missing Data

In general, no imputation of missing data will be done unless specified in the definition of the endpoints below. Rules for censoring for time to event endpoints will also be described in detail in the definitions below. Additional rules for imputation of missing data may be determined during blind review of the data and documented prior to unblinding.

4.2 Covariate Adjustment

In part B only, primary analyses will adjust for stratification factors used in the randomization, but strata may be combined if they are too small. Additional covariate adjustments may be done in sensitivity and exploratory analyses. The stratification factors used in the randomization or covariates of interest will be investigated via the subgroup analysis as detailed below.

4.3 Test Size and Confidence Levels

Analysis for Part A data will be only descriptive. More formal analysis will be done with data from Part B. Unless otherwise noted, all reported confidence intervals will be computed at the 95% confidence level, and all p-values will be assessed at the two-sided 0.05 significance level, with pre-specified multiplicity adjustment (see section on control of type I error below).

4.4 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 order of the secondary endpoints defines a 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. If the hierarchy is changed from the order specified above, the SAP will be amended, and the decision documented in this SAP.

4.6 Safety data

If not further specified, the system organ class (SOC) and preferred term for adverse events analysis will be summarized using Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version current at study initiation will be used for the entire study. Severity grade will be defined by US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

QTc_B and QTc_F results from baseline standard 12-lead ECG's and Alivecor 6-lead ECGs performed the same day will be compared. For calculation of shifts, only Alivecor 6-lead ECGs will be used.

5. Randomization, Allocation Concealment and Blinding

5.1 Randomization

In part A, patients will be stratified by age, <65 or ≥65, then randomization will be done in a 1:1:1 ratio among each dose level and placebo with all patients receiving 2 bottles of medication (active or placebo) and will be instructed to take one pill daily from each.

The randomization sequence will be developed by a qualified FHI Randomization Statistician (RS) who is not otherwise involved in the study using a validated program written in SAS®.

5.2 Allocation Concealment and Blinding

The randomization statistician will prepare an electronic randomization list containing treatment assignments following the randomization sequence to be sent electronically to the Interactive Web Response System (IWRS) vendor, Clinical One.

After a participant has completed all baseline procedures per protocol prior to randomization and is determined to be eligible for the study, site staff will perform online randomization through Clinical One IWRS. Site staff will remain blinded and will be trained in proper randomization and unblinding procedures.

5.3 Blinded Data Review

Prior to scheduled study unblinding and final data cleaning, the data may be reviewed in a blinded fashion per the sponsor's or safety monitoring stakeholder's request. Based on analysis needs, the lead statistician will develop specific listings for this review and will document the sponsor or stakeholders' decisions prior to unblinding. These reviews may include (but not necessarily be restricted to) violations of inclusion/exclusion criteria and/or data points. More specifically, Protocol violations will include those documented by the study team as well as violations that can be detected directly from the data base. Decisions on inclusion into each analysis population, missing data, and final imputation of endpoints will be done during this blinded review. Blinded data review may also include clinical evaluation of safety data for reasonableness or to issue clinical queries to the site if needed. Any decisions affecting analysis will be described in internal documentation and the CSR.

5.4 Study Size and Power

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 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 sustained 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. ***These targets may be adjusted after analysis of Part A.***

The target number of events for this event-based part B portion is 201, taking into account a non-binding futility analysis and sample size-re-assessment that will be performed when 50% of the information (primary events) have been realized (See section 8 below for more details).

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 3 above, 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

6. Analysis Populations

The following analysis populations will be used when performing statistical analyses:

- Screened Population includes all subjects who are screened.
- Randomized Population includes all subjects who are enrolled and randomized in the study. In these analyses, patients will be analyzed according to their randomized treatment.
- Modified Intent to Treat (mITT) Population includes all randomized patients who receive any study treatment. The primary and secondary efficacy analyses will be performed on the modified intent to treat (mITT) population. In these analyses, patients will be analyzed according to their randomized treatment.
- Per Protocol Population includes patients with
    A. no major protocol violations which may affect study outcome and
    B. who receive at least one week of study medication unless the reason for stopping medication is worsening COVID-19 or development of AEs.

Analysis using the per protocol (PP) population will be done according to treatment actually received. Table 2 lists the major protocol violations (also known as major protocol deviations) which remove patients from the per protocol population. The final list of PVs will be reviewed during blinded data review and additional PVs may be determined to be major and added to the list of exclusions.

- Safety Population includes all patients who receive any study medication. Safety analyses will be performed according to the treatment actually received.

Table 1. Summary of Planned Analysis, by Population

Analysis	Screened	Randomized	mITT	Safety	PP
Participant Disposition	√				
Demographics and Baseline		√	√	√	√
Medical History				√	
Study Treatment Dosage				√	
Primary Efficacy			√		√
Secondary Efficacy Endpoints			√		√
Exploratory Endpoints			√		√
Safety				√	
Additional Safety				√	
Concomitant Medications				√	
Subgroup Analysis			√		√

Table 2. Major protocol Deviations/Violations Affecting Outcome

Did not meet inclusion/exclusion criteria
Forbidden medication which may affect outcome taken
Started drug >5 days after onset of symptoms or positive SARS-CoV-2 diagnosis
Missed >3 days of treatment over the 14-day period unless patient was hospitalized, or this was an investigator-directed dose reduction or hold.
Failure to complete symptom diary for ≥7 consecutive days (one full week continuously) through day 29 or early discontinuation, excluding days patient is hospitalized.

7. Data and Safety Monitoring Board Meeting Scope and Time Point

A data and safety monitoring board (DSMB) will be convened for oversight of the study. A DSMB charter is maintained 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 first 60 patients have completed treatment and follow-up (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;

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, as defined above.

In addition to the safety data, proportions of subjects screened, enrolled, and length of follow-up will be provided by site for the Enrolled Population. Screening failure reasons will be summarized. Furthermore, subject disposition based on the Randomized Analysis Population, including subject status. Dose administration status overall and by treatment arm will be provided for the Safety Population.

Baseline information, demographics, treatment status, primary reason for early termination, and baseline laboratory values will be tabulated and summarized for the Safety Population.

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.

The Safety population will be used for safety analysis in this Part A DSMB analysis. Modified ITT population will be used for efficacy endpoints.

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 reviewed 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.

8. Participant Disposition Analysis

Analysis population: Screened population. The frequency and percentage of subjects screened, enrolled, randomized, and who fail each eligibility criterion will be tabulated based on screened population. The number of subject enrolled and randomized at each site will be tabulated by treatment arm using the randomized analysis set.

The subject final status, including frequency and percentage of subjects who complete the study, are lost to follow-up, or terminate early along with primary reason for discontinuation based on CRF will be tabulated using randomized analysis set and by treatment arm.

The frequency of protocol deviations will be summarized with frequency tabulations by treatment arm using randomized analysis set. Furthermore, all protocol deviations classified as major and/or significant with respect to the evaluation of the primary endpoints will be listed individually.

9. Demographics and Baseline Characteristics

Analysis population: Randomized, mITT, PP, and Safety Populations. Baseline demographic and baseline characteristics information (age, gender, height, weight, race, ethnicity) will be summarized by treatment group.

10. Medical History

Analysis population: Safety population. Medical history data separated by active status will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term as for demographic data.

11. Analysis of Study Treatment Dosage

Analysis population: Safety population. All planned and actual doses (mg/day) will be listed and summarized descriptively for each study day and treatment arm, including the number of expected and actual subjects with study drug administered.

The individual listings will be provided to support the descriptive analysis.

12. Analysis of Primary Efficacy Endpoint

Analysis population: The primary efficacy analysis will be done using the mITT population and will be repeated on the PP population. Efficacy analysis for Part A will be only descriptive. Analysis with statistical testing will be done with data from Part B only.

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 28 days or until 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.*** First date of sustained recovery will be defined as the **latest** time among the events below:

1) Start date of the period during which the patient is afebrile (<38 ^{o}C core or rectal/37.5 ^{o}C oral or forehead) for at least 48 hours[1];
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 (through day 7), 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 to sustained recovery 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.

[1] *Use of antipyretics will not be considered in the assessment of sustained recovery as defined in the protocol. Please see appendix for more details regarding this change*

Calculation of time to sustained recovery requires completion of the symptom diary and determination that patient is afebrile. Before recovery is first documented, patients with missing symptom data will be considered as not recovered (i.e., last observation carried forward). If the diary is not completed on a given day after first meeting the definition of recovery as above, the recovery will still be considered sustained if symptom data is missing only intermittently. We will consider missing as intermittent if symptom data is missing for at most 4 consecutive days during the 28-day period when symptoms are expected to be recorded daily or 3 consecutive reporting days in the weeks after Day 28 when symptoms are recorded thrice a week until the end of study. If data gaps are longer than defined above, recovery will be considered as not sustained during these periods, and sustained recovery may be fully documented at a later time. If a patient is hospitalized, he or she will be considered as not recovered on those days, regardless of the reason for hospitalization. However, once a patient has completed the observation period defining sustained recovery (either 14 or 28 days), subsequent diary data gaps will not be considered as loss of sustained recovery status.

The comparison of the time to sustained recovery between active and placebo groups will be performed using log-rank test, at 5% significance level. The stratification factors used for randomization may be used if sample size per stratum is adequate. 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.

12.1 Correction of measured temperature to core temperature

The initial 10 patients' temperatures were measured with a biosticker adherent to the patient's chest. This provided data on surface temperature. This is not corrected to core temperature. In order to correct the measured biosticker temperature to core temperature, the biosticker temperatures closest in time to the oral temperature measurements performed by study staff (i.e., at each study visit) will be compared. The mean [median] difference across all patients for whom there are measurements will be calculated and then applied to correct the temperatures measured orally. Oral temperature is 0.5° C lower than the core (rectal) temperature, so the ultimate correction will be the mean [median] difference between biosticker and oral temperature plus 0.5° C.

To correct from measured oral or forehead temperature to core temperature, add 0.5° C to the measured temperature.

13. Analysis of Secondary Efficacy Endpoints

Analysis population: Analysis will be performed using the mITT and PP populations.

Analysis will be performed not only of symptom resolution and occurrence of new symptoms in aggregate, but also by individual symptoms assessed by investigators as related to COVID-19. This includes both the symptoms in the questionnaire and additional, less common symptoms which are recorded on the AE reports but attributed to COVID-19.

Items 1, 2, and 4 below are first-tier secondary objectives, to be analyzed initially. Items 3, and 5 are second tier objectives, which may be reported subsequently. 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 for part B restricted based on analysis at the end of part A.

   Specific COVID-19 symptoms resulting in hospitalization will be tabulated by SOC, PT and severity. Depending on the number of patients hospitalized, this may be shown either as a table or listing.

   Specific main COVID-19 symptoms resulting in death will be listed per patient.
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;
   COVID-19 symptoms, derived from the symptom questionnaires and those events entered as related to COVID-19 on the AE tables will be summarized as well using MedDRA classification by SOC, PT and severity as new COVID-19 symptoms and those worsening on study by at least one grade
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 (i.e., development of pneumonia diagnosed clinically, hospitalization and mortality) will be summarized using counts and percentages for each group. A 95% confidence interval will be constructed for each proportion. For endpoints other than mortality, (e.g, development of new

disease-related symptom on study), analysis will treat death before the event of interest as the most unfavorable possible outcome for this endpoint. Additional rules for handling missing data will be determined during blind review of the data and documented prior to unblinding.

Changes from baseline in laboratory markers (continuous variables) will be summarized by descriptive statistics. For oxygen saturation, which is measured twice daily throughout the study period, patterns will be presented visually. The median value for each subject from the preceding week will be used (e.g., for the Day 8, the median SpO2 value for Days 2-8 will be used). The daily SpO2 will be the subject's median of the 14 values collected (morning and evening). The morning and evening SpO2 will be the median of the 7 values at that time of day. Descriptive tables will be done for Days 1, 15, 22, 29, 36, 43, 50, 57.

14. Analysis of Exploratory Endpoints

Analysis population: Analysis of exploratory endpoints will be performed using the mITT and PP populations. There are two exploratory endpoints in the study. First, the percent of patients who have household contacts who have developed symptomatic, PCR-confirmed COVID-19 by day 57 will be summarized using counts and percentages for each group. This will be done in the second tier analysis.

15. Safety Analysis

Analysis population: Safety population. 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. Hospitalization or death from COVID-19 will be considered in the efficacy rather than safety analyses. These 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 7, above, to determine which treatment regimen to carry into part B of the study.

All subjects will be assessed regularly for potential adverse events occurring from the time the subject receives the first dose of the study medication until 56 days after the first dose of study medication. AEs collected will include AEs which newly started on or after the first dosing of the study drug or an existing condition being worse on or after the first dosing of the study drug.

A treatment-related AE is defined as an AE which is considered to be of suspected relationship to the study drug. Adverse events with missing relationship to study drug other than laboratory data-derived AEs will be assessed as treatment-related.

The following summaries will be provided:

- AEs will be summarized as follows, overall and by SOC and PT:
    - All AEs
    - All related AEs
    - AEs leading to discontinuation of treatment
    - AEs with toxicity grade >=3
    - Serious AEs
    - Related Serious AEs
    - AEs that led to death
    - AEs leading to dose modification

All AEs will be summarized by maximum toxicity grade, SOC, and PT.

If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC). If a subject experiences the same AE more than once with different toxicity grade, the event with the highest grade will be tabulated in “by maximum toxicity grade” tables.

All newly 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 abstracted from the laboratory data. 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 and creatinine which are below the normal range. If there is a clinical sequela or intervention, the laboratory abnormality is to be entered in an adverse event report and graded according to the criteria used for clinical AEs.

No missing data will be imputed for this part of the analysis, nor will formal hypothesis testing be performed. For safety analysis with adverse events, the observation with highest severity within the study day during treatment period will be used.

Subject level listing of AEs, vital signs, and laboratory assessments will be provided.

16. Additional Safety Analysis

Analysis population: These additional safety analyses will be done using the Safety population.

16.1 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. This is a second-tier analysis.

16.2 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. This will be done in the second-tier analysis.

Supplemental oxygen and ventilator use will be tabulated by treatment arm and overall population. This is applicable only for hospitalized patients; the relevant information will be obtained from hospital records of these patients. This will be prioritized in the first-tier analysis.

The result of rRT-PCR will be tabulated by positive or negative and, for positives, by viral load at each time point assessed and over time. This will be prioritized in the first-tier analysis.

16.3 Analysis of Concomitant Medication

Prior medications are defined as medications taken within 28 days of the Screening Visit until the start of study drug. In addition, COVID-19 vaccinations are recorded in the concomitant medication listings, regardless of how long prior to study entry the vaccinations were received. Concomitant medications are defined as medications with a start date and time after the start of the Day 1 study drug.

Frequency summaries of prior and concomitant medications coded with WHO drug dictionary (version Mar2020) will be provided by treatment group.

At each level of subject summarization, a subject is counted once if the subject reported one or more medications. A listing, including reason for use, duration, frequency and dosage of concomitant and prior medication will be provided.

Only prior COVID-19 vaccination will be a first-tier analysis.

17. Subgroup Analysis

Analysis populations: These analyses will be done using the mITT and PP populations. The primary efficacy endpoint, the first secondary endpoint of death/hospitalization, and other secondary endpoints by subgroups including sex (male/female), BMI (≥30, <30), age, (>65, ≤ 65), presence of additional concerning conditions (none, 1 or more or by specific conditions), whether the patient has received the last primary vaccination at least 14 days prior to study entry, whether patient plan to use an antiviral antibody treatment as assessed at baseline, and study region (US vs non-US).

18. Change from Analysis Specified in the Corresponding Protocol Version

The use of antipyretics will not be included in the assessment of the primary endpoint of sustained recovery as stated in the protocol. This is noted in the endpoint definition above and additional details of this change are provided in the appendix..

19. References

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

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.

Steingrimsson, Hanley, & Rosenblum. (2017). Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions. Contemporary Clinical Trials, 54, 18-24.

20. Appendix. Changes to analysis plan after approval of version 1.0

20.1 Changes implemented in version 2.0

Changes in version 2.0 were implemented prior to any unblinding of any team members.

20.1.1 Definition of primary endpoint of sustained recovery

Change: Use of antipyretics will not be considered to discount that the participant may be afebrile as reported in symptom diary.

Justification: After a review of the concomitant medication by the medical director, it was determined that antipyretics were not consistently reported in detail, and in some instances the same drugs, which are both antipyretics and analgesics, were used for indications other than fever. For example, considering a participant as not having been recovered from fever because s/he has taken an antipyretic/analgesic without either previous signs or symptoms of fever previously was not appropriate.

This constitutes a deviation from the definition and, therefore, analysis, as stated in the protocol (Amendment 4 dated 15 June 2021)

Clarification: Temperature data from the biosticker for the first 10 participants will not be used to determine if a participant is febrile.

Justification: Temperature data from the biostickers for the first 10 patients was compared with the temperatures measured by study staff at patient contacts. It was found that correlation between manually measured temperatures and data collected from the biostickers at the times that patients had temperatures taken was poor. Accordingly, temperatures measured by the biostickers will not be used for determination of recovery from symptomatic COVID; only the diary data will be used.

Clarification: The definition of recovery specifically notes that fatigue, anosmia and ageusia/dysgeusia may be persistent, defined as being “at a level similar to that during the acute illness”. For analysis, we have defined “at a level similar to that during the acute illness” as follows: severity of each symptom is graded as 0, 1, 2 or 3 for questionnaire responses none, mild, moderate or severe, respectively. The median grade for responses during the first 7 days of study (which may contain fewer than 7 responses if the patient missed one or more days) will be calculated. As long as the individual symptom is no worse than the median value during the first week, it will not be considered in determining the date of recovery.

Addition: Additional knowledge of the course of COVID-19 has been gained over the past year and a half, since the protocol definition of recovery was written. Accordingly, several sensitivity analyses using different definitions of recovery may be undertaken. Examples include:

1. First day at which there are no moderate or severe symptoms and ≤2 mild symptoms or symptoms worse than pre-COVID-19 illness, for at least 14 days or until last observation on study, whichever comes first. This will be calculated two ways: including and excluding sense of taste and smell.
2. First day at which there are no symptoms and no occurrence of any symptoms for at least 14 days or until last observation on study, whichever comes first. This will be calculated two ways: including and excluding sense of taste and smell.
3. First day at which the global assessment of symptoms is none and the global usual health response is yes, both continuing for at least 14 days or last observation on study, whichever comes first.

Justification: as noted in the amended procedure, considerable knowledge regarding resolution of COVID-19 symptoms and the occurrence of "long COVID" has been accumulated since the protocol was written. Accordingly, in this pilot analysis which is preparatory to a larger, definitive study, we want to consider several potential ways to look at the data, in order to optimize definition of the endpoint to be used for the pivotal study.

20.1.2 Modified intent-to-treat (mITT) population

Change: A small edit to the definition was made to clarify that the mITT population will include all randomized patients who receive any study treatment regardless of receipt of antibody treatments. The definition now reads:

> Modified Intent to Treat (mITT) Population includes all randomized patients who receive any *study* treatment.

DocuSign

Certificate Of Completion

Envelope Id: 721B272071FA4FD1B348452230398518
Subject: Please DocuSign: RHB-107-01 Part A SAP_v2.0_13Jan2022.pdf
Project/Charge Code: 150026.001.699.001
Source Envelope:
Document Pages: 28
Certificate Pages: 5
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Signatures: 2
Initials: 0

Status: Completed

Envelope Originator:
Timothy Asmar
359 Blackwell St.
Suite 200
Durham, NC 27701
tasmar@fhiclinical.com
IP Address: 68.37.7.35

Record Tracking

Status: Original
1/14/2022 7:59:24 AM

Holder: Timothy Asmar
tasmar@fhiclinical.com

Location: DocuSign

Signer Events	Signature	Timestamp
Mario Chen mchen@fhi360.org Security Level: Email, Account Authentication (Required)	Mario Chen Signature Adoption: Pre-selected Style Signature ID: CD1A4605-A615-4A76-9A07-F2E6D22D38CF Using IP Address: 172.58.157.18 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/14/2022 8:01:27 AM Viewed: 1/14/2022 8:35:39 AM Signed: 1/14/2022 8:38:48 AM
Electronic Record and Signature Disclosure: Accepted: 1/14/2022 8:35:39 AM ID: 9487a8ad-fce8-487b-b7e9-a7efb5c473c8		
Terry F Plasse, MD terry@redhillbio.com Security Level: Email, Account Authentication (Required)	DocuSigned by Terry F Plasse, MD Terry F Plasse, MD | I approve this document 14-Jan-2022 | 08:18:06 EST 160FE011E0124C30A95CBEBDE0EDA1B0 Signature Adoption: Pre-selected Style Signature ID: 160FE011-E012-4C30-A95C-BEBDE0EDA1B0 Using IP Address: 77.234.44.179 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/14/2022 8:01:27 AM Viewed: 1/14/2022 8:05:04 AM Signed: 1/14/2022 8:18:12 AM
Electronic Record and Signature Disclosure: Accepted: 1/14/2022 8:05:04 AM ID: ca0b59a2-b802-49e2-874f-1e95a79651a7		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/14/2022 8:01:27 AM
Certified Delivered	Security Checked	1/14/2022 8:05:04 AM
Signing Complete	Security Checked	1/14/2022 8:18:12 AM
Completed	Security Checked	1/14/2022 8:38:48 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, FHI Clinical, Inc - Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact FHI Clinical, Inc - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: support@fhiclinical.com

To advise FHI Clinical, Inc - Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at support@fhiclinical.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from FHI Clinical, Inc - Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to support@fhiclinical.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with FHI Clinical, Inc - Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to support@fhiclinical.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify FHI Clinical, Inc - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by FHI Clinical, Inc - Part 11 during the course of your relationship with FHI Clinical, Inc - Part 11.