# A Phase 2 Safety and Efficacy Study of Upamostat for Early Outpatient Treatment of COVID-19
# Product-Specific Appendix C

## Appendix C of Master Protocol for Early Treatment and Post-Exposure Prophylaxis of COVID-19 Adaptive Platform Trial (PROTECT-APT 1)

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## ABBREVIATIONS:

| | |
|---|---|
| AE | Adverse Event |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DAIDS | Division of AIDS |
| DSMB | Data and Safety Monitoring Board |
| IP | Investigational Product |
| IxRS | Interactive Voice Web Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intention to Treat |
| PCR | Polymerase Chain Reaction |
| PEP | Post-Exposure Prophylaxis |
| PP | Per Protocol |
| PROTECT-APT 1 | Master Protocol for Early Treatment and Post-Exposure Prophylaxis of COVID-19 Adaptive Platform Trial |
| PSA | Product-Specific Arm |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SDTM | Study Data Tabulation Model |
| SOC | System Organ Class |
| VOC | Variants of Concern |
| VOI | Variants of Interest |
| WHO | World Health Organization |

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# 1. INTRODUCTION

This statistical analysis plan (SAP) expands Section 13 (Statistical Considerations) of the master protocol "Master Protocol for Early Treatment and Post-Exposure Prophylaxis of COVID-19 Adaptive Platform Trial" (PROTECT-APT 1) and Section C 13 (Statistical Considerations) of the Product Specific Appendix (PSA) "Appendix C: A Phase 2 Safety and Efficacy Study of Upamostat for Early Outpatient Treatment of COVID-19". The final SAP approval by the sponsor will occur before data unblinding. Any changes to the planned analysis will be documented in the Clinical Study Report (CSR).

# 2. CHANGES FROM THE PROTOCOL

Pharmacokinetic and exploratory objectives will not be analyzed as a part of this SAP. Available data may be included in final Study Data Tabulation Model (SDTM).

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1. Primary Objective

To determine if early treatment with upamostat can shorten time to sustained symptom alleviation or resolution in participants infected with SARS-CoV-2.

- **Endpoint**: Time to sustained alleviation of resolution of COVID-19 symptoms. Defined as the number of days from randomization in a PSA to the first day the participant reports all symptoms as mild or none (or returning to pre-illness levels) for at least 3 consecutive days (the first day being considered the Event Day). [Timeframe: Day 0 to Day 28]

## 3.2. Secondary

- To evaluate the clinical efficacy of Investigational Product (IP) compared to control.
  - **Endpoints**
    a) Number and proportion of all cause hospitalizations
    [Timeframe: Day 0 to Day 28]
    b) Number and proportion of all cause deaths
    [Timeframe: Day 0 to Day 28]

- To determine if early treatment with upamostat can reduce disease severity in participants infected with SARS-CoV-2.
  - **Endpoints**
    a) Change in overall COVID-19 symptom severity score
    [Timeframe: Day 0 to Day 28]
    b) Number and proportion of participants in each treatment group developing new COVID-19 symptoms graded as severe on the symptom scale
    [Timeframe: Day 0 to Day 28]
    c) Number and proportion of participants who report return to usual state of health

[Timeframe: Days 7, 14, 28, Week 8, Week 12]

d) Number and proportion of participants who report return to usual activities [Timeframe: Days 7, 14, 28, Week 8, Week 12]

- To determine if early treatment with upamostat can decrease the incidence of hospitalization due to COVID-19.
  - **Endpoint**: Number and proportion of participants hospitalized for COVID-19 [Timeframe: Day 0 to Week 12]
- To evaluate virologic efficacy of upamostat compared to placebo.
  - **Endpoint**: Time to negative PCR [Timeframe: Day 0 to Week 12]

## 3.3. 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.
  - **Endpoint**: Assay for anti-SARS-CoV-2 IgM and IgG [Timeframe: Baseline and Week 8]
- To assess the impact of host transmembrane protease polymorphism on drug efficacy
  - **Endpoint**: Targeted analysis of polymorphism of know host transmembrane proteases which may be involved in viral entry into host cells.
- Characterize the impact of SARS-CoV-2 genetic variability on primary and secondary outcomes
  - **Endpoints**
    a) Difference in efficacy outcomes among circulating variants of interest (VOI) and variants of concern (VOC) via geographic and temporal prevalence
    b) Difference in efficacy outcomes among circulating VOI and VOC via SARS-CoV-2 genome sequencing

## 3.4. Safety Objectives

To evaluate the safety and tolerability of upamostat compared to control

- **Endpoints**
  a) Incidence of Serious Adverse Events (SAE)
  b) Comparison between active and placebo treatment groups in proportion of all and Grade 3 or greater adverse events (as assessed by the National Institutes of Health, Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events [DAIDS AE Grading Table], corrected Version 2.1, July 2017)
  c) Incidence of Adverse Events (AE) causing IP discontinuation
  d) Incidence of all-cause IP discontinuation or interruption
  e) Number of participants hospitalized due to adverse events regardless of cause

# 4. STUDY DESIGN

## 4.1. Master Protocol

This study is an adaptive, randomized, double blind, platform trial evaluating promising (IP) for safety and efficacy as early outpatient treatment and post-exposure prophylaxis for SARS-CoV-2. This multicenter trial will be conducted in both domestic and international sites. The study will compare IPs to standard of care in non-hospitalized SARS CoV-2 infected participants and uninfected adult contacts of SARS-CoV-2 confirmed cases. The master protocol outlines the core elements of the study.

An independent Data and Safety Monitoring Board (DSMB) will monitor the study both for futility and early efficacy to manage participant risk appropriately.

Safety will be evaluated based on clinical laboratory studies, vital signs, assessment of AE, symptom monitoring and physical exams. Efficacy will be evaluated based on viral testing, symptom scoring and outcome ascertainment.

## 4.2. Product-Specific Arm

This is 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 product-specific arm (PSA), Appendix C, are eligible for randomization to the upamostat Early Treatment arm of the trial.

Probability of randomization to the upamostat PSA arm (Appendix C) will be dependent on the number of PSA enrolling in the Early Treatment indication and the number of PSA arms for which a participant is eligible. 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. Participants randomized to upamostat PSA arm (Appendix C) will undergo a second blinded randomization to the active agent (upamostat) or placebo. The probability of the second randomization will also be dependent on the number of products enrolling in the indication at that time.

The total sample size was projected to be 300 (150 upamostat, 150 placebo), with safety monitoring planned to allow early stoppage for futility, efficacy, or safety. Details are described in the DSMB Charter.

## 4.3. Treatment Periods and Dosing

## 4.4. Sample Size

The maximum planned sample size for the early treatment indication primary analysis was 300 participants with 1:1 allocation to the IP and its control arm. The maximum sample size of 300

participants (150 active and 150 controls) and the adaptive design would provide 90% power to detect a hazard ratio of 1.50 risk (33% reduction in median time to symptom alleviation or resolution) and approximately 80% power for a hazard ratio of 1.42, a 30% reduction in the median time to symptom alleviation or resolution, assuming a median time to symptom resolution of 9 days for the control arm. This assumption is based on review of relevant literature [Menni 2022, Akavian 2022].

## 4.5. Randomization and blinding (Figure 1)

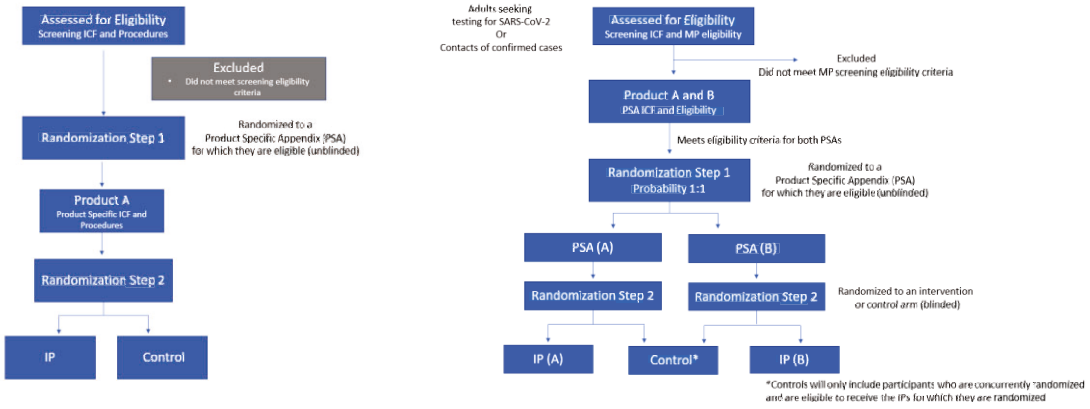
### 4.5.1. Step 1: Master Protocol and Randomization to PSA

Following completion of the screening informed consent and determination of eligibility under that Master Protocol, participants are stratified as either an eligible SARS-CoV-2 positive case or SARS-CoV-2 negative contact. Once identified as a case or contact, participants then undergo product-specific informed consent, followed by completion of all product-specific screening requirements to determine final eligibility for the available PSA (upamostat).

### 4.5.2. Step 2: Randomization within PSA

After PSA eligibility determination, participants undergo randomization to the PSA. Following assignment to the upamostat early treatment indication, participants undergo blinded randomization to either upamostat or placebo through the Interactive Voice/Web Response System (IxRS). A shared placebo (control) pool will be considered only if more than one PSA enrolls concurrently.

**Figure 1**




The randomization statistician prepared an electronic randomization list containing treatment assignments following the randomization sequence uploaded to the Interactive Web Response System (IWRS) operated by the vendor, Clinical One. Details of the specifications are described in the Request for Randomization form. After patient eligibility determination, site staff perform online randomization through Clinical One IWRS. As the study is a double-blind study, neither

patients, nor investigators, nor the Sponsor/CRO study team are aware of treatment assignments prior to the final database lock at the conclusion of the study.

## 4.6. Blinded Data Review

Prior to scheduled study unblinding, the data may be reviewed in a blinded fashion. Protocol deviations will be reviewed and a determination of the population for per protocol analysis will be made.

## 4.7. Blinding and Scheduled Study Unblinding

Participants, study staff, and study investigators are not blinded to the first step, randomization to the PSA. Participants are randomized to a PSA for which they meet the eligibility criteria, and which is enrolling in their strata. Randomization to the arm within the respective PSA is implemented through IxRS. Both participants and study investigators will be blinded to the second randomization.

Unblinding will be permitted during the trial in the following events:

- Emergency Unblinding: where knowledge of the treatment randomization is necessary to provide acute medical care or where there is a safety concern by the treating clinician. Details of the unblinding will be captured in the CRF including:
  - Date/timing
  - Reasons for unblinding
  - Name and roles of staff and participants involved in unblinding
  - Required clinical care
  - Event outcome
- To the DSMB for safety monitoring
- Statistical Analysis: unblinded results will be used in the final analyses following final database lock
- Participant notification: All participants will have the option to learn their randomization assignment after their PSA has been completed

In the event unblinding is required every effort will be made to limit this information to those individuals directly involved in the statistical analysis or care decisions and not with study staff.

After the study completes enrollment and patient follow-up, data entry, discrepancy resolution, blinded results reviews, coding and database lock, then the process for full study unblinding will start. Formal request to unblind should come from the Sponsor via a signed "Request to Reveal the Randomization Schedule" FHI 360 form. Once the Sponsor indicates that all requirements for full unblinding have been met, the lead biostatistician will initiate completion and sign-off of this form and document the unblinding process.

## 4.8. General Issues

General descriptive statistics for numeric variables include

- Continuous variables: mean, standard deviation, percentiles (median, $25^{th}$, $75^{th}$), minimum, maximum

- Categorical variables: frequency, percentage calculated based on subjects with reported values (i.e., subjects with missing data will not contribute to denominators of percentages)

Descriptive statistics and tabular summaries will be presented by treatment group.

For binary endpoints, proportion of participants with the event will be summarized by treatment group. Comparison between groups will be presented as the difference of proportions with its 95% confidence interval. For categorical endpoints, proportion of participants in each category will be summarized by treatment group

Unless otherwise specified, the following guidelines will be followed when displaying statistics:

- measures of central tendency and percentiles will be displayed with one decimal place more than the raw (collected) data
- measures of variability will be displayed with two decimal places more than the raw (collected) data
- percentages will be displayed with one decimal place
- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator.

## 4.9. Analysis Populations

For purposes of analysis, the following analysis sets are defined:

- **Screened Population Master Protocol:** All participants who complete informed consent for the master protocol
- **Screened Population Upamostat PSA:** All participants who complete informed consent for the upamostat PSA
- **Full Analysis Population:** All participants completing the second randomization step (randomization to a PSA).
    - The Full Analysis Population will be used for summaries of baseline demographic and clinical variables.
- **Modified Intention to Treat (mITT) Population:** All participants randomized who receive at least one dose of the IP/control.
    - The mITT population will be used for the primary efficacy assessment and for all other secondary efficacy analyses.

- **Safety Population:** All participants who receive at least one dose of the IP/control. In the unlikely case a participant receives the incorrect study drug, participants will be grouped according to the treatments that they received.
    - The Safety Population will be used in the analysis of the safety data.
- **Per Protocol Population:** All participants in the mITT set who completed treatment with IP/control and without major protocol deviations that impact the primary efficacy evaluation.
    - Prior to study unblinding, protocol deviations will be reviewed and a determination of the population for per protocol analysis will be made.
    - Participants will be excluded from the Per Protocol Population
        - Molnupiravir use
        - Missing 3 or more days of IP (determined by returned pill count of >=8 or treatment discontinuation prior to Study Day 11).
    - The PP analysis population may be used for secondary and exploratory endpoints.
- **Baseline COVID-19 PCR Positive Population**: All participants in the mITT Population who have a positive baseline COVID PCR result.
    - The Primary and Secondary Outcome analyses will be repeated with the Baseline COVID-19 PCR Positive analysis population.

## 4.10. Derivations, Data Handling Conventions and Missing Data

Baseline will be defined as the last assessment prior to the first dose date/time (or randomization if patient was not treated).

Study Day will be derived as (assessment date – date of first dose) + 1.

Event durations in days will be derived as (end date – start date) + 1.

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and concomitant medications. Specific rules for the handling of missing or partially missing dates for adverse events and concomitant medications are provided in Appendix A A.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

### 4.10.1. Resolution of Symptoms

The primary analyses will be based on an intent-to-treat approach. Therefore, every patient in the mITT Population will be analyzed. A single imputation approach for each patient with missing data will be utilized with a range of sensitivity analyses exploring the sensitivity of the results to the missing data.

A single imputation approach will be conducted for the primary analysis for each patient with missing daily observations. The following single imputation will be utilized:

- If the patient's last day was symptom free, then the patient will be assumed symptom free, and their time of resolution will be the first symptom free day.
- If the patient's last day was symptoms alleviated, then the patient will be assumed symptom alleviated and their time of alleviation the first day of alleviated symptoms.
- If the patient's last day was non-alleviated or resolved symptoms, they will be assumed censored without alleviation or resolution at the last observed day.

#### 4.10.2. Time to Negative PCR

Negative PCR is defined as a quantitative PCR result below the lower limit of detection.

Time to negative polymerase chain reaction (PCR) will be defined as the number of days from baseline positive PCR (Day 0) to the first of 2 consecutive negative PCR results.

- If only the final collected PCR is negative, this will be the date of negative PCR.
- If the final collected result is positive, the participant will be assumed censored without negative PCR

# 5. STATISTICAL ANALYSES

## 5.1. Description of participant population

### 5.1.1. Disposition

The number of subjects screened and in each study population will be tabulated by treatment group. Similarly, number of subjects in each study population will be tabulated additionally by country.

The subjects' final status, including number and percentage of subjects who complete the study, are lost to follow-up, or terminate early along with primary reason for discontinuation and reason for treatment discontinuation based on Case Report Form (CRF) will be tabulated using the Safety Population and by treatment group.

### 5.1.2. Protocol Deviations

The frequency of protocol deviations will be summarized with frequency tabulations by treatment group and major/minor classification using the Safety Population. Furthermore, all protocol deviations will be listed individually, including major/minor classification.

### 5.1.3. Study Intervention Compliance

Treatment compliance (percentage of planned doses received) will be calculated as

- Participant- Reported Compliance: (number of participant-reported doses via diary / expected doses x 100%)
- Observed Compliance: (30 minus number of pills returned / expected number of pills taken x100%)

summarized by treatment group for the Safety Population. Dosing details will be provided in listings.

### 5.1.4. Demographics and Baseline Characteristics

Baseline demographic and baseline characteristics information (age, sex, height, weight, BMI, race) will be summarized by treatment group for the Safety Population. Results will also be stratified by country.

### 5.1.5. Medical History

Medical history data, including prior procedures and therapies, will be summarized for the Safety Population by treatment group using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or higher) system organ class and preferred term.

### 5.1.6. Concomitant Therapy

Patient-reported medication history during the 30 days prior to ICF signing will be recorded at Screening. Thereafter, any changes in concomitant medications or new medications added will be recorded in the data collection forms.

While most systemic medications taken by the subject, other than study drug, are considered concomitant medications and should be recorded, the following specific exceptions do not need to be recorded: topical medications (eye drops, ear drops, intranasal drops or sprays, dermatologic treatments, topical lidocaine).

In contrast, the following should be recorded: vitamins and supplements (e.g., vitamins, minerals, herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacements) and nicotine replacement products (e.g., patches, lozenges, gums, nasal sprays).

Concomitant medications will be coded using the WHO Drug (version WHO_DDE_B3_sep2020 or higher) and summarized by treatment group for the Safety Population. A separate summary of concomitant medications considered rescue medications (i.e. those taken for COVID-19 symptoms) will be provided.

By-participant listings will accompany the tables.

## 5.2. Efficacy Assessments

The key efficacy assessment in the early treatment indication is time to sustained alleviation or resolution of symptoms among patients who were SARS-CoV-2 positive on initial screening at a local laboratory, either by PCR or rapid antigen test. Time to sustained alleviation or resolution of targeted COVID-19 symptoms will be defined as the number of days from randomization in a PSA (Step 2 of randomization) to the first day the participant reports all symptoms as mild or none (≤ 1 on the Daily Follow Up Symptom Questionnaire), or no worse than the usual severity, for at least 3 consecutive days (the first day being considered the Event Day).

Targeted symptoms include stuffy or runny nose, hoarse voice, sore throat, difficulty breathing, cough, fatigue, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, loss or taste, loss of smell. The Symptom Severity Score is collected in the Symptom Follow Up Questionnaire as the Overall Symptom Severity. Overall Symptom Severity may be rated none (0), mild (1), moderate (2), or severe (3). Loss of taste and loss of smell may be rated as the same as usual (0), less than usual (1), or no sense of taste/smell (2, considered a "severe" rating).

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.

Unless otherwise specified, 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 with box plots (means, medians, and inter-quartile ranges).

Sustained alleviation or resolution will be defined as the number of days from randomization within a PSA to the first day the participant reports all symptoms as mild or none (≤ 1 or returning to pre-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). Symptoms will be collected at Enrollment using the Screening Symptom Questionnaire to establish baseline symptom status.

### 5.2.1. 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
    - Analysis population: mITT

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 primary analysis population is the Modified Intent-to-Treat Population.

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 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 fixed

covariate with proportional effect. 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.

Additional sensitivity analyses for the primary analysis will utilize additional covariate adjustments in the Cox proportional hazards model. The analysis will be repeated for the Per Protocol Population and the Baseline COVID-19 PCR Positive Population.

### 5.2.2. Secondary Outcomes: Clinical

- Number and proportion of all cause hospitalizations
  - Timeframe: Day 0 to Day 28
- Number and proportion of all cause deaths
  - Timeframe: Day 0 to Day 28
- Change in overall COVID-19 symptom severity score
  - Timeframe: Day 0 to Day 28
  - A mixed model repeated measure model will be used to model the symptom severity score (Overall Symptom Severity) at each day using the baseline symptom score, participant, day, and treatment by day as covariates. The treatment effect by day will be summarized.
- Number and proportion of participants in each treatment group developing new COVID-19 symptoms rated as severe
  - Timeframe: 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 from 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 ration will be summarized.
- Proportion of participants who report a return to usual state of health
  - Timeframe: Day 7, Day 14, Day 28, Week 8, Week 12
  - A Cox proportional hazards model will be used to analyze the rime to return to usual state of health. Participants without symptomatic COVID-19 will be considered a 0 for return to usual health. Treatment arm will be modeled with a proportional hazard effect. The hazard ration will be summarized.
  - A Kaplan-Meier curve of time to return to usual state of health will be presented.
- Proportion of participants who report a return to usual activities
  - Timeframe: Day 7, Day 14, Day 28, Week 8, 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.
  - A Kaplan-Meier curve of time to return to usual activities will be presented.

Analysis population: The mITT population will be used for secondary endpoint analyses. Change in overall COVID-19 symptom severity score will be repeated with the Per Protocol Population and the Baseline COVID-19 PCR Positive Population.

### 5.2.3. Secondary Outcomes: Virological

- Comparison of active and placebo treatment groups in time to negative RT-PCR
  - Timeframe: 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.
  - A Kaplan-Meier curve of time to negative PCR will be presented.

Analysis population: The mITT population will be used for secondary endpoint analyses and will be repeated with the Per Protocol Population and the Baseline COVID-19 PCR Positive Population.

### 5.2.4. Exploratory

Exploratory endpoints will not be included in this SAP.

### 5.2.5. 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 when sufficient data are available (i.e. if a listed group makes up at least 20% of the analysis population):

- Age: <30 years, 30-50 years, >50 years
- Sex: Female, Male
- SARS-Cov-2 vaccination status
- Location (country): Thailand, USA, South Africa

### 5.2.6. Adverse events

An adverse event is any untoward medical occurrence associated with the use of an intervention in humans, regardless of whether the event is considered intervention-related or not. All adverse events that occur from the first dose of study medication through Week 12 after enrollment must be recorded.

AEs will be coded using MedDRA, version 24.0 or higher; AE severities will be graded using the Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017.

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the IP or any event already present that worsens in either intensity or frequency following exposure to the IP.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, medical monitor, or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Adverse events can be classified as/by:

- Investigational Product-related or not Investigational Product-related.
    - Relationships reported as definitely, probably, or possibly related are considered related to IP;
    - Relationships reported as unlikely or unrelated are considered not related to IP.
- Severity of Event

For AE not included in the protocol-defined grading system, the following guidelines will be used to describe severity:

- Grade 1 (Mild) – Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.
- Grade 2 (Moderate) – Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Grade 3 (Severe) – Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
- Grade 4 (Life-threatening) – Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
- Grade 5 (Death)

Safety analyses will include

- Incidence of Serious Adverse Events
- Adverse Events
- Adverse Events ≥ Grade 3
- IP discontinuation due to AE
- All-cause IP discontinuation
- Hospitalization due to any adverse events

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 AE 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 (e.g. 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.

All AE will be summarized by worst DAIDS grade and presented by System Organ Class (SOC), Preferred Term (PT), and treatment group, as follows.

- All AE
- All Related AE
- All AE leading to study drug discontinuation
- All SAE

All AE data will be provided in listings. A listing of any on-study deaths will be presented.

### 5.2.7. Electrocardiogram

Observed and changes from baseline QTc Fridericia (QTcF) internal data will be summarized by treatment group, cohort and scheduled visit. A listing of all results will be provided.

QTcF will be calculated as

$$QTc = \frac{QT}{RR^{1/3}}$$

where QT is the QT interval duration and RR is the interval between R waves.

### 5.2.8. Safety Laboratory

Observed and changes from baseline in laboratory values will be summarized by treatment group and scheduled visit. Safety laboratory parameters to be summarized include complete blood count (hemoglobin, platelets, leukocytes), differential (absolute counts of basophils, eosinophils, lymphocytes, monocytes, total neutrophils), renal/liver (BUN, creatinine, alanine

aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, total protein), and coagulation (aPTT, INR).

Laboratory abnormalities considered clinically significant will be entered by the investigators as adverse events and graded, classified by causality and included in the AE listings and tables accordingly.

By-subject listings will be provided for laboratory parameters of blood chemistry, hematology, and coagulation studies. Laboratory values outside the corresponding normal ranges will be flagged in listings.

# 6. INTERIM ANALYSIS

An interim analysis will not be performed.

# 7. PHARMACOKINETICS

Pharmacokinetic analyses are not covered by this SAP.

# 8. DATA SAFETY AND MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will consist of a panel of experts who will review the safety and efficacy data for the trial. The DSMB will convene at least every 6 months and/or at the interim triggers to help ensure the safety of the participants in the study. The DSMB will provide recommendations to the study, including termination or modification for safety reasons or if there is persuasive evidence of superiority or inferiority of the IP versus the control in its effect on the primary or secondary outcomes. Additional details on the DSMB will be provided in the DSMB Charter.

# APPENDIX A. CHANGES FROM PROTCOL

Version 1.0 of the SAP incorporated all analyses envisioned in the protocol version approved prior to study initiation. Any changes to the SAP to address amendments to the protocol or modifications to planned analyses, and their temporal relationship to unblinding, will be documented here.

| Type | Summary | Relationship to Unblinding |
|---|---|---|
| **Removed** | Exploratory endpoints indicated in protocol removed from planned analyses due to timing of data availability for inclusion in CSR | Prior |
| **Removed** | References to additional PSA and procedures for placebo sharing/randomization to PSA removed as only a single PSA enrolled participants. | Prior |
| **Removed** | Interim Analysis indicated in protocol removed due to enrollment end prior to analysis trigger. | Prior |
| **Removed** | Events of Special Interest were not defined for this PSA; all references have been removed | Prior |

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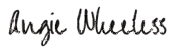
| Angie Wheeless<br>awheeless@fhiclinical.com<br>Director, Biostatistics<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>53C23FED-6A02-4550-9372-FD171EE32DFA<br>Using IP Address: 66.207.237.101<br><br>With Signing Authentication via Docusign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 7/28/2025 5:01:51 PM<br>Viewed: 7/28/2025 5:02:10 PM<br>Signed: 7/28/2025 5:02:43 PM |
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| Kimberly Malone<br>KMalone@FHIClinical.com<br>Security Level: Email, Account Authentication (Required) |  <br><br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>3C6361E2-3601-447C-B2EE-2F0856158AEC<br>Using IP Address: 65.190.87.91<br><br>With Signing Authentication via Docusign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 7/28/2025 5:01:52 PM<br>Viewed: 7/28/2025 5:05:26 PM<br>Signed: 7/28/2025 5:20:14 PM |
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| Signing Complete | Security Checked | 7/28/2025 7:57:55 PM |
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