CLINICAL STUDY PROTOCOL

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of FP-025 in Patients With Severe to Critical COVID-19 With Associated Acute Respiratory Distress Syndrome (ARDS)

Investigational Product: FP-025
Protocol Number: FP02C-20-001
Investigational New Drug Number: IND 151602

Sponsor:
Foresee Pharmaceuticals, Co. Ltd.
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Version Number: 3.0
Original Protocol: 16 December 2020
Amendment 1: 27 January 2021
Amendment 2: 12 May 2021

SIGNATURE PAGE

STUDY TITLE: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of FP-025 in Patients With Severe to Critical COVID-19 With Associated Acute Respiratory Distress Syndrome (ARDS)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
_____	_____
David Lau, PhD Senior Vice President, NCE Development Foresee Pharmaceuticals, Co. Ltd.	
_____	_____
Yisheng Lee, MD Chief Medical Officer Foresee Pharmaceuticals, Co. Ltd.	

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Foresee Pharmaceuticals, Co. Ltd. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Foresee Pharmaceuticals, Co. Ltd. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Foresee Pharmaceuticals, Co. Ltd., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of FP-025 in Patients With Severe to Critical COVID-19 With Associated Acute Respiratory Distress Syndrome (ARDS)

PROTOCOL NUMBER: FP02C-20-001

INVESTIGATIONAL PRODUCT: FP-025 (a selective small molecule inhibitor of matrix metalloproteinase [MMP]-12)

PHASE: 2/3

INDICATION: Severe to critical coronavirus (CoV) disease 2019 (COVID-19) with associated acute respiratory distress syndrome (ARDS)

OBJECTIVES:

The primary objectives of this study are the following:

- To evaluate the efficacy of FP-025, compared to placebo, in adult patients with severe to critical COVID-19 with associated ARDS, when used with standard of care treatment for COVID-19; and
- To evaluate the safety and tolerability of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS.

The secondary objectives of this study are the following:

- To evaluate the efficacy of FP-025, compared to placebo, in improving acute COVID-19 outcomes as measured by the change over time in the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale for COVID-19 and hospitalization outcomes, when used with standard of care treatment for COVID-19;
- To evaluate the efficacy of FP-025, compared to placebo, in reducing or preventing pulmonary fibrosis as determined by quantitative high-resolution, non-contrast computed tomography (CT) scan, when used with standard of care treatment for COVID-19;
- To evaluate the effect of FP-025, compared to placebo, on pulmonary function testing, when used with standard of care treatment for COVID-19;
- To evaluate the effect of FP-025, compared to placebo, on renal function in adult patients with severe to critical COVID-19 with associated ARDS; and
- To assess the pharmacokinetics (PK) of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS.

The exploratory objective of this study is to evaluate the effect of FP-025, compared to placebo, on inflammatory and fibrotic biomarkers in blood when used with standard of care treatment for COVID-19.

POPULATION:

The population for this study will include male or female patients ≥18 years with a diagnosis of severe to critical COVID-19 with associated ARDS.

Inclusion criteria:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Is willing to provide informed consent (or has a legally authorized representative [LAR] willing to provide informed consent) and is willing and able (or has an LAR willing and able) to comply with the protocol-required therapy, monitoring, and follow-up;
2. Is a male or female aged ≥18 years;
3. Has a COVID-19 diagnosis confirmed by a documented, positive severe acute respiratory syndrome (SARS)-CoV-2 reverse transcriptase polymerase chain reaction test (or equivalent test) immediately prior to or during the current hospitalization;
4. Is hospitalized with severe to critical COVID-19 within a 72-hour period prior to the Screening Visit and meeting the following characteristics:
    - Diagnosed with ARDS based on the Berlin criteria as follows:
        - Respiratory symptoms developed within 1 week of a known clinical insult or new or worsening respiratory symptoms developed during the past week;
        - Chest radiograph or computed tomography scan shows bilateral opacities not fully explained by pleural effusions, lobar or lung collapse, or pulmonary nodules; and
        - Respiratory failure is not fully explained by cardiac failure or fluid overload; and
    - Requiring at least 1 of the following:
        - Endotracheal intubation and mechanical ventilation;
        - Oxygen delivered by high flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20 L/minute with a fraction of delivered oxygen ≥0.5);
        - Non-invasive positive pressure ventilation; or
        - Clinical diagnosis of respiratory failure (ie, the clinical need for 1 of the preceding therapies, but preceding therapies are unable to be administered in the setting of resource limitations);
5. If female, is post-menopausal for at least 1 year, surgically sterile (documented by medical record), or a woman of childbearing potential (WCBP) who agrees to use a highly effective method of birth control (ie, method with a failure rate <1% per year) from enrollment until 30 days following the last dose of study drug. Highly effective methods of birth control are defined as follows: complete sexual abstinence, intrauterine device, intrauterine hormone-releasing system, progestogen-only hormonal contraception (implant, injectable, or oral), and combined (estrogen and progestogen) contraception (oral, intravaginal, or transdermal);

6. If a WCBP, must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at the Screening Visit (or have a negative historical serum hCG within the 24 hours before the Screening Visit) and must agree to monthly urine pregnancy tests during the study; and
7. If male, must be surgically sterile for at least 1 year prior to the Screening Visit (documented by medical record), or must agree to use a double barrier approach (eg, condoms with spermicide) during sexual intercourse between the Screening Visit and at least 90 days after administration of the last dose of study drug. Male patients must ensure that non-pregnant female partners of childbearing potential comply with the contraception requirements in Inclusion Criterion 5.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Is not expected to survive more than 24 hours;
2. Is on extracorporeal membrane oxygenation (ECMO) at the Screening Visit;
3. Has an underlying clinical condition where, in the opinion of the Investigator, it would be extremely unlikely that the patient would come off ventilation (eg, motor neuron disease, Duchenne muscular dystrophy, or rapidly progressive pulmonary fibrosis);
4. Has a known history of idiopathic pulmonary fibrosis or interstitial lung disease as defined by the American Thoracic Society 2018 guidelines;
5. Has known active tuberculosis (TB), a history of incompletely treated TB, and/or suspected or known extrapulmonary TB;
6. Has Child-Pugh Class B or C active liver disease or an alanine aminotransferase or aspartate aminotransferase level >4 × the upper limit of normal at the Screening Visit;
7. Has moderate to severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2, at the Screening Visit or requires hemodialysis;
8. Has a malignant tumor (excluding a malignant tumor cured with no recurrence in the past 5 years, completely resected basal cell and squamous cell carcinoma of skin, and/or completely resected carcinoma in situ of any type);
9. Has an uncontrolled systemic or local autoimmune or inflammatory disease besides COVID-19;

10. Has evidence of an active concurrent non-COVID-19 pneumonia that requires additional antimicrobial treatment at the time of the Screening Visit and is caused by a known or suspected bacterial pathogen, respiratory syncytial virus (RSV), influenza virus, SARS-CoV-1, Middle East respiratory syndrome-CoV, aspergillus, mucormycosis-causing fungi, or other pulmonary pathogen(s);

    Note: If a viral respiratory panel has not been collected within the 24 hours prior to the Screening Visit, a viral respiratory panel will be administered at the Screening Visit to determine eligibility. At a minimum, the panel will evaluate for RSV, influenza A, and influenza B.

11. Has received any other investigational therapeutic products within 4 weeks or 5 half-lives, whichever is longer, prior to randomization;
12. Has a known history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection;
13. Has a known serious allergic reaction or hypersensitivity to any components of FP-025;
14. Is pregnant or breastfeeding;
15. Has a history of drug or alcohol abuse within the past 2 years;
16. Is currently on another systemic immunomodulatory therapy that is not considered standard of care treatment for COVID-19 (eg, calcineurin inhibitor, hydroxychloroquine, anti-cytokine therapy, or Janus kinase inhibitor);

    Note: Corticosteroids, including dexamethasone, in doses used for standard of care treatment for COVID-19 are allowed.

    Note: Corticosteroids that are being used for other indications are also allowed as long as the daily prednisone (or other corticosteroid equivalent) dose is ≤10 mg. Inhaled corticosteroids and nasal corticosteroids are also acceptable.

    Note: As therapies for COVID-19 are rapidly evolving, other medications that may be considered standard of care can be considered with prior approval from the Sponsor or Medical Monitor.

17. Is currently on a strong cytochrome P450 inducer or inhibitor; or
18. Has any other condition that, in the opinion of the Investigator, could interfere with (or for which the treatment might interfere with) the conduct of the study or interpretation of the study results or that would place the patient at undue risk by participating in the study.

STUDY DESIGN AND DURATION:

This is a Phase 2/3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS. The patients in each phase (Phase 2 and Phase 3) will be analyzed separately.

Each phase will consist of a Screening Visit, Treatment Period, and Follow-Up Period for a total study duration of approximately 60 days.

Phase 2:

After eligibility is confirmed, approximately 99 patients will be randomized in a 1:1:1 ratio to receive FP-025 100 mg twice daily (BID), FP-025 300 mg BID, or placebo BID for 28 days. During Phase 2, randomized patients will be stratified by the use of invasive mechanical ventilation at the time of randomization (yes or no). At least one-third of patients should be on invasive mechanical ventilation to ensure that treatment benefits can be assessed for patients at different severity levels.

Patients with Grade 3 to Grade 4 heart failure, Stage 3 or greater chronic obstructive pulmonary disease, persistent asthma, and mild liver disease (ie, Child-Pugh Class A) will not be excluded from the study. The independent Data Monitoring Committee (iDMC) will independently monitor safety of the entire population and in different subgroups and may make recommendations as it deems appropriate. During Phase 2, no limitation in enrollment of subgroups is expected, unless clear safety signals arise in those subgroups during iDMC reviews.

The reason for hospital admission, the standard of care followed for each patient and center, and whether any care decisions were based on resource limitations will be clearly documented for all patients beginning on Day 1 (Visit 2). All patients will be allowed to receive standard of care and/or emergency use authorization (EUA) medications and treatment for COVID-19; however, the study drug should be discontinued for other non-standard of care concomitant medications used with the intent of directly treating COVID-19 unless there is prior Medical Monitor or Sponsor approval for the patient to remain on the study drug. If the use of concomitant medications necessitates study drug discontinuation, the patient should be encouraged to remain in the study and to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. If the patient withdraws, he/she should complete the Early Termination Visit.

Standard of care procedures for mechanical ventilation (eg, low tidal volume protective mechanical ventilation) and standard of care procedures for weaning from mechanical ventilation will be followed.

Study drug administration will begin on Day 1 (Visit 2) following randomization. All patients will receive standard of care and/or EUA treatment for COVID-19 in addition to the study drug. Patients will continue study drug treatment BID through Day 27 and take 1 dose on Day 28. If a patient is discharged from the hospital prior to Day 28, he/she will continue treatment as an outpatient at home with his/her assigned treatment (FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID) until Day 28. Dosing instructions will be provided prior to discharge. Although treatment will be identical for inpatients and outpatients, patients discharged from the hospital will follow a different Schedule of Procedures, characterized by telemedicine (or telephone, if sites and/or patients do not have video capability) visits. The End of Treatment (EOT) Visit on Day 28 will be identical for all patients (with the exception of the arterial oxygen partial pressure [PaO_2]/fractional inspired oxygen [FiO_2] ratio, performed only in patients on invasive or non-invasive ventilation) and will include a high-resolution, non-contrast CT scan, in addition to other assessments.

After treatment is completed, all patients will undergo 2 follow-up assessments during the Follow-Up Period. The first follow-up will be a telephone visit on Day 45 to assess concomitant medications, adverse events (AEs), and the NIAID 8-point ordinal scale for COVID-19 and hospitalization outcomes score. The second follow-up will be an in-person visit on Day 60 and

will include a high-resolution, non-contrast CT scan and pulmonary function tests, in addition to other assessments.

An iDMC will convene to oversee safety and efficacy assessments during and after the Phase 2 study. The first iDMC meeting will occur after approximately 10 to 15 patients have been enrolled. The second iDMC meeting will occur after approximately 50% to 60% of patients have been enrolled. No formal statistical testing will be conducted. In addition, when all patients in the Phase 2 study have completed the EOT Visit on Day 28, a primary analysis will be conducted by an independent statistician and reviewed by the iDMC.

Phase 3:

Based on the results of the primary analysis of Phase 2, 1 optimal dose will be selected to carry into Phase 3. Once the optimal dose has been selected, the study may proceed to Phase 3. Patients will be randomized in a 1:1 ratio to receive FP-025 or placebo for 28 days. Similar procedures will be followed as for Phase 2; however, study design (eg, eligibility criteria, sample size number, protocol-defined procedures, and timing of procedures) or dosing may be changed based on iDMC recommendations after data from the primary analysis in Phase 2 becomes available. If the iDMC recommends modification of the protocol, and the Sponsor is in agreement, the protocol will be amended and submitted to regulatory authorities and Institutional Review Boards for approval. An interim analysis will be conducted after approximately 70% (213 out of 304) of the randomized patients have completed the EOT Visit on Day 28 or have discontinued early, but would have reached Day 28 had they remained in the study, to assess for safety, early futility, and potential sample size recalculation.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

FP-025 is supplied as an oral capsule (amorphous solid dispersion-in-capsule) at a dose strength of 50 mg per capsule, and will be stored at room temperature (ie, 20°C to 25°C [68°F to 77°F]) under secure conditions. It will be administered orally as capsules or via a polyvinyl chloride nasogastric tube (by opening up the capsules and delivering as a suspension in orange juice). Capsules can also be opened and added to orange juice to drink. During Phase 2, patients will be randomized in a 1:1:1 ratio to receive FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID for 28 days, starting on Day 1 (Visit 2). Patients in each dose group will receive a total of 6 capsules during each dosing session as follows:

- FP-025 100 mg BID: Two 50 mg capsules and 4 placebo capsules;
- FP-025 300 mg BID: Six 50 mg capsules; and
- Placebo: 6 placebo capsules.

Based on the results of the primary analysis of Phase 2, 1 optimal dose will be selected to carry into Phase 3, and patients will be randomized in a 1:1 ratio to receive FP-025 or placebo for 28 days. No dose adjustments will be performed for renal impairment.

EFFICACY ENDPOINTS:

For all endpoints defined by events, the time points are defined as the number of days after randomization.

The primary efficacy endpoint is the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 28, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo.

The key secondary efficacy endpoints include the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- Proportion of patients on invasive mechanical ventilation at Day 28;
- Proportion of patients alive at Day 28;
- Proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 60;
- Proportion of patients on invasive mechanical ventilation at Day 60; and
- Proportion of patients alive at Day 60.

The other secondary efficacy endpoints include the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- Quantitative assessment of lung fibrosis at Day 28 and at Day 60 using high-resolution, non-contrast CT scan;
- Proportion of patients who were randomized on invasive mechanical ventilation who are free of invasive mechanical ventilation at Day 28 and at Day 60;
- Number of ventilator-free days (ie, days free of invasive mechanical ventilation) at Day 28 and at Day 60;
- Number of intensive care unit (ICU)-free days at Day 28 and at Day 60;
- Number of days in the hospital at Day 28 and at Day 60;
- Change from baseline in peripheral capillary oxygen saturation at Day 28 and at Day 60;
- Change from baseline in PaO2/FiO2 ratio at Day 28 and at Day 60 (patients on invasive or non-invasive ventilation only);
- Proportion of patients alive and not hospitalized at Day 28 and at Day 60;
- Proportion of patients with disease progression (defined as a ≥2-point decrease in the NIAID 8-point ordinal scale score or death) at Day 28 and at Day 60;
- Proportion of patients who improve by ≥2 points on the NIAID 8-point ordinal scale scores at Day 28 and proportion of patients who improve by ≥2 points at Day 60;

- Pulmonary function at Day 28 (if possible based on the patient's clinical condition per the judgment of the Investigator) and at Day 60 (all patients) based on the following scores:
  - Forced vital capacity (FVC);
  - Forced expiratory volume in 1 second (FEV_1);
  - FEV_1/FVC ratios; and
  - Diffusing capacity of the lungs for carbon monoxide; and
- Change from baseline in eGFR, blood urea nitrogen, and serum creatinine at Day 28 and Day 60.

Exploratory endpoints will include the change from baseline (pre-dose on Day 1) in biomarkers related to pulmonary inflammation, fibrosis and/or lung injury at Day 7, Day 14, Day 28, and Day 60, including but not limited to the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- MMP-12, MMP-7, and MMP-9;
- Transforming growth factor-β;
- Connective tissue growth factor;
- C-reactive protein (CRP);
- Cytokines (interferon-γ, tumor necrosis factor-α, interleukin [IL]-6, IL-1β, and C-C motif chemokine ligand 2 [monocyte chemoattractant protein-1]);
- Ferritin;
- Released N-terminal pro-peptide of type III collagen;
- Internal epitope in the 7S domain of type IV collagen;
- C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin);
- Neo-epitope of MMP-2, 9, and 13-mediated degradation of type I collagen;
- Neo-epitope of MMP-2, 9, and 12-mediated degradation of type IV collagen;
- Neo-epitope of MMP-2-mediated degradation of type VI collagen;
- Neo-epitope of MMP-1 and 8-mediated degradation of CRP; and
- Neo-epitope of plasmin-mediated degradation of cross-linked fibrin.

Additional biomarkers not listed here may be evaluated at a future date.

SAFETY ENDPOINTS:

The safety endpoints include the following:

- AEs and serious AEs (SAEs);
- Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis);
- Vital signs;

- Physical examinations; and
- 12-lead electrocardiograms (ECGs).

AEs will be monitored and recorded from the time of the first dose of study drug (Day 1 [Visit 2]) until the end of the study (Day 60). All events occurring prior to the first dose of study drug will be recorded as medical history.

Any SAE that is ongoing at the end of the study (Day 60) will be followed by the Investigator until the SAE has subsided or until the condition(s) becomes chronic in nature, until the patient begins alternative treatment for COVID-19, until the condition(s) stabilizes (in the case of persistent impairment), or until the patient dies.

As events of progression of the patient's underlying COVID-19 diagnosis will be captured as efficacy endpoints, these events should not be reported as AEs or SAEs unless considered related to the study drug or a study procedure or if the outcome is fatal during the study and within the safety reporting period. Additionally, expected events for ARDS that are perceived by the Investigator to occur with reasonable frequency in the day-to-day care of patients with ARDS treated in an ICU setting with mechanical ventilation will not be reported as AEs. Examples of events that are expected in the course of ARDS include transient hypoxemia, agitation, delirium, etc. Such events, which are often the focus of prevention efforts as part of standard ICU care, will not be considered reportable AEs unless the event is considered by the Investigator to be associated with the study drug or study procedures, is unexpectedly severe or frequent, or is a change of severity for an individual patient with ARDS.

PHARMACOKINETIC ENDPOINT:

The PK endpoint is the plasma exposure of FP-025 at each dose level. Sampling times will be as follows:

- Day 1 (Visit 2): pre-dose, 1 hour (±10 minutes), 3 hours (±10 minutes), and 8 hours (±10 minutes) post the first morning dose of study drug;

  Note: If the patient is randomized in the afternoon on Day 1 (Visit 2), this will be performed after the morning dose of study drug on Day 2.
- Day 4, Day 7, Day 14, and Day 21: within 1 hour (±10 minutes) prior to the morning dose; and
- Day 28: within 1 hour (±10 minutes) prior to the morning dose and 1 hour (±10 minutes) post-morning dose.

STATISTICAL ANALYSES:

The following analysis populations are defined for this study:

Intent-to-Treat (ITT) Population: The ITT Population is defined as all randomized patients. The ITT Population will be the primary population for analysis of efficacy data. Efficacy analyses will be based on the assigned treatment group.

Safety Population: The Safety Population is defined as all randomized patients who receive at least 1 dose of study drug. All safety data will be analyzed using the Safety Population. Safety analyses will be based on the treatment actually received.

Per-Protocol (PP) Population: The PP Population is defined as all patients in the ITT Population who complete the study with no major protocol deviations that may impact the primary efficacy assessment. The primary analysis will be repeated on the PP Population. Major protocol deviations will include violations of key entry criteria or deviations that could significantly impact the assessment or interpretation of efficacy data.

PK Population: The PK Population is defined as all patients with at least 1 PK measurement drawn during the study.

Patients who discontinue the study drug will remain in the study to have safety and efficacy assessments performed. Patients should be encouraged to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. The data observed on-study will be used for analysis regardless of any intercurrent events. Patients who die or discontinue treatment prior to the assessment time point (Day 28 or Day 60) because of lack of efficacy, and cannot have clinical status determined at the time point, will be considered treatment failures. Details regarding data handling and imputation method will be provided in the Statistical Analysis Plan (SAP).

The primary efficacy endpoint is the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 28. The treatment group difference of the response proportions, along with the corresponding 95% confidence interval and p-value, will be provided using the logistic regression model by Guo et al. (2012) and Ge et al. (2011), adjusted for stratification factor (use of invasive mechanical ventilation at the time of randomization [yes or no]). Additional prognostic baseline covariates (eg, age, region, body mass index) may be added as covariates/factors into the model to increase precision in the estimation of difference in proportions. Details will be provided in the SAP.

The primary analysis will be repeated on the PP Population.

The key secondary endpoints of the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 60, the proportion of patients on invasive mechanical ventilation at Day 28 and at Day 60, and the proportion of patients alive at Day 28 and Day 60, will be analyzed using the same method as for the primary analysis.

Tipping point method will be used as a sensitivity analysis for evaluating the robustness of the results for the primary endpoint and key secondary endpoints.

Other secondary endpoints will be analyzed as described in the SAP. For all endpoints defined by events, the time points are defined as the number of days after randomization.

The Phase 2 study is not powered. No alpha controlling strategy will be implemented.

To control the overall Type I error in the final analysis for Phase 3, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 1-sided 0.025 level first, followed by testing the secondary efficacy endpoints at the 1-sided 0.025 level in the following hierarchical manner: (1) proportion of patients on invasive mechanical ventilation at Day 28, (2) proportion of patients alive at Day 28, (3) proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive

mechanical ventilation, or ECMO) at Day 60, (4) proportion of patients on invasive mechanical ventilation at Day 60, and (5) proportion of patients alive at Day 60.

Inferential conclusions about these efficacy endpoints will require statistical significance of the previous endpoints and the primary efficacy endpoint.

This is not applicable to Phase 2 since Phase 2 is not powered.

PK data will be summarized.

Safety data will be summarized by actual treatment received, and in total for selected analyses/summaries, based on the Safety Population, and include the following:

- AEs and SAEs;
- Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis);
- Vital signs;
- Physical examinations; and
- 12-lead ECGs.

ANALYSIS TIMING:

Primary analysis (Phase 2):

A primary analysis will be conducted once all patients in Phase 2 complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. The results will be conducted by an independent statistician and reviewed by the iDMC following the procedures defined in the iDMC Charter. The iDMC will convene to recommend dose selection and whether to adjust study design for Phase 3 based on this analysis. The study team will remain blinded. Designated personnel from the Sponsor will have access to the analysis results. The Phase 3 sample size and interim analysis boundaries will be recalculated based on the Phase 2 primary analysis results.

Final analysis (Phase 2 and Phase 3):

For each phase (Phase 2 and Phase 3), after all the patients have completed (discontinued) the study and the database is locked, the data will be unblinded and the final analysis will be performed.

Interim analysis:

No interim analysis is planned for Phase 2.

For Phase 3, an interim analysis will be performed once approximately 70% of the randomized patients complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. The iDMC will convene to evaluate for safety, early futility, and potential sample size recalculation.

INDEPENDENT DATA MONITORING COMMITTEE:

An iDMC with multidisciplinary representation and pertinent expertise will be established to evaluate accumulating study data and to oversee the ongoing safety of the study for the patients enrolled. The iDMC will be external to the Sponsor. The iDMC will meet at 4 scheduled times, as

described below, and more frequently if needed, to provide safety oversight for patients. Only the iDMC members and an independent statistician will have access to unblinded comparative results. The study team will remain blinded, except as noted above for the Phase 2 primary analysis.

The iDMC will convene during the Phase 2 study at 2 pre-planned time points, once after approximately 10 to 15 patients have been enrolled and a second time after approximately 50% to 60% of patients have been enrolled. For each pre-planned meeting, the decision to have an associated pause in enrollment will be made by the chairperson of the iDMC (with input from the Medical Monitor). The decision will be based on the type of safety data to be provided for review and taking into account whether continuing enrollment could place study patients at risk. Based on safety and efficacy evaluations using unblinded data, the iDMC may make recommendation(s) to the Sponsor to continue the study with or without modifications or, for safety reasons, terminate the study. The Sponsor will make the final decision to terminate the study. No formal statistical testing will be conducted.

In addition, a primary analysis will be conducted once all patients in the Phase 2 study complete the EOT Visit on Day 28. The analysis will be conducted by an independent statistician and reviewed by the iDMC. The Sponsor (key personnel only) will also be able to review the data at this time. The iDMC will convene to recommend dose selection and whether to adjust study design (eg, eligibility criteria, sample size number, protocol-defined procedures, and timing of procedures) for Phase 3 based on this analysis. If the iDMC recommends modification of the protocol, and the Sponsor is in agreement, the protocol will be amended. Enrollment of any patients for Phase 3 will not begin until after completion of the assessment of the primary analysis.

During the Phase 3 study, an interim analysis will be performed once approximately 70% of the randomized patients (approximately 213 patients) complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. Enrollment of new patients will be paused during the interim analysis. The iDMC will convene, evaluating for safety, early futility, and potential sample size recalculation. The interim analysis of the primary endpoint will be for early futility only. The study will not be stopped for overwhelming efficacy.

Based on ongoing safety monitoring of the study, additional ad hoc iDMC reviews may be conducted. For these ad hoc meetings, the decision to have an associated pause in enrollment will be made by the chairperson of the iDMC (with input from the Medical Monitor). Further details regarding the role, responsibilities, and procedures of the iDMC will be provided in the iDMC Charter.

In addition, manual reviews of safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor. Study personnel and the Medical Monitor will be blinded to the patient treatment assignments throughout the study; however, in the event of an emergency or AE for which it is necessary to know the study drug to determine an appropriate course of therapy for the patient, unblinding may occur.

SAMPLE SIZE DETERMINATION:

For the Phase 2 study, approximately 99 patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID. No formal statistical assessment for sample size determination has been performed. The sample size is considered adequate to provide the necessary data to evaluate the objectives of the study.

For Phase 3, a total of 304 patients (152 patients per treatment group) will provide approximately 80% power to detect a 15% improvement in response rate, based on a control response rate of 60% and assuming a response rate of 75% with the study drug treatment group, using a 1-sided 0.025 level test. The sample size estimate assumes that an interim analysis will be conducted after approximately 70% of patients (approximately 213 patients) have completed the EOT Visit on Day 28 or have discontinued early, but would have reached Day 28 had they remained in the study, to assess early futility and potential sample size recalculation. The sample size was calculated using EAST 6.4. The Phase 3 sample size will be formally recalculated based on results from the Phase 2 part of the study. A maximum of 608 patients may be included. If the iDMC, in consultation with the Sponsor determines that a sample size of more than 608 patients is needed, a protocol amendment will be required.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
BID	Twice daily
CD	Cluster of differentiation
CFR	Code of Federal Regulations
COPD	Chronic obstructive pulmonary disease
CoV	Coronavirus(es)
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
EOT	End of Treatment
EUA	Emergency use authorization
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FiO_2	Fractional inspired oxygen
FVC	Forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
iDMC	Independent Data Monitoring Committee
IFN	Interferon
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation	Definition
LAR	Legally authorized representative
LPS	Lipopolysaccharide
MERS	Middle East respiratory syndrome
MMP	Matrix metalloproteinase
NIAID	National Institute of Allergy and Infectious Diseases
PaO_2	Arterial oxygen partial pressure
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PP	Per-Protocol
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TGF	Transforming growth factor
TNF	Tumor necrosis factor
WCBP	Woman/women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

FP-025 is a novel, non-hydroxamate, selective small molecule inhibitor of matrix metalloproteinase (MMP)-12, a protease implicated in many inflammatory and fibrotic diseases in the lung and other tissues. FP-025 is being evaluated as a treatment for adult patients with severe to critical coronavirus (CoV) disease 2019 (COVID-19) and associated acute respiratory distress syndrome (ARDS).

1.1 Coronavirus Disease 2019

CoV are widely found in nature and possess the largest single-stranded positive-sense ribonucleic acid genome known.[1] Although CoV are common causes of respiratory infections in humans, most of these strains cause mild respiratory symptoms in immunocompetent hosts.[1] Three of these CoV strains, however, have been observed to be highly pathogenic. The severe acute respiratory syndrome (SARS)-CoV-1 and Middle East respiratory syndrome (MERS)-CoV strains of past outbreaks led to both severe pneumonia[1] and ARDS,[2] a frequently fatal condition caused by a viral infection-induced elevation of inflammatory cytokines. In December 2019, in Wuhan, China, the third highly pathogenic CoV, SARS-CoV-2, emerged in the human population.[3] As of 08 November 2020, the United States has reported a total of 9,808,411 cases of COVID-19 with 236,547 deaths from the disease.[4]

Symptoms of COVID-19 appear 2 to 14 days after exposure (median of 5 to 7 days) and range from mild symptoms to severe illness and death, although approximately 40% to 45% of infected humans develop no symptoms.[5] Adults who are immunocompromised (eg, human immunodeficiency virus [HIV] infections) or over 65 years of age, particularly those with comorbidities such as hypertension, chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular disease, are more susceptible to severe respiratory complications and pneumonia. In those who develop severe lower respiratory symptoms, pulmonary infection is typically accompanied by a sustained, extreme, inflammatory response or cytokine storm, which can lead to severe complications, such as ARDS and subsequent pulmonary edema, systemic hypoxia, septic shock, metabolic acidosis, and multiple organ failure.[6]

According to the United States Centers for Disease Control (updated 30 June 2020), approximately 3% to 17% of COVID-19 patients develop ARDS. Among hospitalized patients, that number increases to 20% to 40%, and up to 67% to 85% for those admitted to the intensive care unit (ICU).[7] ARDS is associated with mortality rates of approximately 40%;[8] however, mortality from COVID-19–induced ARDS is even higher, with reported death rates of at least 50%.[9,10] Computed tomography (CT) scanning of the lungs of ARDS survivors often demonstrates abnormalities similar to those seen in pulmonary fibrosis.[11] This is also consistent with findings from patients with previous SARS and MERS infections, many of whom exhibited post-viral pulmonary fibrosis.[12,13] Although long-term lung fibrosis in recovered COVID-19 patients has not been studied in detail due to the recent emergence of the disease, it is reasonable to expect that pulmonary fibrosis will be a significant issue in patients recovering from COVID-19. In the literature, it was reported that histological features of lung fibrosis were found to relate to the duration of ARDS.[14] Potential anti-inflammatory and anti-fibrotic treatments could probably benefit COVID-19 patients if given at early onset of ARDS.[15]

1.2 FP-025

FP-025 is a selective small molecule inhibitor of MMP-12, which is a potential mediator of both inflammatory responses and structural remodeling that can occur in patients with COVID-19–associated respiratory disease.

MMP-12 expression and secretion are tightly regulated and limited to a few cell types. Its expression is increased in various disease states. Key functions of MMP-12 include the modulation of numerous components of the extracellular matrix, namely elastin and collagen. MMP-12 also modulates effector proteins and cells, such as the influx of monocytes and macrophages involved in inflammation and fibrosis.

MMP-12 is mainly produced and secreted by activated macrophages, as well as by pulmonary epithelial cells and chondrocytes. As such, MMP-12 is implicated in many inflammatory and fibrotic diseases of the lung. For instance, Rhinovirus-induced interferon (IFN)-γ stimulates MMP-12 expression, particularly in cluster of differentiation (CD)11b+/CD11c+ macrophages, which may degrade alveolar walls and lead to emphysema progression in mice.[16] MMP-12 is also upregulated after the induction of an asthmatic reaction using allergens.[17] MMP-12 inhibition is associated with protective effects on both emphysema and small airway remodeling in animal models.[18] In COPD patients, the expression of pulmonary MMP-12 in bronchial tissues, bronchoalveolar lavage (BAL) cells (macrophages), and fluids is significantly higher than that of normal controls.[19] MMP-12 is also implicated in interstitial lung diseases. MMP-12 is involved in both the acute and chronic phases of the inflammatory response in granulomatous diseases. Reduction in granuloma formation in the MMP-12 knockout mice compared to wild type supports a critical role for MMP-12 in granuloma formation.[20] MMP-12 gene and protein expression are also both increased in BAL samples from patients with sarcoidosis, correlating with disease severity.[21,22]

Foresee Pharmaceuticals, Co. Ltd. (hereafter, Foresee) is developing a potent and selective MMP-12 inhibitor, known as FP-025. FP-025 has shown preclinical efficacy in a lipopolysaccharide (LPS)-induced acute lung injury mouse model in reducing inflammatory cells in BAL fluid, as well as reducing the bronchial, arteriole, and alveolar damage and lung injury induced by LPS. In a bleomycin-induced unilateral lung fibrosis rat model, FP-025 reduced fibrosis, reduced bronchial and arterial damage in the lung, and attenuated the level of fibrotic biomarkers such as collagen 1, collagen 4, and transforming growth factor (TGF)-β1. FP-025 has undergone repeated-dose Good Laboratory Practice (GLP) toxicity studies in 2 species (up to 28 days of dosing in rats and dogs), as well as GLP safety, pharmacology, and genotoxicity studies.

In humans, single and multiple ascending dose studies of FP-025 have been conducted in healthy human patients, demonstrating dose-proportional and time-independent pharmacokinetics (PK) up to 400 mg twice daily (BID) for 7 days. In these studies, FP-025 was safe and well tolerated. FP-025 is currently undergoing a house dust mite-induced allergen-challenge study in the Netherlands (Study FP02C-18-001). The objective of the study is to test the potential of FP-025 to reduce the late allergic response and other inflammatory biomarkers due to the allergen challenge. A dose regimen of 400 mg BID for 12 days is being used. At this time, there have been no safety issues identified in this ongoing study. All doses have been well tolerated with no deaths or treatment-emergent serious adverse events (SAEs).

1.3 Rationale

MMP-12 is upregulated in pulmonary injury and fibrotic conditions. FP-025, a selective and potent MMP-12 inhibitor, was shown to have effects in preclinical inflammation and fibrosis models of the lung, making it a promising treatment for inflammatory airway diseases. Severe to critical COVID-19 with associated ARDS is likely associated with fibrosis and remodeling in the lung. It is postulated that FP-025 may potentially avert the lung injury and fibrosis caused by COVID-19 infections.

Preclinical and clinical studies suggest that administration of FP-025 in doses of 100 mg to 300 mg BID for 28 days in COVID-19 patients should be safe and efficacious. In healthy subjects, FP-025 has been found to be safe and well tolerated at dosages up to 400 mg BID for 7 days. Efficacy has been demonstrated in non-clinical studies, including the LPS-induced acute lung injury study in mice, at doses of 10 mg/kg and below, which is lower than the human equivalents of 100 mg and 300 mg. At those levels, the projected plasma exposure of FP-025 would be lower than the doses of 100 and 300 mg. FP-025 is currently being given at 400 mg BID for 12 days in a clinical study of patients with asthma. That study is ongoing and remains blinded. The dose level of FP-025 in that study is 400 mg BID for 12 days.

Foresee plans to initiate this study in severe to critical COVID-19 patients with ARDS to test the potential of FP-025 in reducing lung injury in these patients. Foresee is proposing a randomized, placebo-controlled, double-blind, parallel-designed, 28-day dosing study in adult patients with severe to critical COVID-19 with associated ARDS.

1.4 Risk/Benefit

This study will evaluate the efficacy and safety of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS. Scientific data suggest that a benefit to the patients may exist from participating in the study.

Preclinical and clinical studies suggest that risks to the patient will be minimal with administration of FP-025. In both preclinical species (rat and dog), FP-025 showed a very benign toxicity profile. Safety pharmacology studies were conducted in rats to evaluate central nervous system and respiratory safety and in dogs to evaluate cardiovascular safety. No treatment-related effects of FP-025 were revealed in these studies. In humans, single and multiple ascending dose studies of FP-025 have demonstrated that FP-025 is safe and well tolerated. In the ongoing house dust mite-induced allergen-challenge study in asthmatic patients, no safety issues have been identified to date. All doses have been well tolerated with no deaths or treatment-emergent SAEs.

Refer to the Investigator's Brochure for additional information.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are the following:

- To evaluate the efficacy of FP-025, compared to placebo, in adult patients with severe to critical COVID-19 with associated ARDS, when used with standard of care treatment for COVID-19; and
- To evaluate the safety and tolerability of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy of FP-025, compared to placebo, in improving acute COVID-19 outcomes as measured by the change over time in the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale for COVID-19 and hospitalization outcomes, when used with standard of care treatment for COVID-19;
- To evaluate the efficacy of FP-025, compared to placebo, in reducing or preventing pulmonary fibrosis as determined by quantitative high-resolution, non-contrast CT scan, when used with standard of care treatment for COVID-19;
- To evaluate the effect of FP-025, compared to placebo, on pulmonary function testing, when used with standard of care treatment for COVID-19;
- To evaluate the effect of FP-025, compared to placebo, on renal function in adult patients with severe to critical COVID-19 with associated ARDS; and
- To assess the PK of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS.

2.3 Exploratory Objective

The exploratory objective of this study is to evaluate the effect of FP-025, compared to placebo, on inflammatory and fibrotic biomarkers in blood when used with standard of care treatment for COVID-19.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2/3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of FP-025 in adult patients with severe to critical COVID-19 with associated ARDS. The patients in each phase (Phase 2 and Phase 3) will be analyzed separately.

Each phase will consist of a Screening Visit, Treatment Period, and Follow-Up Period for a total study duration of approximately 60 days.

3.1.1 Phase 2

After eligibility is confirmed, approximately 99 patients will be randomized in a 1:1:1 ratio to receive FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID for 28 days. During Phase 2, randomized patients will be stratified by the use of invasive mechanical ventilation at the time of randomization (yes or no). At least one-third of patients should be on invasive mechanical ventilation to ensure that treatment benefits can be assessed for patients at different severity levels.

Patients with Grade 3 to Grade 4 heart failure, Stage 3 or greater COPD, persistent asthma, and mild liver disease (ie, Child-Pugh Class A) will not be excluded from the study. The independent Data Monitoring Committee (iDMC) will independently monitor safety of the entire population and in different subgroups and may make recommendations as it deems appropriate. During Phase 2, no limitation in enrollment of subgroups is expected, unless clear safety signals arise in those subgroups during iDMC reviews.

The reason for hospital admission, the standard of care followed for each patient and center, and whether any care decisions were based on resource limitations will be clearly documented for all patients beginning on Day 1 (Visit 2). All patients will be allowed to receive standard of care and/or emergency use authorization (EUA) medications and treatment for COVID-19; however, the study drug should be discontinued for other non-standard of care concomitant medications used with the intent of directly treating COVID-19 unless there is prior Medical Monitor or Sponsor approval for the patient to remain on the study drug. If the use of concomitant medications necessitates study drug discontinuation, the patient should be encouraged to remain in the study and to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. If the patient withdraws, he/she should complete the Early Termination Visit.

Standard of care procedures for mechanical ventilation (eg, low tidal volume protective mechanical ventilation) and standard of care procedures for weaning from mechanical ventilation will be followed. The clinical criteria for weaning readiness testing and discontinuation from mechanical ventilation are described in Appendix D.

Study drug administration will begin on Day 1 (Visit 2) following randomization. All patients will receive standard of care and/or EUA treatment for COVID-19 in addition to the study drug. Patients will continue study drug treatment BID through Day 27 and take 1 dose on Day 28. If a patient is discharged from the hospital prior to Day 28, he/she will continue treatment as an outpatient at home with his/her assigned treatment (FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID) until Day 28. Dosing instructions will be provided prior to discharge. Although treatment will be identical for inpatients and outpatients, patients discharged from the hospital will follow a different Schedule of Procedures, characterized by telemedicine (or telephone, if sites and/or patients do not have video capability) visits. The End of Treatment (EOT) Visit on Day 28

will be identical for all patients (with the exception of the arterial oxygen partial pressure [PaO_2]/fractional inspired oxygen [FiO_2] ratio, performed only in patients on invasive or non-invasive ventilation) and will include a high-resolution, non-contrast CT scan, in addition to other assessments.

After treatment is completed, all patients will undergo 2 follow-up assessments during the Follow-Up Period. The first follow-up will be a telephone visit on Day 45 to assess concomitant medications, adverse events (AEs), and the NIAID 8-point ordinal scale for COVID-19 and hospitalization outcomes score. The second follow-up will be an in-person visit on Day 60 and will include a high-resolution, non-contrast CT scan and pulmonary function tests, in addition to other assessments.

An iDMC will convene to oversee safety and efficacy assessments during and after the Phase 2 study. The first iDMC meeting will occur after approximately 10 to 15 patients have been enrolled. The second iDMC meeting will occur after approximately 50% to 60% of patients have been enrolled. No formal statistical testing will be conducted. In addition, when all patients in the Phase 2 study have completed the EOT Visit on Day 28, a primary analysis will be conducted by an independent statistician and reviewed by the iDMC.

3.1.2 Phase 3

Based on the results of the primary analysis of Phase 2, 1 optimal dose will be selected to carry into Phase 3. Once the optimal dose has been selected, the study may proceed to Phase 3. Patients will be randomized in a 1:1 ratio to receive FP-025 or placebo for 28 days. Similar procedures will be followed as for Phase 2; however, study design (eg, eligibility criteria, sample size number, protocol-defined procedures, and timing of procedures) or dosing may be changed based on iDMC recommendations after data from the primary analysis in Phase 2 becomes available. If the iDMC recommends modification of the protocol, and the Sponsor is in agreement, the protocol will be amended and submitted to regulatory authorities and Institutional Review Boards (IRBs) for approval. An interim analysis will be conducted after approximately 70% (213 out of 304) of the randomized patients have completed the EOT Visit on Day 28 or have discontinued early, but would have reached Day 28 had they remained in the study, to assess for safety, early futility, and potential sample size recalculation.

3.2 Study Indication

The indication for this study is the treatment of patients with severe to critical COVID-19 with associated ARDS.

4 SELECTION AND WITHDRAWAL OF PATIENTS

The population for this study will include male or female patients ≥18 years with a diagnosis of severe to critical COVID-19 with associated ARDS.

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Is willing to provide informed consent (or has a legally authorized representative [LAR] willing to provide informed consent) and is willing and able (or has an LAR willing and able) to comply with the protocol-required therapy, monitoring, and follow-up;
2. Is a male or female aged ≥18 years;
3. Has a COVID-19 diagnosis confirmed by a documented, positive SARS-CoV-2 reverse transcriptase polymerase chain reaction test (or equivalent test) immediately prior to or during the current hospitalization;
4. Is hospitalized with severe to critical COVID-19 within a 72-hour period prior to the Screening Visit and meeting the following characteristics:
    - Diagnosed with ARDS based on the Berlin criteria as follows:
        - Respiratory symptoms developed within 1 week of a known clinical insult or new or worsening respiratory symptoms developed during the past week;
        - Chest radiograph or computed tomography scan shows bilateral opacities not fully explained by pleural effusions, lobar or lung collapse, or pulmonary nodules; and
        - Respiratory failure is not fully explained by cardiac failure or fluid overload; and
    - Requiring at least 1 of the following:
        - Endotracheal intubation and mechanical ventilation;
        - Oxygen delivered by high flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20 L/minute with a fraction of delivered oxygen ≥0.5);
        - Non-invasive positive pressure ventilation; or
        - Clinical diagnosis of respiratory failure (ie, the clinical need for 1 of the preceding therapies, but preceding therapies are unable to be administered in the setting of resource limitations);
5. If female, is post-menopausal for at least 1 year, surgically sterile (documented by medical record), or a woman of childbearing potential (WCBP) who agrees to use a highly effective method of birth control (ie, method with a failure rate <1% per year) from enrollment until 30 days following the last dose of study drug. Highly effective methods of birth control are defined as follows: complete sexual abstinence, intrauterine device, intrauterine hormone-releasing system, progestogen-only hormonal contraception (implant, injectable, or oral), and combined (estrogen and progestogen) contraception (oral, intravaginal, or transdermal);

6. If a WCBP, must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at the Screening Visit (or have a negative historical serum hCG within the 24 hours before the Screening Visit) and must agree to monthly urine pregnancy tests during the study; and
7. If male, must be surgically sterile for at least 1 year prior to the Screening Visit (documented by medical record), or must agree to use a double barrier approach (eg, condoms with spermicide) during sexual intercourse between the Screening Visit and at least 90 days after administration of the last dose of study drug. Male patients must ensure that non-pregnant female partners of childbearing potential comply with the contraception requirements in Inclusion Criterion 5.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Is not expected to survive more than 24 hours;
2. Is on extracorporeal membrane oxygenation (ECMO) at the Screening Visit;
3. Has an underlying clinical condition where, in the opinion of the Investigator, it would be extremely unlikely that the patient would come off ventilation (eg, motor neuron disease, Duchenne muscular dystrophy, or rapidly progressive pulmonary fibrosis);
4. Has a known history of idiopathic pulmonary fibrosis or interstitial lung disease as defined by the American Thoracic Society 2018 guidelines;[23]
5. Has known active tuberculosis (TB), a history of incompletely treated TB, and/or suspected or known extrapulmonary TB;
6. Has Child-Pugh Class B or C active liver disease or an alanine aminotransferase or aspartate aminotransferase level >4 × the upper limit of normal at the Screening Visit;
7. Has moderate to severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2, at the Screening Visit or requires hemodialysis;
8. Has a malignant tumor (excluding a malignant tumor cured with no recurrence in the past 5 years, completely resected basal cell and squamous cell carcinoma of skin, and/or completely resected carcinoma in situ of any type);
9. Has an uncontrolled systemic or local autoimmune or inflammatory disease besides COVID-19;
10. Has evidence of an active concurrent non-COVID-19 pneumonia that requires additional antimicrobial treatment at the time of the Screening Visit and is caused by a known or suspected bacterial pathogen, respiratory syncytial virus (RSV), influenza virus, SARS-CoV-1, MERS-CoV, aspergillus, mucormycosis-causing fungi, or other pulmonary pathogen(s);

    Note: If a viral respiratory panel has not been collected within the 24 hours prior to the Screening Visit, a viral respiratory panel will be administered at the Screening Visit to determine eligibility. At a minimum, the panel will evaluate for RSV, influenza A, and influenza B.
11. Has received any other investigational therapeutic products within 4 weeks or 5 half-lives, whichever is longer, prior to randomization;

12. Has a known history of HIV, hepatitis B, or hepatitis C infection;
13. Has a known serious allergic reaction or hypersensitivity to any components of FP-025;
14. Is pregnant or breastfeeding;
15. Has a history of drug or alcohol abuse within the past 2 years;
16. Is currently on another systemic immunomodulatory therapy that is not considered standard of care treatment for COVID-19 (eg, calcineurin inhibitor, hydroxychloroquine, anti-cytokine therapy, or Janus kinase inhibitor);

    Note: Corticosteroids, including dexamethasone, in doses used for standard of care treatment for COVID-19 are allowed.

    Note: Corticosteroids that are being used for other indications are also allowed as long as the daily prednisone (or other corticosteroid equivalent) dose is ≤10 mg. Inhaled corticosteroids and nasal corticosteroids are also acceptable.

    Note: As therapies for COVID-19 are rapidly evolving, other medications that may be considered standard of care can be considered with prior approval from the Sponsor or Medical Monitor.
17. Is currently on a strong cytochrome P450 inducer or inhibitor (see Appendix E); or
18. Has any other condition that, in the opinion of the Investigator, could interfere with (or for which the treatment might interfere with) the conduct of the study or interpretation of the study results or that would place the patient at undue risk by participating in the study.

4.3 Stopping Criteria

All AEs should be considered possibly related to study drug unless clearly unrelated or if there is a clear etiology other than study drug such as a pre-existing medical condition, an underlying disease, or a concomitant medication. The decision to have an associated pause in enrollment will be made by the chairperson of the iDMC (with input from the Medical Monitor). The iDMC will oversee the safety and tolerability of FP-025 during the study and determine if it is acceptable to continue, as described in Section 9.2.4. However, safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first patient.

4.3.1 Criteria for Potential Interruption or Discontinuation of Study Drug in Individual Patients

In the event that any of the following is encountered, the Investigator, Sponsor, or Medical Monitor may choose to interrupt the study drug (in consultation with the Medical Monitor) or discontinue a patient from the study drug (but continue to follow the patient for safety and key efficacy endpoints):

- ≥Grade 3 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) AE or clinically significant laboratory abnormality considered related to study drug;

  Note: All ≥Grade 3 (CTCAE) laboratory abnormalities should be confirmed with a repeat test within 24 hours to confirm the abnormality.

- Severe anaphylactic reaction, including bronchospasm; or
- Requirement for a prohibited concomitant medication (eg, non-standard of care concomitant medications for COVID-19).

For any patient who prematurely discontinues from study drug, the reason and date of discontinuation will be documented in the electronic case report form (eCRF) and the patient should continue to complete all safety assessments at subsequent study visits.

4.3.2 Criteria for Potential Study Termination

In the event that any of the following is encountered, the iDMC will convene to determine if the study must stop enrollment and/or to recommend modification to the protocol (ie, decrease or change the dose of study drug, modify dosing schedule, or terminate the study, as described in the iDMC Charter):

- ≥Grade 4 (CTCAE version 5.0) reaction considered related to study drug;
- ≥3 patients are discontinued from treatment for safety reasons; or
- ≥3 patients experience similar SAEs or Grade 3 (CTCAE version 5.0) AEs regardless of relatedness to study drug.

Note: All ≥Grade 3 (CTCAE) laboratory abnormalities should be confirmed with a repeat test within 24 hours to confirm the abnormality.

The following will not be considered as criteria for study termination:

- Grade 3 nausea if resolves to ≤Grade 1 within 72 hours;
- Grade 3 fatigue, malaise, or insomnia if resolves to ≤Grade 1 within 72 hours; and
- ≤Grade 4 isolated electrolyte abnormalities that resolve with or without intervention to ≤Grade 1 within 72 hours.

4.4 Withdrawal Criteria

Participation of a patient in this study may be discontinued for any of the following reasons:

- Withdrawal of consent or request for discontinuation from the study for any reason; and
- Loss to follow-up.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for patient withdrawal must be documented in the eCRF.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Study drug treatment may be discontinued (although the patient should be encouraged to remain in the study and to follow-up for key study visits) for any of the following reasons:

- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;

  Note: Patients who discontinue study drug for safety or tolerability reasons will not be replaced.
- Pregnancy; or
- Patient failure to comply with protocol requirements or study-related procedures.

5 STUDY TREATMENTS

5.1 Treatment Groups

During Phase 2, patients will be randomized in a 1:1:1 ratio to receive FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID for 28 days, starting on Day 1 (Visit 2). Patients in each dose group will receive a total of 6 capsules during each dosing session as follows:

- FP-025 100 mg BID: Two 50 mg capsules and 4 placebo capsules;
- FP-025 300 mg BID: Six 50 mg capsules; and
- Placebo: 6 placebo capsules.

Based on the results of the primary analysis of Phase 2, 1 optimal dose will be selected to carry into Phase 3, and patients will be randomized in a 1:1 ratio to receive FP-025 or placebo for 28 days. No dose adjustments will be performed for renal impairment.

5.2 Rationale for Dosing

Preclinical and clinical studies suggest that administration of FP-025 in doses of 100 mg to 300 mg BID for 28 days in COVID-19 patients should be safe and efficacious. In healthy subjects, FP-025 has been found to be safe and well tolerated at dosages up to 400 mg BID for 7 days. Efficacy has been demonstrated in non-clinical studies, including the LPS-induced acute lung injury study in mice, at doses of 10 mg/kg and below, which is lower than the human equivalents of 100 mg and 300 mg. At those levels, the projected plasma exposure of FP-025 would be lower than the doses of 100 and 300 mg. A clinical study in patients with asthma is ongoing and remains blinded. The dose level of FP-025 in that study is 400 mg BID for 12 days.

5.3 Randomization and Blinding

During Phase 2, patients will be randomized in a 1:1:1 ratio to receive FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID for 28 days. Patients in each dose group will receive a total of 6 capsules during each dosing session as described in Section 5.1 in order to maintain blinding. Randomized patients will be stratified by the use of invasive mechanical ventilation at the time of randomization (yes or no). Patients, Investigators, and study personnel involved in the administration and assessment of the study drug will be blinded to the patient treatment assignments throughout the study.

5.4 Breaking the Blind

Unblinding by request of an Investigator should occur only in the event of an emergency or AE for which it is necessary to know the study drug to determine an appropriate course of therapy for the patient. If the Investigator must identify the treatment assignment of an individual patient, the Investigator or qualified designee should request the treatment assignment from the centralized randomization system. The Investigator is advised not to reveal the study drug assignment to other centers or Sponsor personnel.

Prior to unblinding, and if the situation allows, the Investigator should consult with the Medical Monitor. If this is impractical, the Investigator must notify the Medical Monitor as soon as possible, without revealing the treatment assignment of the unblinded patient. The Investigator must

document the patient identification and the date and time for breaking the blind and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the patient based on the patient's signs/symptoms without waiting for the unblinding process to be completed).

Patients who are unblinded and discontinue study drug but are not withdrawn from the study should continue to complete all safety assessments at subsequent study visits.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

FP-025 is supplied as an oral capsule (amorphous solid dispersion-in-capsule) at a dose strength of 50 mg per capsule.

Foresee will supply sufficient quantities of study drug (FP-025 and matching placebo) to allow for completion of the study. The lot numbers will be recorded in the final clinical study report.

5.5.2 Study Drug Preparation and Dispensing

The study drug (FP-025 and matching placebo) will be dispensed by the pharmacist or qualified designee.

5.5.3 Study Drug Administration

The study drug (FP-025 and matching placebo) will be administered orally as capsules or via a polyvinyl chloride nasogastric tube (by opening up the capsules and delivering as a suspension in orange juice). Capsules can also be opened and added to orange juice to drink. During Phase 2, each patient will receive either FP-025 (100 mg or 300 mg) or placebo BID for 28 days. Based on the results of the primary analysis of Phase 2, 1 optimal dose will be selected to carry into Phase 3, and patients will be randomized in a 1:1 ratio to receive FP-025 or placebo for 28 days.

5.5.4 Treatment Compliance

To ensure treatment compliance, all inpatient doses will be administered by center staff.

For outpatients, treatment compliance will be assessed by pill counts. Center staff will counsel patients on the importance of adhering to the study drug administration schedule prior to hospital discharge. At the next inpatient visit on Day 28, center staff will count the number of capsules left in the bottle and compare that to the number of capsules the patient was given at hospital discharge.

The exact time of study drug administration and the volume of study drug administered will be recorded in the eCRF.

5.5.5 Storage and Accountability

At the center, FP-025 will be stored at room temperature (ie, 20°C to 25°C [68°F to 77°F]) under secure conditions.

The pharmacist (or designee) will acknowledge receipt of all shipments of the study drug and maintain an inventory. The study drugs must be kept in a locked area with restricted access and

stored and handled in accordance with the manufacturer's instructions. The pharmacist (or designee) will also keep accurate records of the quantities of the study drugs dispensed and used by each patient. The clinical research associate (CRA) will periodically check the supplies of study drugs held by the pharmacist to verify accountability of all study drugs used.

At the conclusion of the study, the CRA will account for all used and unused study drug. After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor or a delegate. Additional information can be found in the Pharmacy Manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications, taken within 4 weeks or 5 half-lives, whichever is longer, are prohibited:

- Systemic immunomodulatory therapy that is not considered standard of care treatment for COVID-19 (eg, calcineurin inhibitors, hydroxychloroquine, anti-cytokine therapies, or Janus kinase inhibitors);

  Note: Corticosteroids, including dexamethasone, in doses used for standard of care treatment for COVID-19 are allowed.

  Note: Corticosteroids that are being used for other indications are also allowed as long as the daily prednisone (or other corticosteroid equivalent) dose is ≤10 mg. Inhaled corticosteroids and nasal corticosteroids are also acceptable.

  Note: As therapies for COVID-19 are rapidly evolving, other medications that may be considered standard of care can be considered with prior approval from the Sponsor or Medical Monitor.

- Strong cytochrome P450 inducers or inhibitors as listed in Appendix E; or
- Any other investigational therapeutic products.

5.6.2 Documentation of Prior and Concomitant Medication Use

Any investigational and off-label therapies for COVID-19–related infections for each patient (eg, hydroxychloroquine or interleukin [IL]-6 inhibitors), along with the time, dose, and duration of their administration, must be recorded. All patients will be allowed to receive standard of care and/or EUA medications and treatment for COVID-19; however, the study drug should be discontinued for other non-standard of care concomitant medications used with the intent of directly treating COVID-19 unless there is prior Medical Monitor or Sponsor approval for the patient to remain on the study drug. If the use of concomitant medications necessitates study drug discontinuation, the patient should be encouraged to remain in the study and to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. If the patient withdraws, he/she should complete the Early Termination Visit.

Any treatment given in addition to the study drug during the study is regarded as a concomitant medication and must be recorded on the appropriate eCRF.

Any relevant medications received in the 14 days prior to study drug administration must be recorded on the appropriate eCRF, along with the reason for use, dates of administration, and dosages.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the Investigator and recorded in the patient's source documents and the eCRF.

Any care decisions that are made due to resource limitation (eg, ventilation not available) must be documented.

Data surrounding major changes in background therapy will be collected. The standard of care that is followed for each patient and center must be recorded. If standard of care therapies are not able to be delivered due to resource limitations, this should also be recorded.

Any reasons for discontinuation of ventilation must be recorded on the appropriate eCRF, including all data related to clinical decision making that guides removal from mechanical ventilation in relation to clinical deterioration or lack of clinical response.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures in Appendix A.

7 EFFICACY AND PHARMACOKINETIC ASSESSMENTS

7.1 Efficacy and Pharmacokinetic Endpoints

For all endpoints defined by events, the time points are defined as the number of days after randomization.

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 28, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo.

7.1.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints include the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- Proportion of patients on invasive mechanical ventilation at Day 28;
- Proportion of patients alive at Day 28;
- Proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 60;
- Proportion of patients on invasive mechanical ventilation at Day 60; and
- Proportion of patients alive at Day 60.

7.1.3 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints include the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- Quantitative assessment of lung fibrosis at Day 28 and at Day 60 using high-resolution, non-contrast CT scan;
- Proportion of patients who were randomized on invasive mechanical ventilation who are free of invasive mechanical ventilation at Day 28 and at Day 60;
- Number of ventilator-free days (ie, days free of invasive mechanical ventilation) at Day 28 and at Day 60;
- Number of ICU-free days at Day 28 and at Day 60;
- Number of days in the hospital at Day 28 and at Day 60;
- Change from baseline in peripheral capillary oxygen saturation (SpO_2) at Day 28 and at Day 60;
- Change from baseline in PaO_2/FiO_2 ratio at Day 28 and at Day 60 (patients on invasive or non-invasive ventilation only);
- Proportion of patients alive and not hospitalized at Day 28 and at Day 60;

- Proportion of patients with disease progression (defined as a ≥2-point decrease in the NIAID 8-point ordinal scale score or death) at Day 28 and at Day 60;
- Proportion of patients who improve by ≥2 points on the NIAID 8-point ordinal scale scores at Day 28 and proportion of patients who improve by ≥2 points at Day 60;
- Pulmonary function at Day 28 (if possible based on the patient's clinical condition per the judgment of the Investigator) and at Day 60 (all patients) based on the following scores:
  - Forced vital capacity (FVC);
  - Forced expiratory volume in 1 second (FEV_1);
  - FEV_1/FVC ratios; and
  - Diffusing capacity of the lungs for carbon monoxide; and
- Change from baseline in eGFR, blood urea nitrogen, and serum creatinine at Day 28 and Day 60.

7.1.4 Exploratory Endpoints

Exploratory endpoints will include the change from baseline (pre-dose on Day 1) in biomarkers related to pulmonary inflammation, fibrosis and/or lung injury at Day 7, Day 14, Day 28, and Day 60, including but not limited to the following, with each dose (Phase 2) or the optimal dose (Phase 3) of FP-025 compared to placebo:

- MMP-12, MMP-7, and MMP-9;
- Transforming growth factor-β;
- Connective tissue growth factor;
- C-reactive protein (CRP);
- Cytokines (IFN-γ, tumor necrosis factor [TNF]-α, IL-6, IL-1β, and C-C motif chemokine ligand 2 [monocyte chemoattractant protein-1]);
- Ferritin;
- Released N-terminal pro-peptide of type III collagen;
- Internal epitope in the 7S domain of type IV collagen;
- C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin);
- Neo-epitope of MMP-2, 9, and 13-mediated degradation of type I collagen;
- Neo-epitope of MMP-2, 9, and 12-mediated degradation of type IV collagen;
- Neo-epitope of MMP-2-mediated degradation of type VI collagen;
- Neo-epitope of MMP-1 and 8-mediated degradation of CRP; and
- Neo-epitope of plasmin-mediated degradation of cross-linked fibrin.

Additional biomarkers not listed here may be evaluated at a future date.

7.1.5 Pharmacokinetic Endpoint

The PK endpoint is the plasma exposure of FP-025 at each dose level. Sampling times will be as follows:

- Day 1 (Visit 2): pre-dose, 1 hour (±10 minutes), 3 hours (±10 minutes), and 8 hours (±10 minutes) post the first morning dose of study drug;

  Note: If the patient is randomized in the afternoon on Day 1 (Visit 2), this will be performed after the morning dose of study drug on Day 2.

- Day 4, Day 7, Day 14, and Day 21: within 1 hour (±10 minutes) prior to the morning dose; and
- Day 28: within 1 hour (±10 minutes) prior to the morning dose and 1 hour (±10 minutes) post-morning dose.

7.2 Efficacy Assessments

7.2.1 Arterial Oxygen Partial Pressure/Fractional Inspired Oxygen Ratio

A PaO_2, obtained via arterial blood gas will be used to calculate the PaO_2/FiO_2 ratio, only in patients on invasive or non-invasive ventilation.

7.2.2 Pulmonary Function Tests

Pulmonary function tests (PFTs) will be performed at the times indicated in Appendix A. PFTs will include measurement of FVC, FEV_1, FEV_1/FVC ratio, and diffusing capacity of the lungs for carbon monoxide.

7.2.3 Computed Tomography Scan

A high-resolution, non-contrast CT scan will be performed at the times indicated in Appendix A to assess for lung fibrosis. The CT scan will be acquired with a single acquisition of reduced dose (ie, 6 mSv total). A chest radiograph may be substituted for the high-resolution, non-contrast CT scan at the Screening Visit only for study eligibility.

7.2.4 Inflammatory and Fibrotic Biomarker Analysis

Biomarker analyses will be performed at the times indicated in Appendix A. Biomarkers include, but are not limited to, assessments of MMP-12, MMP-7, MMP-9, TGF-β, connective tissue growth factor, CRP, cytokines (IFN-γ, TNF-α, IL-6, IL-1β, and C-C motif chemokine ligand 2 [monocyte chemoattractant protein-1]), ferritin levels, released N-terminal pro-peptide of type III collagen, internal epitope in the 7S domain of type IV collagen, C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin), neo-epitope of MMP-2, 9, and 13-mediated degradation of type I collagen, neo-epitope of MMP-2, 9, and 12-mediated degradation of type IV collagen, neo-epitope of MMP-2-mediated degradation of type VI collagen, neo-epitope of MMP-1 and 8-mediated degradation of CRP, and neo-epitope of plasmin-mediated degradation of cross-linked fibrin in blood.

Blood will be collected from patients that have consented (or whose LAR has consented) to the procedure. The blood samples will be collected per the laboratory manual instructions and analyzed. Samples may be stored at the central laboratory for future analyses.

7.2.5 National Institute of Allergy and Infectious Diseases 8-Point Ordinal Scale

The NIAID 8-point ordinal scale score will be assessed at the times indicated in Appendix A. The NIAID 8-point ordinal scale is described in detail in Appendix C.

7.3 Other Assessments

7.3.1 Severe Acute Respiratory Syndrome Coronavirus-2 Testing

SARS-CoV-2 testing may be performed at the Screening Visit. The patient must have a documented, laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcriptase polymerase chain reaction (or an equivalent test) immediately prior to or during the current hospitalization to be included in the study.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs will be monitored and recorded from the time of the first dose of study drug (Day 1 [Visit 2]) until the end of the study (Day 60). All events occurring prior to the first dose of study drug will be recorded as medical history. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at Day 1 (Visit 2), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present prior to the first dose of study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, electrocardiogram [ECG]) findings that are detected during the study or are present at the Day 1 (Visit 2) and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal

relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the current Investigator's Brochure.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of severity

The severity of all AEs should be graded according to the CTCAE Version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs [including alternative, novel treatments for COVID-19], therapies, complications, etc) is suspected; or
- Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration;

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases;

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug;

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug;

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses; and

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug.

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Expected Acute Respiratory Distress Syndrome Events

As events of progression of the patient's underlying COVID-19 diagnosis will be captured as efficacy endpoints (see Section 7.1), these events should not be reported as AEs or SAEs unless considered related to the study drug or a study procedure or if the outcome is fatal during the study and within the safety reporting period. Additionally, expected events for ARDS that are perceived by the Investigator to occur with reasonable frequency in the day-to-day care of patients with ARDS treated in an ICU setting with mechanical ventilation will not be reported as AEs. Examples of events that are expected in the course of ARDS include transient hypoxemia, agitation, delirium, etc. Such events, which are often the focus of prevention efforts as part of standard ICU care, will not be considered reportable AEs unless the event is considered by the Investigator to be associated with the study drug or study procedures, is unexpectedly severe or frequent, or is a change of severity for an individual patient with ARDS.

8.2 Serious Adverse Events

Any SAE that is ongoing at the end of the study (Day 60) will be followed by the Investigator until the SAE has subsided or until the condition(s) becomes chronic in nature, until the patient begins alternative treatment for COVID-19, until the condition(s) stabilizes (in the case of persistent impairment), or until the patient dies.

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline (ie, Day 1 [Visit 2]). However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

As events of progression of the patient's underlying COVID-19 diagnosis will be captured as efficacy endpoints (see Section 7.1), these events should not be reported as SAEs unless considered related to the study drug or a study procedure or if the outcome is fatal during the study and within the safety reporting period. Examples of events that are expected in the course of ARDS are provided above in Section 8.1.4. If the event has a fatal outcome during the timeframe, the event of "Progression of COVID-19" must be recorded as an SAE with a fatal outcome.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of the first dose of study drug until Day 60 (approximately 30 days following the last dose of study drug) must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study procedures must be reported to the Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (telephone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition(s) becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early Termination Visit procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/center the Exposure In Utero (EIU) form for completion. The Investigator/center must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy is known, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s);
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects;
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects;
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of study drug are not considered reportable as medication error; and
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.7 Safety Endpoints

The safety endpoints include the following:

- AEs and SAEs;
- Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis);
- Vital signs;
- Physical examinations; and
- 12-lead ECGs.

8.8 Clinical Laboratory Assessments

Samples for blood chemistry and hematology will be obtained as indicated in Appendix A. See Appendix B for a complete list of analytes. If any additional laboratory evaluations are performed for standard of care, these data should be entered into the eCRF. If a blood chemistry or hematology assessment was performed within 24 hours prior to the first dose of study drug, it is not necessary to repeat the assessment on Day 1. Effort should be made to obtain blood chemistry and hematology at approximately the same time on each day as indicated in Appendix A; however, it should not be considered a protocol deviation if this is not possible.

Samples for urinalysis will be obtained as indicated in Appendix A. See Appendix B for a complete list of analytes.

Screening and eligibility laboratory assessments may be performed at the local laboratory. All other laboratory assessments during the study will be assessed by a central laboratory.

8.9 Pregnancy Test

A serum hCG will be performed at the Screening Visit for all WCBP. If performed within 24 hours before the Screening Visit, a historical serum hCG test can be used. A urine pregnancy test will be performed at subsequent visits as indicated in Appendix A.

8.10 Vital Signs

Vital signs will be collected as indicated in Appendix A. Vital signs will include temperature, heart rate, respiratory rate, blood pressure, and SpO_2. For outpatients, pulse oximeters, thermometers, and blood pressure cuffs will be provided for home use.

8.11 Electrocardiograms

ECGs should be performed 2 hours (±30 minutes) after the first study drug administration on Day 1 and 2 hours (±30 minutes) after the morning dose on Day 4 and Day 7. ECGs may be performed at any time at subsequent visits. ECGs will be collected as indicated in Appendix A. Patients should be in a supine position for at least 10 minutes prior to ECG measurement.

8.12 Physical Examinations

A full physical examination will be performed at the Screening Visit, the EOT Visit, and Day 60. A full physical examination may include assessments of general condition, skin,

eyes/ears/nose/mouth/throat, neck/thyroid, chest/lungs, heart, vascular system, lymph nodes, abdomen, extremities, nervous systems/reflexes, musculoskeletal system, and spine.

A brief physical examination or a telemedicine-based physical examination (if the patient and site have video capabilities) will be performed at the other visits as indicated in Appendix A. For inpatients, a brief physical examination, targeted to patient symptoms, will be performed at the other visits. For outpatients, telemedicine-based physical examinations will be performed at the other visits (if the patient and site have video capabilities). Telemedicine-based physical examinations may include assessments of general condition (eg, overall appearance and patient orientation) and an assessment of the work of breathing (eg, speech cadence, lifting hands above head). If the patient or the site do not have video capabilities, the video portion of the telemedicine-based physical examination will be omitted, and the visit will be performed by phone. In this case and in lieu of the physical or video examination, clinicians will document whether the patient is having audible shortness of breath or difficulty speaking. If there are any concerns, then the patient will be instructed to call to his/her local physician or be seen at his/her local emergency department.

9 STATISTICS

9.1 Analysis Populations

The following analysis populations are defined for this study:

Intent-to-Treat (ITT) Population: The ITT Population is defined as all randomized patients. The ITT Population will be the primary population for analysis of efficacy data. Efficacy analyses will be based on the assigned treatment group.

Safety Population: The Safety Population is defined as all randomized patients who receive at least 1 dose of study drug. All safety data will be analyzed using the Safety Population. Safety analyses will be based on the treatment actually received.

Per-Protocol (PP) Population: The PP Population is defined as all patients in the ITT Population who complete the study with no major protocol deviations that may impact the primary efficacy assessment. The primary analysis will be repeated on the PP Population. Major protocol deviations will include violations of key entry criteria or deviations that could significantly impact the assessment or interpretation of efficacy data.

PK Population: The PK Population is defined as all patients with at least 1 PK measurement drawn during the study.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

Patients who discontinue the study drug will remain in the study to have safety and efficacy assessments performed. Patients should be encouraged to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. The data observed on-study will be used for analysis regardless of any intercurrent events. Patients who die or discontinue treatment prior to the assessment time point (Day 28 or Day 60) because of lack of efficacy, and cannot have clinical status determined at the time point, will be considered treatment failures. Details regarding data handling and imputation method will be provided in the Statistical Analysis Plan (SAP).

9.2.1.1 Primary efficacy analysis

The primary efficacy endpoint is the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 28. The treatment group difference of the response proportions, along with the corresponding 95% confidence interval and p-value, will be provided using the logistic regression model by Guo et al. (2012)[24] and Ge et al. (2011),[25] adjusted for stratification factor (use of invasive mechanical ventilation at the time of randomization [yes or no]). Additional prognostic baseline covariates (eg, age, region, body mass index) may be added as covariates/factors into the model to increase precision in the estimation of difference in proportions. Details will be provided in the SAP.

The primary analysis will be repeated on the PP Population.

9.2.1.2 Secondary efficacy analysis

The key secondary endpoints of the proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure

ventilation, invasive mechanical ventilation, or ECMO) at Day 60, the proportion of patients on invasive mechanical ventilation at Day 28 and at Day 60, and the proportion of patients alive at Day 28 and Day 60, will be analyzed using the same method as for the primary analysis.

Tipping point method will be used as a sensitivity analysis for evaluating the robustness of the results for the primary endpoint and key secondary endpoints.

Other secondary endpoints will be analyzed as described in the SAP. For all endpoints defined by events, the time points are defined as the number of days after randomization.

The Phase 2 study is not powered. No alpha controlling strategy will be implemented.

9.2.1.3 Multiplicity in Phase 3

To control the overall Type I error in the final analysis for Phase 3, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 1-sided 0.025 level first, followed by testing the secondary efficacy endpoints at the 1-sided 0.025 level in the following hierarchical manner: (1) proportion of patients on invasive mechanical ventilation at Day 28, (2) proportion of patients alive at Day 28, (3) proportion of patients alive and not requiring non-invasive or invasive ventilation (ie, not receiving high-flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, or ECMO) at Day 60, (4) proportion of patients on invasive mechanical ventilation at Day 60, and (5) proportion of patients alive at Day 60.

Inferential conclusions about these efficacy endpoints will require statistical significance of the previous endpoints and the primary efficacy endpoint.

This is not applicable to Phase 2 since Phase 2 is not powered.

9.2.1.4 Pharmacokinetic analysis

PK data will be summarized.

9.2.2 Analysis of Safety

Safety data will be summarized by actual treatment received, and in total for selected analyses/summaries, based on the Safety Population, and include the following:

- AEs and SAEs;
- Clinical laboratory assessments (including clinical chemistry, hematology, and urinalysis);
- Vital signs;
- Physical examinations; and
- 12-lead ECGs.

9.2.3 Analysis Timing

<u>Primary analysis (Phase 2)</u>

A primary analysis will be conducted once all patients in Phase 2 complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. The results will be conducted by an independent statistician and reviewed by the iDMC following the procedures defined in the iDMC Charter. The iDMC will convene to recommend dose selection

and whether to adjust study design for Phase 3 based on this analysis. The study team will remain blinded. Designated personnel from the Sponsor will have access to the analysis results. The Phase 3 sample size and interim analysis boundaries will be recalculated based on the Phase 2 primary analysis results.

Final analysis (Phase 2 and Phase 3)

For each phase (Phase 2 and Phase 3), after all the patients have completed (discontinued) the study and the database is locked, the data will be unblinded and the final analysis will be performed.

Interim analysis

No interim analysis is planned for Phase 2.

For Phase 3, an interim analysis will be performed once approximately 70% of the randomized patients complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. The iDMC will convene to evaluate for safety, early futility, and potential sample size recalculation.

For the futility interim analyses, the iDMC will be guided by a pre-specified non-binding futility monitoring boundary based on the gamma family spending function (with parameter $\Upsilon = -4$, calculated using EAST 6.4, see Table 1). Non-binding for the futility indicates that the futility boundary is constructed in such a way that it can be overruled by the iDMC without inflating the type I error and without decreasing power. The iDMC will also consider all available efficacy and safety data prior to formulating its recommendations regarding continuation or termination of the study due to early futility.

Although the study does not intend to stop early for outstanding efficacy in the interim analysis, a small alpha (0.0001) will be spent in order to protect data integrity and to preserve an overall 1-sided significant level of 0.025 for the primary analysis.

Table 1. Futility Boundaries in the Interim and Final Analyses of Overall Success Rate Based on a 1-Sided Test at the 0.025 Level

Planned Analysis	Total Completers [1]	Information Fraction	Futility Boundary		Boundary Crossing Probability (Incremental)		Cumulative Beta Spent
			Z Scale	Nominal P-Value	Under H_0	Under H_1	
Interim	213	0.7	0.789	0.2151	0.785	0.057	0.0572
Final	304	1	1.960	0.025	0.191	0.141	0.198

1. Patients who complete the Day 28 visit or discontinue early, but would have reached Day 28.

Futility testing (Phase 3)

The process is as follows:

- Futility at the interim analysis: If the 1-sided p-value is ≥0.2151 (or the observed z-statistic is ≤0.789), then the futility boundary is crossed and the null hypothesis will be accepted; and
- At the final analysis: The final hypothesis is tested at the 1-sided significance level of 0.025.

In case the number of patients at the interim analyses are not exactly equal to the planned number of patients (ie, the first 213 patients who completed the EOT Visit on Day 28 or have discontinued early but would have reached Day 28), the futility boundary will be revised based on the actual number of patients at the interim analysis.

Sample size recalculation (Phase 3)

At the interim analysis for early futility, when the first 213 patients complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28, the iDMC will also assess for potential sample size recalculation for the study using the promising-zone method. Wald conditional probabilities will be calculated using the actual observed proportions from both treatment arms. The maximum sample size allowed is 608 patients. Sample size will be increased only if the observed data at the interim analysis are promising; that is, if the conditional power is ≥36% and <80%, as described in the SAP.

Possible recommendations by the iDMC

After reviewing the results of the interim analysis, the iDMC may select 1 of 4 or more possible recommendations, based on the test statistics obtained at the interim analysis, as follows:

- Stop for early futility: Stop study early due to strong evidence for futility due to test statistic being in the futility region;
- Continue without change: Continue with no changes due to test statistic not being in the futility region or the conditional power being <36% or ≥80%;
- Add required additional sample size, n, without exceeding the maximum sample size and continue the study; or
- Stop for safety concerns.

9.2.4 Independent Data Monitoring Committee

An iDMC with multidisciplinary representation and pertinent expertise will be established to evaluate accumulating study data and to oversee the ongoing safety of the study for the patients enrolled. The iDMC will be external to the Sponsor. The iDMC will meet at 4 scheduled times, as described below, and more frequently if needed, to provide safety oversight for patients (see Section 4.3). Only the iDMC members and an independent statistician will have access to unblinded comparative results. The study team will remain blinded, except as noted above for the Phase 2 primary analysis.

The iDMC will convene during the Phase 2 study at 2 pre-planned time points, once after approximately 10 to 15 patients have been enrolled and a second time after approximately 50% to 60% of patients have been enrolled. For each pre-planned meeting, the decision to have an associated pause in enrollment will be made by the chairperson of the iDMC (with input from the Medical Monitor). The decision will be based on the type of safety data to be provided for review and taking into account whether continuing enrollment could place study patients at risk. Based on safety and efficacy evaluations using unblinded data, the iDMC may make recommendation(s) to the Sponsor to continue the study with or without modifications or, for safety reasons, terminate the study. The Sponsor will make the final decision to terminate the study. No formal statistical testing will be conducted.

In addition, a primary analysis will be conducted once all patients in the Phase 2 study complete the EOT Visit on Day 28. The analysis will be conducted by an independent statistician and reviewed by the iDMC. The Sponsor (key personnel only) will also be able to review the data at this time. The iDMC will convene to recommend dose selection and whether to adjust study design (eg, eligibility criteria, sample size number, protocol-defined procedures, and timing of procedures)

for Phase 3 based on this analysis. If the iDMC recommends modification of the protocol, and the Sponsor is in agreement, the protocol will be amended. Enrollment of any patients for Phase 3 will not begin until after completion of the assessment of the primary analysis.

During the Phase 3 study, an interim analysis will be performed once approximately 70% of the randomized patients (approximately 213 patients) complete the EOT Visit on Day 28 or have discontinued early but would have reached Day 28 had they remained in the study. Enrollment of new patients will be paused during the interim analysis. The iDMC will convene, evaluating for safety, early futility, and potential sample size recalculation. The interim analysis of the primary endpoint will be for early futility only. The study will not be stopped for overwhelming efficacy.

Based on ongoing safety monitoring of the study, additional ad hoc iDMC reviews may be conducted. For these ad hoc meetings, the decision to have an associated pause in enrollment will be made by the chairperson of the iDMC (with input from the Medical Monitor). Further details regarding the role, responsibilities, and procedures of the iDMC will be provided in the iDMC Charter.

In addition, manual reviews of safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor. Study personnel and the Medical Monitor will be blinded to the patient treatment assignments throughout the study; however, in the event of an emergency or AE for which it is necessary to know the study drug to determine an appropriate course of therapy for the patient, unblinding may occur (see Section 5.4).

9.2.5 Sample Size Determination

For the Phase 2 study, approximately 99 patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: FP-025 100 mg BID, FP-025 300 mg BID, or placebo BID. No formal statistical assessment for sample size determination has been performed. The sample size is considered adequate to provide the necessary data to evaluate the objectives of the study.

For Phase 3, a total of 304 patients (152 patients per treatment group) will provide approximately 80% power to detect a 15% improvement in response rate, based on a control response rate of 60% and assuming a response rate of 75% with the study drug treatment group, using a 1-sided 0.025 level test. The sample size estimate assumes that an interim analysis will be conducted after approximately 70% of patients (approximately 213 patients) have completed the EOT Visit on Day 28 or have discontinued early, but would have reached Day 28 had they remained in the study, to assess early futility and potential sample size recalculation. The sample size was calculated using EAST 6.4. The Phase 3 sample size will be formally recalculated based on results from the Phase 2 part of the study. A maximum of 608 patients may be included. If the iDMC, in consultation with the Sponsor determines that a sample size of more than 608 patients is needed, a protocol amendment will be required.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the center on eCRFs and reviewed by the CRA during monitoring visits or during remote monitoring. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All center personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary (latest) for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the center for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the center. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a study necessary for the evaluation and reconstruction of the study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible.

11.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at centers where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the center for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the

Investigator and center personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the center, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the center by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 2. Schedule of Procedures: Inpatient Admission Through Day 28

	Screening Visit	Treatment Period						Follow-Up Period		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOT**	**8**	**9**	
Study Day	**-1 to 1**	**1**	**4**	**7**	**14**	**21**	**28**	**45[a]**	**60**	**ET Visit[b]**
Visit Window (Days)	**–**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**Unscheduled**
Informed consent[c]	X									
I/E criteria	X	X[d]								
Demographic information	X									
Medical/surgical history	X	X[d]								
Assessment of standard of care[e]		X----------					----------X			
Prior/concomitant medications	X	X----------					----------X	X	X	X
Weight and height[f]	X	X					X		X	X
Physical examination[g]	X	X	X	X	X	X	X		X	X
Vital signs including SpO_2[h]	X	X	X	X	X	X	X		X	X
PaO_2/FiO_2 ratio[i]	X	X	X	X	X	X	X		X	X
hCG[j]	X						X		X	X
Viral respiratory panel[k]	X									
12-lead ECG[l]		X	X	X	X	X	X			X
SARS-CoV-2 PCR[m]	X									
Clinical laboratory assessments[n]	X	X	X	X	X	X	X		X	X
PK blood sampling[o]		X	X	X	X	X	X			
Randomization		X								

Footnotes at the end of table.

Table 2. Schedule of Procedures: Inpatient Admission Through Day 28 (Continued)

	Screening Visit	Treatment Period						Follow-Up Period		ET Visit[b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOT**	**8**	**9**	
Study Day	**-1 to 1**	**1**	**4**	**7**	**14**	**21**	**28**	**45[a]**	**60**	
Visit Window (Days)	**–**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**Unscheduled**
Study drug administration[p]		X	X	X	X	X	X			
High resolution, non-contrast CT scan of the chest[q]	X						X		X	X
PFTs[r]									X	X
Biomarker assessment (blood)[s]		X		X	X		X		X	X
NIAID 8-point ordinal scale assessment		X	X	X	X	X	X	X	X	X
AEs/SAEs[t]		X----------X								X

Note: If the study drug is discontinued but the patient is remaining in the study, the patient should be encouraged to remain in the study and to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. If the patient withdraws, he/she should complete the ET Visit.

a. The Day 45 visit will be a telephone visit only.
b. If a patient withdraws prematurely from the study, study staff should make every effort to complete the full panel of assessments scheduled for the ET visit. The reason for patient withdrawal must be documented in the eCRF.
c. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed.
d. I/E criteria and medical/surgical history will be reviewed again on Day 1 (Visit 2) prior to randomization. Any updates since the Screening Visit will be assessed.
e. The standard of care followed for each patient and center and whether any care decisions were based on resource limitations will be clearly documented for all patients.
f. Height will be collected at the Screening Visit only and will be used to calculate body mass index. Height and weight may also be obtained from the most recent medical record if the site is unable to obtain these values.
g. A full physical examination will be performed at the Screening Visit, the EOT Visit, and Day 60. A full physical examination may include assessments of general condition, skin, eyes/ears/nose/mouth/throat, neck/thyroid, chest/lungs, heart, vascular system, lymph nodes, abdomen, extremities, nervous systems/reflexes, musculoskeletal system, and spine. A brief physical examination, targeted to patient symptoms, will be performed at the other visits.
h. Vital signs include temperature, heart rate, respiratory rate, blood pressure, and SpO_2.
i. A PaO_2, obtained via arterial blood gas will be used to calculate the PaO_2/FiO_2 ratio, only in patients on invasive or non-invasive ventilation.
j. For WCBP only. Serum hCG will be performed at the Screening Visit. If performed within 24 hours before the Screening Visit, a historical serum hCG test can be used. Urine hCG will be performed at all other visits.
k. See Appendix B for a list of viruses that will be tested.
l. ECGs should be performed 2 hours (±30 minutes) after the first study drug administration on Day 1 and 2 hours (±30 minutes) after the morning dose on Day 4 and Day 7. ECGs may be performed at any time at subsequent visits. Patients should be in a supine position for at least 10 minutes prior to ECG measurement.
m. SARS-CoV-2 testing may be performed at the Screening Visit. The patient must have a documented, laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcriptase PCR (or an equivalent test) immediately prior to or during the current hospitalization to be included in the study.

n. Clinical laboratory assessments include clinical chemistry, hematology, and urinalysis. See Appendix B for a list of clinical laboratory analytes.
o. PK sampling times will be as follows: Day 1 (Visit 2) pre-dose and at 1 hour (±10 minutes), 3 hours (±10 minutes), and 8 hours (±10 minutes) post the first morning dose of study drug (if the patient is randomized in the afternoon on Day 1 [Visit 2], this will be performed after the morning dose of study drug on Day 2); Day 4, Day 7, Day 14, and Day 21 within 1 hour (±10 minutes) prior to the morning dose; and Day 28 within 1 hour (±10 minutes) prior to the morning dose and 1 hour (±10 minutes) post-morning dose.
p. The study drug (FP-025 100 mg, FP-025 300 mg, or placebo) will be administered orally as capsules or via a polyvinyl chloride nasogastric tube (by opening up the capsules and delivering as a suspension in orange juice) BID for 28 days. Capsules can also be opened and added to orange juice to drink.
q. A chest radiograph may be substituted for the high-resolution, non-contrast CT scan at the Screening Visit only for study eligibility. High-resolution, non-contrast CT scans should be performed at subsequent visits (Day 28 and Day 60) to assess for lung fibrosis.
r. PFTs will include measurement of FVC, FEV_1, FEV_1/FVC ratio, and diffusing capacity of the lungs for carbon monoxide.
s. Inflammatory and fibrotic biomarkers assessed may include, but are not limited to, MMP-12, MMP-7, MMP-9, TGF-β, connective tissue growth factor, PRO-C3, PRO-C4, PRO-C6, reC1M, C4M, C6M, CRPM, X-FIB (D-dimer), C-reactive protein, cytokines (IFN-γ, TNF-α, IL-6, IL-1β, and C-C motif chemokine ligand 2 [monocyte chemoattractant protein-1]), and ferritin levels in blood.
t. AEs will be monitored and recorded from the time of the first dose of study drug (Day 1 [Visit 2]) until the end of the study (Day 60). Any SAE that is ongoing at the end of the study (Day 60) will be followed by the Investigator until the SAE has subsided or until the condition(s) becomes chronic in nature, until the patient begins alternative treatment for COVID-19, until the condition(s) stabilizes (in the case of persistent impairment), or until the patient dies.

AE = adverse event; BAL = bronchoalveolar lavage; BID = twice daily; C4M = neo-epitope of MMP-2, 9-, and 12-mediated degradation of type IV collagen; C6M = neo-epitope of MMP-2-mediated degradation of type VI collagen; CoV = coronavirus; CRPM = neo-epitope of MMP-1 and 8-mediated degradation of C-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; EOT = End of Treatment; ET = Early Termination; FEV_1 = forced expiratory volume in 1 second; FiO_2 = fractional inspired oxygen; FVC = forced vital capacity; hCG = human chorionic gonadotropin; I/E = inclusion and exclusion; ICF = informed consent form; IFN = interferon; IL = interleukin; MMP = matrix metalloproteinase; NIAID = National Institute of Allergy and Infectious Diseases; PaO_2 = arterial oxygen partial pressure; PCR = polymerase chain reaction; PFT = pulmonary function test; PK = pharmacokinetic(s); PRO-C3 = released N-terminal pro-peptide of type III collagen; PRO-C4 = internal epitope in the 7S domain of type IV collagen; PRO-C6 = C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin); reC1M = neo-epitope of MMP-2, 9-, and 13-mediated degradation of type I collagen; SARS = severe acute respiratory syndrome; SpO_2 = peripheral capillary oxygen saturation; TGF = transforming growth factor; TNF = tumor necrosis factor; WCBP = woman/women of childbearing potential; X-FIB (D-dimer) = neo-epitope of plasmin-mediated degradation of cross-linked fibrin.

Table 3. Modified Schedule of Procedures for Discharged Patients

	Treatment Period					Follow-Up Period		
Visit	**Day of Discharge[a]**	**O1[b]**	**O2[b]**	**O3[b]**	**11/EOT**	**12**	**13**	
Study Day	**X[c]**	**X + 7[d]**	**X + 14[d]**	**X + 21[d]**	**28**	**45[e]**	**60**	**ET Visit[f]**
Visit Window (Days)	**±2**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**Unscheduled**
Assessment of standard of care treatment[g]	X----------X							
Prior/concomitant medications	X----------X					X	X	X
Weight	X				X		X	X
Physical examination[h]	X	X	X	X	X		X	X
Vital signs including SpO_2[i]	X	X	X	X	X		X	X
Urine hCG[j]					X		X	X
12-lead ECG[k]	X				X			X
Clinical laboratory assessments[l]	X				X		X	X
PK blood sampling[m]					X			
Study drug provided for rest of study period	X							
Study drug self-administration[n]		X	X	X	X			
High resolution, non-contrast CT scan of the chest					X		X	X
PFTs[o]							X	X
Biomarker assessment (blood)[p]	X				X		X	X
NIAID 8-point ordinal scale assessment	X				X	X	X	X
AEs/SAEs[q]	X	X----------X						X

Note: If the study drug is discontinued but the patient is remaining in the study, the patient should be encouraged to remain in the study and to follow-up for key study visits (Day 28 and Day 60) but will not be required to attend every study visit. If the patient withdraws, he/she should complete the ET Visit.

a. Discharge visit procedures do not need to be completed if they were done within 24 hours of the discharge date.
b. Outpatient visits during the treatment period will be telemedicine visits (if the patient and site have video capabilities). If the patient or the site do not have video capabilities, a telephone visit will be performed instead.
c. The listed assessments will occur on the day of discharge, regardless of what day this occurs on.
d. The first outpatient visit will be 1 week after discharge. Visits will continue weekly until Day 28. The number of outpatient visits will vary depending on the day of discharge.
e. The Day 45 visit will be a telephone visit only.

f. If a patient withdraws prematurely from the study, study staff should make every effort to complete the full panel of assessments scheduled for the ET visit. The reason for patient withdrawal must be documented in the eCRF.
g. The standard of care followed for each patient and center and whether any care decisions were based on resource limitations will be clearly documented for all patients.
h. A full physical examination will be performed at EOT and Day 60. A full physical examination may include assessments of general condition, skin, eyes/ears/nose/mouth/throat, neck/thyroid, chest/lungs, heart, vascular system, lymph nodes, abdomen, extremities, nervous systems/reflexes, musculoskeletal system, and spine. Telemedicine-based physical examinations will be performed at the other visits. Telemedicine-based physical examinations (if the patient and site have video capabilities) may include assessments of general condition (eg, overall appearance and patient orientation) and an assessment of the work of breathing (eg, speech cadence, lifting hands above head). If the patient or the site do not have video capabilities, the video portion of the telemedicine-based physical examination will be omitted, and the visit will be performed by phone. In this case and in lieu of the physical or video examination, clinicians will document whether the patient is having audible shortness of breath or difficulty speaking. If there are any concerns, then the patient will be instructed to call to his/her local physician or be seen at his/her local emergency department.
i. Vital signs include temperature, heart rate, respiratory rate, blood pressure, and SpO_2. Pulse oximeters, thermometers, and blood pressure cuffs will be provided for home use.
j. For WCBP only.
k. Patients should be in a supine position for at least 10 minutes prior to ECG measurement.
l. Clinical laboratory assessments include clinical chemistry, hematology, and urinalysis. See Appendix B for a list of clinical laboratory analytes.
m. PK analysis will occur on Day 28 within 1 hour (±10 minutes) prior to the morning dose and 1 hour (±10 minutes) post-morning dose.
n. The study drug (FP-025 100 mg, FP-025 300 mg, or placebo) will be administered orally as capsules BID for 28 days.
o. PFTs will include measurement of FVC, FEV_1, FEV_1/FVC ratios, and diffusing capacity of the lungs for carbon monoxide.
p. Inflammatory and fibrotic biomarkers assessed may include, but are not limited to, MMP-12, MMP-7, MMP-9, TGF-β, connective tissue growth factor, PRO-C3, PRO-C4, PRO-C6, reC1M, C4M, C6M, CRPM, X-FIB (D-dimer), C-reactive protein, cytokines (IFN-γ, TNF-α, IL-6, IL-1β, and C-C motif chemokine ligand 2 [monocyte chemoattractant protein-1]), and ferritin levels in blood.
q. AEs will be monitored and recorded from the time of the first dose of study drug (Day 1 [Visit 2]) until the end of the study (Day 60). Any SAE that is ongoing at the end of the study (Day 60) will be followed by the Investigator until the SAE has subsided or until the condition(s) becomes chronic in nature, until the patient begins alternative treatment for COVID-19, until the condition(s) stabilizes (in the case of persistent impairment), or until the patient dies.

AE = adverse event; BID = twice daily; C4M = neo-epitope of MMP-2, 9-, and 12-mediated degradation of type IV collagen; C6M = neo-epitope of MMP-2-mediated degradation of type VI collagen; CRPM = neo-epitope of MMP-1 and 8-mediated degradation of C-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; EOT = End of Treatment; ET = Early Termination; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; hCG = human chorionic gonadotropin; ICF = informed consent form; IFN = interferon; IL = interleukin; MMP = matrix metalloproteinase; NIAID = National Institute of Allergy and Infectious Diseases; O = outpatient visit; PFT = pulmonary function test; PK = pharmacokinetic(s); PRO-C3 = released N-terminal pro-peptide of type III collagen; PRO-C4 = internal epitope in the 7S domain of type IV collagen; PRO-C6 = C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin); reC1M = neo-epitope of MMP-2, 9-, and 13-mediated degradation of type I collagen; SpO_2 = peripheral capillary oxygen saturation; TGF = transforming growth factor; TNF = tumor necrosis factor; WCBP = woman/women of childbearing potential; X-FIB (D-dimer) = neo-epitope of plasmin-mediated degradation of cross-linked fibrin.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Screening and eligibility laboratory assessments may be performed at the local laboratory. All other laboratory assessments during the study will be assessed by a central laboratory.

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Endocrinology

Human chorionic gonadotropin (hCG) [1]

1. hCG will be performed in women of childbearing potential only.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review will only be performed only if white blood cell count and/or differential values are out of reference range.

Severe Acute Respiratory Syndrome Coronavirus-2 Testing

Reverse transcriptase polymerase chain reaction (PCR) for severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 or equivalent test [1]

1. SARS-CoV-2 reverse transcriptase PCR may be performed at the Screening Visit, if not done previously. The patient must have a documented, laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcriptase PCR (or an equivalent test) immediately prior to or during the current hospitalization.

Viral Respiratory Panel [1]

Influenza A [2]	Influenza B

Respiratory syncytial virus

1. Additional viruses may be tested for at the Investigator's discretion and based on local laboratory panels. Actual viruses tested for may vary depending on local standards of care.
2. Influenza A may include H1 and H3 subtypes.

Urinalysis

Bilirubin	Blood
Creatinine	Glucose
Ketones	Leukocyte esterase
Microscopy [1]	Nitrite
pH	Protein
Specific gravity	Urine albumin to creatinine ratio
Urobilinogen	

1. Microscopy will only be performed as needed based on positive dipstick test results.

Inflammatory and Fibrotic Biomarkers [1]

C-reactive protein	C4M
C6M	Connective tissue growth factor
CRPM	Cytokines [2]
Ferritin	MMP-7
MMP-9	MMP-12
PRO-C3	PRO-C4
PRO-C6	reC1M
Transforming growth factor-β	X-FIB (D-dimer)

1. Additional biomarkers not listed here may be evaluated at a future date.
2. Cytokines evaluated will include interferon-γ, tumor necrosis factor-α, IL-6, IL-1β, and C-C motif chemokine ligand 2 (monocyte chemoattractant protein-1).

C4M = neo-epitope of MMP-2, 9, and 12-mediated degradation of type IV collagen; C6M = neo-epitope of MMP-2-mediated degradation of type VI collagen; CRPM = neo-epitope of MMP-1 and 8-mediated degradation of C-reactive protein; IL = interleukin; MMP = matrix metalloproteinase; PRO-C3 = released N-terminal pro-peptide of type III collagen; PRO-C4 = internal epitope in the 7S domain of type IV collagen; PRO-C6 = C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin); reC1M = neo-epitope of MMP-2, 9, and 13-mediated degradation of type I collagen; X-FIB (D-dimer) = neo-epitope of plasmin-mediated degradation of cross-linked fibrin.

APPENDIX C: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES 8-POINT ORDINAL SCALE FOR COVID-19 AND HOSPITALIZATION OUTCOMES

Table 4. NIAID 8-Point Ordinal Scale for COVID-19 and Hospitalization Outcomes

Numerical Score	Definition
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19–related or otherwise)
6	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitation on activities

COVID-19 = coronavirus disease 2019; NIAID = National Institute of Allergy and Infectious Diseases.
Source: Adaptive COVID-19 treatment trial (ACTT). NIH clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04280705. Accessed 09 November 2020

APPENDIX D: SUGGESTED CRITERIA FOR MECHANICAL VENTILATION WEANING AND EXTUBATION

Table 5. Suggested Criteria for Mechanical Ventilation Weaning and Extubation

Suggested criteria for weaning
FiO_2 ≤40% and PEEP ≤8 cm of H_2O or FiO_2 <50% and PEEP ≤5 cm of H_2O
Acceptable spontaneous breathing efforts [1]
Not receiving any neuromuscular blocking agents or blockade
Suggested criteria for extubation [2]
SpO_2 ≥90% and/or PaO_2 ≥60 mmHg
Spontaneous tidal volume ≥4 mL/kg predicted body weight
Respiratory rate ≤35 breaths per minute
pH ≥7.3
No respiratory distress [3]

1. Acceptable spontaneous breathing efforts may be detected by decreasing the ventilation rate by 50% for 5 minutes.
2. If the patient meets criteria for conducting a spontaneous breathing trial and has been in the study for at least 12 hours, a trial of up to 2 hours (120 minutes) of spontaneous breathing with FiO_2 <50% and PEEP ≤5 cm H_2O should be conducted. The patient should be placed on a T-piece, tracheostomy collar, or CPAP (≤5 cm H_2O with pressure support ≤8 cm H_2O). If the patient does not tolerate weaning, pre-weaning ventilator settings should be resumed. If tolerated for at least 30 minutes, extubation may be considered.
3. Respiratory distress is defined by at least 2 of the following:
   - Heart rate >120% of baseline;
   - Marked accessory muscle use;
   - Abdominal paradox;
   - Diaphoresis; or
   - Marked dyspnea.

CPAP = continuous positive airway pressure; FiO_2 = fractional inspired oxygen; PaO_2 = arterial oxygen partial pressure; PEEP = positive end-expiratory pressure; SpO_2 = peripheral capillary oxygen saturation.

Sources:

- National Institutes of Health. NIH NHLBI ARDS clinical network mechanical ventilation protocol summary. http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf. Accessed 29 June 2020
- Schmidt GA, Girard TD, Kress JP, et al. Official executive summary of an American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. *Am J Respir Crit Care Med*. 2017;195(1):115-119

APPENDIX E: STRONG CLINICAL INHIBITORS AND INDUCERS FOR CYTOCHROME P450-MEDIATED METABOLISMS

Table 6. Strong Inhibitors and Inducers of Cytochrome P450

	Strong Inhibitors	Strong Inducers
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine [1]	NA
CYP2B6	NA	Carbamazepine [2]
CYP2C8	Gemfibrozil [3]	NA
CYP2C19	Fluconazole [4], fluoxetine [5], fluvoxamine [1], ticlopidine	Rifampin [6]
CYP2D6	Bupropion, fluoxetine [5], paroxetine, quinidine [7], terbinafine	NA
CYP3A	Boceprevir, cobicistat [7], danoprevir and ritonavir [8], elvitegravir and ritonavir [8], grapefruit juice [9], indinavir and ritonavir [8], itraconazole [7], ketoconazole, lopinavir and ritonavir [7,8], paritaprevir and ritonavir (and ombitasvir and/or dasabuvir) [8], posaconazole, ritonavir [7,8], saquinavir and ritonavir [7,8], telaprevir [7], tipranavir and ritonavir [7,8], telithromycin, troleandomycin, voriconazole Clarithromycin [7], idelalisib, nefazodone, nelfinavir [7]	Apalutamide, carbamazepine [2] enzalutamide [10], mitotane, phenytoin [11], rifampin [6], St. John's wort [12]

Note: Strong inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold. Strong inhibitors of CYP3A causing ≥10-fold increase in AUC of sensitive index substrate(s) are shown in the second row to the right of "CYP3A."

Note: Strong inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.

This table is prepared to provide examples of clinical inhibitors and inducers and is not intended to be an exhaustive list.

1. Strong inhibitor of CYP1A2 and CYP2C19. Moderate inhibitor of CYP3A and weak inhibitor of CYP2D6.
2. Strong inducer of CYP2B6 and CYP3A and weak inducer of CYP2C9.
3. Strong inhibitor of CYP2C8 and inhibitor of OATP1B1 and OAT3.
4. Strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.
5. Strong inhibitors of CYP2C19 and CYP2D6.
6. Strong inducer of CYP3A and moderate inducer of CYP1A2 and CYP2C19.
7. Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
8. Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
9. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
10. Strong inducer of CYP3A and moderate inducer of CYP2C9, and CYP2C19.
11. Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, and CYP2C9.
12. The effect of St. John's wort varies widely and is preparation-dependent.

AUC = area under the concentration-time curve; CYP = cytochrome P450; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not applicable; OAT3 = organic anion transporter 3; OATP1B1 = organic anion transporting polypeptide 1B1; P-gp = P-glycoprotein.

Source: United States Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1. Accessed 23 March 2021.