TITLE PAGE

Protocol Title: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

Master Protocol Number: COV-01

Product: Multiple candidate agents

Short Title: COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY)

Study Phase: 3

Sponsor Name: Amgen, Inc.

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Regulatory Agency Identifying Number(s): **IND 150485**
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Date of Protocol: 16 April 2021

Version: Protocol Amendment 4

Responsible Medical Expert:

PPD **Amgen, Inc.**

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

PPD

April 16, 2021

PPD **Amgen, Inc.**

Date

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

PROTOCOL AMENDMENT SUMMARY

Protocol Amendment 4

Protocol Amendment 4 (dated 16 April 2021) replaces Protocol Amendment 3 (dated 22 October 2020). The amendment incorporates the following main changes:

- Provides updated statistics regarding coronavirus disease 2019 (COVID-19) cases and deaths as well as racial and ethnic disparities related to the disease.
- Adds clarification that in regions where more than one sub-protocol has received local regulatory and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, it is required that participating sites are activated for enrollment for all approved sub-protocols.
- Adds the inclusion criterion "randomized within 5 days of hospitalization."
- Modifies exclusion criterion from "patient has any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the patient (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments (eg, patients unable to swallow study medication tablets)" to "patient with past medical/surgical history and/or any current condition for which, in the opinion of the Investigator, participation would be a safety risk or could affect the integrity of data."
- Adds the exclusion criterion "where, in the opinion of the Investigator, progression to death is imminent and inevitable within the next 48 hours, irrespective of the provision of treatments."
- Modifies description of emergency unblinding procedures to indicate that "if the Investigator decides that unblinding is warranted, the Investigator ***may, at his/her discretion, contact the Sponsor to discuss the situation*** prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient."
- Regarding concomitant therapy, adds collection of data regarding receipt of any COVID-19 vaccine regardless of when the vaccine was received.
- Updates clarifications regarding the 8-point ordinal scale scores.

Protocol Amendment 3

Protocol Amendment 3 (dated 22 October 2020) replaced Protocol Amendment 2 (dated 05 October 2020). The amendment incorporated the following main changes:

- Expanded background information to include data regarding the epidemiology of COVID-19 as well as racial and ethnic disparities related to the disease.
- In the Schedule of Activities:
  - Clarified procedures for obtaining/recording patient height and weight.
  - Removed the optional clinical safety laboratory assessments (hematology, clinical chemistry, and liver function tests) on Days 5, 11, and 18.

- Removed language regarding operational adjustment of the number of enrolled patients.
- Removed language regarding adjustment of alpha spending as part of the interim analyses.
- Updated methods for primary efficacy endpoint analyses.
- Removed language regarding analysis methods for continuous other endpoints.
- In Appendix 7:
  - Provided p-values for the boundary of futility, non-binding.
  - Removed the summary of futility probabilities and boundaries for the primary analysis.
  - Removed language regarding enrollment rate assumption and negative treatment effect scenario.

Protocol Amendment 2

Protocol Amendment 2 (dated 05 October 2020) replaced Protocol Amendment 1 (dated 24 August 2020). The amendment incorporated the following main changes:

- Clarified that this Master Protocol will continue enrolling patients as long as there is at least ***one active sub-protocol***.
- Clarified that other secondary endpoint (distribution of 8-point ordinal scale at Days 8, 15, and 29, as well as the worst postbaseline score on 8-point ordinal scale from ***baseline*** to Day 29) and CCI [redacted]
- Clarified that interim analyses will evaluate futility and safety, but not efficacy, of candidate agents; the two-sided alpha level was updated to reflect this change. Also, provided updated summary of futility probabilities and boundaries in Appendix 7.
- Clarified how patients who are discharged from the hospital to hospice care will be handled in the analyses.
- In the Schedule of Activities:
  - Clarified that medical history includes the date of diagnosis of acute respiratory distress syndrome, if present.
  - Clarified that for patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation ***only***, provide FiO_2 requirement.
  - Clarified that on Day 1, the National Early Warning Score 2 is to be assessed prior to study drug administration.
  - Added that clinical safety laboratory assessments are to be completed 'all other days while in hospital' and these data are to be collected on the electronic case report form.

- Clarified that patients will be stratified ***at randomization*** by baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no).
- Added the following exclusion criteria:
  - Active tuberculosis or a history of incompletely treated tuberculosis.
  - Active, uncontrolled systemic bacterial or fungal infection(s).
- Clarified the definition of 'sustained' clinical recovery as clinical recovery without readmission to a hospital by Day 60.
- Removed the definition of clinically significant abnormal laboratory findings. Also, clarified which abnormal laboratory test results meet the adverse event definition.
- Clarified serious adverse event reporting procedures and removed language regarding reporting of events not reported per the standard process for expedited reporting of serious adverse events.
- Clarified that contact information for the candidate agent owner will be listed in the corresponding sub-protocol.
- Clarified how missing data for the primary endpoint will be handled.

Protocol Amendment 1

Protocol Amendment 1 (dated 24 August 2020) replaced the final Version 4 protocol (dated 20 July 2020). The amendment incorporated the following main changes:

- The study design was modified to be a double-blind, placebo-controlled platform study:
  - Study design section was updated.
  - Randomization and blinding details were added.
  - Where appropriate, references to 'candidate agent' were amended to 'study treatment' (ie, candidate agent or placebo).
  - Sample size details were modified.
  - Safety data collection procedures were modified to collect all adverse events.
  - Summary of early success and futility probabilities and boundaries tables was modified in Appendix 7.
- Key secondary endpoint (and corresponding objective) was added: incidence of patients achieving ≥2-point improvement from baseline or fit-for-discharge on the ordinal scale at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale.
- Clarified that key secondary endpoint is ***incidence of*** oxygen-free recovery.
- The endpoint to evaluate distribution of 8-point ordinal scale at Days 8, 15, and 29, as well as the worst postbaseline score on 8-point ordinal scale from randomization to Day 29 was moved from key secondary endpoints to other secondary endpoints.
- CCI [redacted]

- Specified the categories of adverse events to be analyzed as secondary endpoints.
- CCI [redacted]
- Some endpoints included Day 22 as a time point; as some patients will have been discharged by this point, this time point was removed from those endpoints.
- Specified that the Sequential Organ Failure Assessment score will no longer be assessed.
- Clarified that arterial blood gases will no longer be assessed.
- Clarified that severe acute respiratory syndrome coronavirus 2 antigen testing can be the diagnostic test performed at screening; this included a modification to inclusion criterion #1.
- Exclusion criterion #6 was modified to clarify patients participating in another clinical study of an investigational medicinal product or other ***unapproved (or investigational)*** treatment for COVID-19 would be excluded.
- A concomitant medication review at Day 60 was added. Clarified that concomitant medication review would also occur at screening (Day -1 or Day 1) so that medication(s) the patient is receiving at the time of, ***or during the two weeks prior to***, enrollment (including screening) would be captured.
- Clarified that the sub-protocols could define additional endpoints.
- Clarified that patients randomized to study treatments in a specific sub-protocol would follow the Schedule of Activities in that sub-protocol.
- Expanded details of clinical safety laboratory testing added, and time points refined.

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

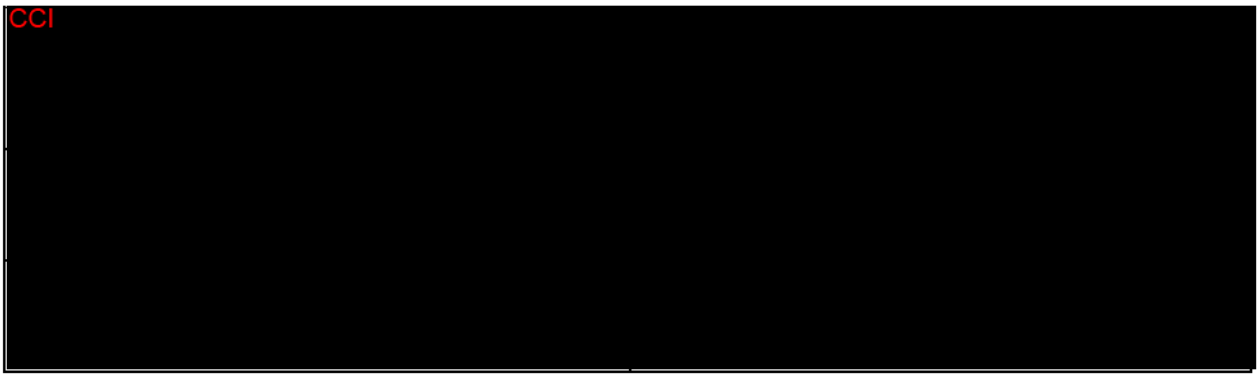
Rationale:

There is a high unmet medical need for therapeutic agents available to treat coronavirus disease 2019 (COVID-19), an inflammatory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and there is an urgent public health need for rapid development of such interventions. This adaptive, randomized, placebo-controlled platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19 in hospitalized patients. Candidate agents will be evaluated frequently (through ongoing monitoring) for futility and safety, with candidate agents being added to and/or removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study are required to be hospitalized with confirmed active SARS-CoV-2 infection and may require either ongoing medical care, supplemental oxygen, noninvasive ventilation or high-flow oxygen devices, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate time to confirmed clinical recovery	• Time to confirmed clinical recovery through Day 29, ie, fit-for-discharge, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, without being rehospitalized through Day 29: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on noninvasive 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 limitations on activities
Key Secondary	
• To evaluate oxygen-free recovery	• Incidence of oxygen-free recovery at Day 29, defined as patients who are alive, discharged, and not receiving supplemental oxygen.

• To evaluate improvement or being fit-for-discharge	• Incidence of ≥2-point improvement from baseline or fit-for-discharge on the ordinal scale at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale.
• To evaluate all-cause mortality	• Incidence of all-cause mortality through Day 29.
Other Secondary	
• To evaluate the distribution across categories on the 8-point ordinal scale, and the worst outcome	• Distribution of 8-point ordinal scale at Days 8, 15, and 29, as well as the worst postbaseline score on 8-point ordinal scale from baseline to Day 29.
• To evaluate intensive care unit (ICU) days	• Number of ICU days from Day 1 through Day 29.
• To evaluate invasive mechanical ventilator days	• Number of invasive mechanical ventilator days from Day 1 through Day 29.
• To evaluate clinical recovery	• Incidence of clinical recovery, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status by Days 8, 15, and 29.
• To evaluate sustained clinical recovery	• Incidence of sustained clinical recovery as confirmed by Day 60 follow-up.
• To evaluate the safety of candidate agents as add-on therapy to standard of care (SoC) in patients with COVID-19	• Incidence of adverse events (AEs) in the following categories: – All treatment-emergent AEs – Serious AEs – AEs with Common Terminology Criteria for Adverse Events Grade 3 or higher – AEs leading to dose modifications – AEs leading to study treatment discontinuation
Exploratory	
CCI [redacted]	[redacted]



Overall Design:

COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY) is an adaptive, randomized, placebo-controlled platform study, designed to rapidly evaluate candidate agents for the treatment of COVID-19. The study will include hospitalized adult patients (≥18 years of age) who have infection with SARS-CoV-2, the virus that causes COVID-19, as confirmed by laboratory tests and/or point-of-care tests. For inclusion, patients will need to be hospitalized with a clinical status of Grade 2 (hospitalized, on invasive mechanical ventilation or ECMO) to Grade 5 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]), as defined by an 8-point ordinal scale of clinical severity (see above).

This study aims to identify efficacious candidate agents for treatment of COVID-19. The candidate agents may include, but will not be limited to, antivirals, vascular agents, or immunomodulatory agents. Each sub-protocol will specify a single candidate agent or a combination of candidate agents to be administered.

This Master Protocol outlines the overall design of the study, including the population, inclusion and exclusion criteria, randomization scheme, primary, secondary, and exploratory outcomes, study design, statistical methodology, and planned analyses that are common for all candidate agents to be evaluated. The Master Protocol is structured such that multiple candidate agents from different pharmaceutical companies can be evaluated simultaneously. The plan is to add candidate agents as they are identified, and/or to remove therapies based on results of interim analyses (eg, due to futility or if they are considered unsafe). The shared placebo control group for a candidate agent will include only patients randomized during the same period in which the candidate agent group is randomized, which will be defined in the Statistical Analysis Plan. Patients will be randomized equally to either the candidate agent plus SoC or placebo plus SoC in a double-blind fashion. Patients who are randomized to placebo plus SoC will subsequently be randomized equally to a matching placebo corresponding to an available agent whose sub-protocol the patient qualified for (ie, a 2-stage randomization). Each patient in the placebo plus SoC group will only receive one type of placebo. Therefore, patients may be aware of which sub-protocol they were randomized to but not to whether they will receive active agent or placebo investigational product. The comparator group for a candidate agent will include patients randomized to any matching placebo for a candidate agent available at the time of randomization for that agent.

Sub-protocols will outline the scientific rationale, additional eligibility criteria (if necessary), treatment dose and regimen, statistical analysis populations, and other specifics unique to each candidate agent. The sub-protocols may define adverse events of special interest and can include pharmacokinetic (PK) and/or pharmacodynamic assessments that are appropriate for the specific candidate agent. The endpoints specified in this Master Protocol will not be altered in the sub-protocols, but the sub-protocol may define additional endpoints. In order to enroll, a patient must meet all entry criteria for both the Master Protocol and at least one active sub-protocol.

The study will evaluate each candidate agent separately as an add-on to the SoC to assess safety and efficacy. Interim analyses may be performed for each candidate agent during the course of the study to evaluate futility for candidate agents.

Randomization will be stratified by baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no).

Enrollment of patients will be continuous throughout the study for each candidate agent until the total number of planned patients for that agent is enrolled, until futility criteria is met at an interim analysis, or if the agent is considered unsafe. The Master Protocol will continue enrolling patients as long as there is at least one active sub-protocol.

In addition, centers may elect to participate in separate Investigator-initiated studies collecting additional data on patients (eg, PK analyses), as their resources permit.

Number of Patients:

The expected number of patients is presented as part of the sample size determination below.

Treatment Groups and Duration:

Patients will be screened on Day -1 (the day before the first dose of study treatment [candidate agent or placebo/SoC] is scheduled) or Day 1 and will remain in the hospital from Day 1 until discharge. All patients will receive SoC treatment, either with a blinded candidate agent or its matching blinded placebo. The SoC will be based on appropriate local written guidelines in place at a site at the time of treatment in the study; the SoC may change during the course of the study as new information becomes available about treating COVID-19. Dosing with the study treatment (as an add-on to SoC) will commence on Day 1. Patients will be assessed daily while hospitalized. If they are discharged from the hospital prior to Day 15, they will have study visits at Days 15 and 29 as an outpatient by telemedicine. The last day of primary assessments will be Day 29. An end-of-study visit will be conducted on Day 60 (±4 days) via telemedicine (unless the patient is still hospitalized in which case it would be conducted in person).

Statistical methods:

Sample size determination:

Assuming a median time to clinical recovery of 11 days for patients randomized to an active treatment group plus SoC compared with 15 days for those randomized to placebo plus SoC, 350 patients are needed per arm in order to observe 490 clinical recovery events between the 2 treatment groups being compared at the primary analysis. This sample size will provide approximately 88% power to detect a hazard ratio (HR) of 1.364 for the occurrence of a clinical recovery event, when comparing each candidate agent plus SoC with placebo plus SoC, at a 1-sided significance level of 0.025.

This sample size will provide the following information about the key secondary endpoints: assuming the oxygen-free recovery rate at Day 29 is 65% for the placebo group, a sample size of 350 patients per arm will provide approximately 80% power to detect at least a 9.7% absolute increase in the proportion of patients who achieve oxygen-free recovery at Day 29. Assuming 70% of patients randomized to placebo plus SoC achieve at least 2-point improvement from baseline or fit-for-discharge on the 8-pt ordinal scale, 350 patients per arm will provide approximately 80% power to detect a 9.2% absolute increase in this proportion with a candidate agent plus SoC at Day 29. Assuming the all-cause mortality rate through Day 29 is 15% for the placebo plus SoC group, a sample size of 350 patients per arm will provide 80% power to detect an absolute reduction of 6.75% (8.25% rate for any candidate agent plus SoC) in the mortality rate by Day 29. Assuming a mortality rate of 15% for the placebo plus SoC group and 19% for a candidate agent plus SoC (ie, an adverse treatment effect of 4%), with a sample size of 350 per arm, the chance to observe a decrease in the mortality rate of at least 1% with a candidate agent plus SoC compared to placebo plus SoC is approximately 4%.

For a sub-protocol where the primary analysis population is a subset of the randomized population, the sample size may be adjusted in a sub-protocol as applicable to power the designated primary analysis population.

Analysis sets:

- Full Analysis Set: All patients who are randomized.
- Safety Set: All patients who are randomized and take at least one dose of study treatment or placebo.

Analysis methods:

Patients who achieve a 7 on the 8-pt ordinal scale but are discharged to hospice care will not be considered as having met clinical recovery or oxygen-free recovery.

Primary Efficacy Endpoint Analyses

The time to confirmed clinical recovery through Day 29, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, ie, fit-for-discharge, without being rehospitalized through Day 29, will be compared between the selected candidate agent plus SoC and contemporaneous placebo plus SoC, using a stratified log-rank test, stratifying for baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no), with patients who have died prior to or on Day 29 censored at Day 29. The p-value associated with the stratified log-rank test statistic at the time of the primary analysis will be compared at the 2-sided 0.05 alpha level. The p-value will also be compared with the specified boundaries at the interim analyses for futility in order to serve as guidance for the Independent Data Monitoring Committee (IDMC) to make recommendations based on the totality of available information at the time of the interim analyses. The HR for the treatment arm plus SoC versus placebo plus SoC will be estimated using a Cox regression, adjusting for randomization stratification factors, with deaths censored at Day 29.

Key Secondary Endpoint Analyses

The key secondary endpoint of incidence of oxygen-free recovery at Day 29, defined as patients who are alive, discharged, and not receiving supplemental oxygen at Day 29, will be analyzed using a logistic regression with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

The key secondary endpoint of incidence of patients achieving ≥2 point improvement from baseline or being fit-for-discharge on the ordinal scale at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale at Day 29, will be analyzed using logistic regression with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

The key secondary endpoint of the incidence of all-cause mortality through Day 29 will be analyzed using a logistic regression with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

If a candidate agent plus SoC achieves statistical significance on the primary endpoint compared to placebo plus SoC, the three key secondary endpoints will be tested in a hierarchical testing sequence in the following order: oxygen-free recovery at Day 29, at least a 2 point improvement from baseline on the 8-point ordinal scale or being fit for discharge at Day 29, and all-cause mortality through Day 29.

Other Endpoint Analyses

For the other secondary endpoints, a binary endpoint will be analyzed by logistic regression including baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) as covariates. For ordinal other secondary endpoints, the number and percentage of patients in each category will be provided for each treatment arm and will be analyzed using a proportional odds model, including the baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity (yes or no) and remdesivir use at baseline (yes or no) as stratification variables.

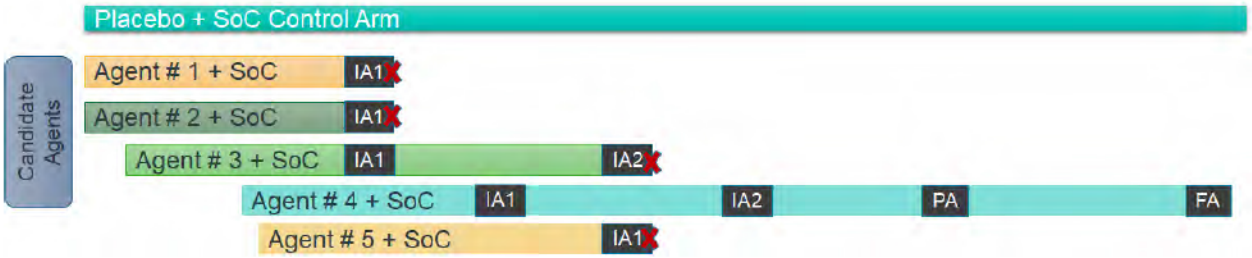
CCI [redacted]

Data Monitoring Committee:

An IDMC will monitor ongoing data to ensure patient well-being and safety as well as study integrity. The IDMC will be asked to make recommendations to the Joint Steering Committee regarding early termination or modification of the evaluation of a candidate agent. More details will be provided in the IDMC charter.

1.2 Schema

Figure 1 Study Schema (with Hypothetical Example)



FA=final analysis; IA=interim analysis; PA=primary analysis; SoC=standard of care. '×' indicates that futility boundary has been met.

IA1 and IA2 will be planned at information fractions of approximately 25% and 55% of expected number of recoveries, ie, after approximately 123 and 270 patients have met the primary endpoint of clinical recovery on a particular candidate agent plus SoC and placebo plus SoC, respectively.

PA will occur after approximately 350 patients have been randomized to an active agent plus SoC and have had the opportunity to complete the Day 29 visit.

FA will occur after all patients randomized to that agent plus SoC and the concurrent placebo plus SoC controls have had the opportunity to complete the Day 60 visit.

Note: In the above example, Agents #1, #2, and #5 met the futility boundary at IA1 while Agent #3 met the futility boundary at IA2, and so those agents could be discontinued in the study due to futility.

Note: Patients who are randomized to placebo plus SoC will be subsequently randomized equally to a matching placebo corresponding to an available agent whose sub-protocol the patient qualified for (ie, a 2-stage randomization).

1.3 Example Schedule of Activities

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
ELIGIBILITY						
Informed consent	X					
Demographics	X					
Relevant medical history[b]	X					
Review of SARS-CoV-2 diagnostic tests (obtained during the previous 72 hours, if available)	X					
SARS-CoV-2 diagnostic test[c]	X					
Inclusion and exclusion criteria	X	X				
12-lead electrocardiogram	X					
STUDY INTERVENTION						
Randomization		X				
Administration of study treatment		Defined in sub-protocol				
Treatment with SoC		SoC will be based on the practices of the study center				
STUDY PROCEDURES						
Physical examination (including height and weight)[d]	X					
Vital signs, including body temperature, pulse rate, blood pressure, respiratory rate, SpO_2, FiO_2[e]		X[f]	X	X[g]	X[g]	
CCI						
Ordinal scale		X[f]	X	X	X	X

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
Clinical assessments[h]		X[f]	X	X	X	X[i]
Assessment of floor status (ICU yes/no)		X	X[g]	X[g]	X[g]	
Assessment of rehospitalization for discharged patients[j]				X	X	X
Concomitant medication review (including use of vasopressors)	X	X[f]	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X
SAFETY LABORATORY						
Clinical safety laboratory assessments	X[k,l]	X[f,m,n]	Days 3[o], 8[m], 22[m], and at discharge[m,p] All other days while in hospital[q]	X[m,r]	X[m]	
Pregnancy test for females of childbearing potential	X[k]					
RESEARCH LABORATORY						
CCI [redacted]						

Abbreviations: ARDS=acute respiratory distress syndrome; eCRF=electronic case report form; FiO_2=fraction of inspired oxygen; ICF=informed consent form; ICU=intensive care unit; CCI [redacted]; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; SoC=standard of care; SpO_2=oxygen saturation.

Note: Additional assessments, if required, will be defined in the sub-protocol.

[a] These visits will be performed even if a patient has already been discharged. If discharged prior to scheduled visit, these visits will be conducted via telemedicine. For visits conducted by telephone, it may not be possible to perform some scheduled assessments (eg, vital signs). The Day 29 assessments will also be performed, where possible, for patients who discontinue the study prematurely.

[b] Medical history includes estimated date and time of first COVID-19 related symptoms and co-morbidities (eg, respiratory [including date of diagnosis of ARDS, if present], cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, renal).

[c] Oropharyngeal/nasal swab for polymerase chain reaction determination of SARS-CoV-2 or for SARS-CoV-2 antigen testing. Only to be performed if no diagnostic test results are available that have been obtained during the previous 72 hours.

[d] If height and/or weight cannot be obtained at the Screening Visit (Day -1 or Day 1), these parameters can be recorded as a combination of patient-reported data and data obtained from recent medical records (ie, at hospital admission).

[e] For patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation only, provide FiO_2 requirement.

[f] Baseline assessments should be performed prior to study drug administration.

[g] To be assessed only while hospitalized.

[h] Includes oxygen requirement (ie, mode of delivery/liters of oxygen flow, FiO_2 requirement), stop date of oxygen for patients who were discharged on home oxygen, extracorporeal membrane oxygenation support, noninvasive or invasive ventilator requirement, including start and stop of low- or high-flow oxygen supply or of any form of ventilation, and need for renal replacement therapy. Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.

[i] Only stop date of oxygen for patients who were discharged on home oxygen.

[j] Information recorded is yes/no, hospitalization date, discharge date.

[k] Laboratory tests performed within the 48 hours prior to enrollment will be accepted for determination of eligibility.

[l] Hematology and clinical chemistry.

[m] Hematology, clinical chemistry, liver function tests, cardiac panel, and coagulation.

[n] Any laboratory tests performed as part of routine clinical care can be used for safety laboratory testing.

[o] Hematology, clinical chemistry, and liver function tests.

[p] If not done or entered into the eCRF within previous day.

[q] Hematology, clinical chemistry, and liver function tests will be collected on the eCRF, if available, while the patient is in hospital.

[r] This assessment will be performed on Day 15 or date of discharge, if earlier.

2.0 INTRODUCTION

2.1 Study Rationale

There is a high unmet medical need for therapeutic agents available to treat coronavirus disease 2019 (COVID-19), an inflammatory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and there is an urgent public health need for rapid development of such interventions. This adaptive platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19 in hospitalized patients. Candidate agents will be evaluated frequently (through ongoing monitoring) for futility and safety, with candidate agents being added to and/or removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study are required to be hospitalized with confirmed active SARS-CoV-2 infection and may require either ongoing medical care, supplemental oxygen, noninvasive ventilation or high-flow oxygen devices, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

2.2 Background

Coronaviruses are single-stranded RNA viruses capable of causing life-threatening disease in humans and animals. The novel coronavirus SARS-CoV-2, first identified during an outbreak of viral pneumonia cases of unknown cause in China, binds via the angiotensin-converting enzyme 2 receptor located on alveolar cells and intestinal epithelia.[1] The virus is mutating, indicating that virulence and transmission will shift over time, and showing diversity in critical surface protein. Evidence suggests there are 2 groups of SARS-CoV-2; L-type and S-type.[2] S-type is the less aggressive (30%); the L-type is now the most prevalent version (70%) and is more aggressive.

Most of the initial SARS-CoV-2 infections outside of China were travel associated (ie, from people who had traveled from the infected regions of China to other countries), although person-to-person transmission of SARS-CoV-2 in other countries was quickly established. On 11 March 2020, reports of 118,000 cases and 4,291 deaths in 114 countries prompted the World Health Organization to declare COVID-19 a pandemic. Less than a month later, worldwide cases had reached over 3.5 million, with over 240,000 deaths attributed to COVID-19. By the end of March 2021, over 126 million cases of COVID-19 and over 2.7 million deaths had been reported globally.[3]

Central to elucidating the epidemiology of SARS-CoV-2 is surveillance of the clinical characteristics and outcomes of individuals diagnosed with COVID-19.[4] Traditional epidemiologic risk factors such as geographic variation, advanced age, and comorbid conditions have emerged as clear risk factors for COVID-19.[5] Sex-related differences in COVID-19 health outcomes have also been reported; despite equal numbers of COVID-19 cases between sexes, fatality rates are higher in men than in women.[6]

In addition to factors of geography, age, comorbidity, and sex, concern is growing that racial and ethnic minority communities experience a disproportionate burden of COVID-19 morbidity and mortality. Indeed, in the United States, compared to White, non-Hispanic persons, the COVID-19 case rate, hospitalization rate, and death rate are higher among Black or African American non-Hispanic persons (1.1, 2.9, and 1.9 times higher, respectively), Hispanic or Latino persons (1.3, 3.1, and 2.3 times higher, respectively), and American Indian or Alaska native, non-Hispanic persons (1.7, 3.7, and 2.4 times higher, respectively).[7]

These data highlight the urgent need for immediate comprehensive studies and robust analyses that combine genomic data, chart records, clinical symptoms, and demographic data to help better understand COVID-19 and enable risk assessment, triage, and public health resource planning. Current clinical studies involve the use of already approved medications for other indications (repurposing) where it is thought that they might also be effective in the treatment of COVID-19, as well as development of antiviral agents and antibody-based therapies against the virus.

Inclusion of a population that encompasses the epidemiologic and demographic risk factors relevant to COVID-19 in clinical studies is critical to development of efficacious treatments that will stem the impact of this disease. Given that the racial and ethnic minorities most impacted by COVID-19 are historically under-represented in clinical studies generally, proactive efforts and ongoing attention should be given to ensuring these populations are included at a rate commensurate with the overall population at a minimum, if not closer to COVID-19 case rates.

This platform study will test multiple candidate agents, with the aim of identifying potentially efficacious treatments in the shortest timeframe possible. In addition, it will support secondary research objectives that are critical for understanding the disease, spread of infection, and robust tests to track it.

2.3 Benefit/Risk Assessment

There exists a high unmet medical need for therapeutic agents to treat COVID-19; it can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death.

While there may not be direct benefits for an individual patient participating in this study, there may be benefits to society if a safe and efficacious therapeutic agent can be identified during the global COVID-19 outbreak.

Detailed information about the known and expected risks and reasonably expected adverse events (AEs) of each candidate agent may be found in the corresponding sub-protocol for that agent.

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate time to confirmed clinical recovery	• Time to confirmed clinical recovery through Day 29, ie, fit-for-discharge, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, without being rehospitalized through Day 29: 1. Death 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) 3. Hospitalized, on noninvasive 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 limitations on activities
Key Secondary	
• To evaluate oxygen-free recovery	• Incidence of oxygen-free recovery at Day 29, defined as patients who are alive, discharged, and not receiving supplemental oxygen.
• To evaluate improvement or being fit-for-discharge	• Incidence of ≥2-point improvement from baseline or fit-for-discharge on the ordinal scale at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale.
• To evaluate all-cause mortality	• Incidence of all-cause mortality through Day 29.
Other Secondary	
• To evaluate the distribution across categories on the 8-point ordinal scale, and the worst outcome	• Distribution of 8-point ordinal scale at Days 8, 15, and 29, as well as the worst postbaseline score on 8-point ordinal scale from baseline to Day 29.
• To evaluate intensive care unit (ICU) days	• Number of ICU days from Day 1 through Day 29.
• To evaluate invasive mechanical ventilator days	• Number of invasive mechanical ventilator days from Day 1 through Day 29.

• To evaluate clinical recovery	• Incidence of clinical recovery, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status by Days 8, 15, and 29.
• To evaluate sustained clinical recovery	• Incidence of sustained clinical recovery as confirmed by Day 60 follow-up.
• To evaluate the safety of candidate agents as add-on therapy to standard of care in patients with COVID-19	• Incidence of AEs in the following categories: – All treatment-emergent AEs – Serious AEs – AEs with Common Terminology Criteria for Adverse Events Grade 3 or higher – AEs leading to dose modifications – AEs leading to study treatment discontinuation
Exploratory	
CCI [redacted]	

4.0 STUDY DESIGN

4.1 Overall Design

COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY) is an adaptive, randomized, placebo-controlled platform study designed to rapidly evaluate candidate agents in the treatment of COVID-19. The study will include hospitalized adult patients (≥18 years of age) who have infection with SARS-CoV-2, the virus that causes COVID-19, as confirmed by laboratory tests and/or point-of-care tests. For inclusion, patients will need to be hospitalized with a clinical status of Grade 2 (hospitalized, on invasive mechanical ventilation or ECMO) to Grade 5 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]), as defined by an 8-point ordinal scale of clinical severity (see Section 8.1.1).

This study aims to identify efficacious candidate agents for treatment of COVID-19. The candidate agents may include, but will not be limited to, antivirals, vascular agents, or immunomodulatory agents. Each sub-protocol will specify a single candidate agent or a combination of candidate agents to be administered. In regions where more than one sub-protocol has received local regulatory and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, it is required that participating sites are activated for enrollment for all approved sub-protocols.

This Master Protocol outlines the overall design of the study, including the population, inclusion and exclusion criteria, randomization scheme, primary, secondary, and exploratory endpoints, study design, statistical methodology, and planned analyses that are common for all candidate agents to be tested. The Master Protocol is structured such that multiple candidate agents from different pharmaceutical companies can be evaluated simultaneously. The plan is to add candidate agents as they are identified, and/or to remove therapies based on results of interim analyses (eg, due to futility or if they are considered unsafe). The shared placebo control group for a candidate agent will include only patients randomized during the same period in which the candidate agent group is randomized, which will be defined in the sub-protocol Statistical Analysis Plan (SAP). Patients will be randomized equally to either the candidate agent plus standard of care (SoC) or placebo plus SoC in a double-blind fashion. Patients who are randomized to placebo plus SoC will be subsequently randomized equally to a matching placebo corresponding to an available agent whose sub-protocol the patient qualified for (ie, a 2-stage randomization). Each patient in the placebo plus SoC group will only receive one type of placebo. Therefore, patients may be aware of which sub-protocol they were randomized to but not to whether they will receive active agent or placebo investigational product. The comparator group for a candidate agent will include patients randomized to any matching placebo for a candidate agent available at the time of randomization for that agent.

Patients will be screened on Day -1 (the day before the first dose of study treatment [candidate agent or placebo/SoC] is scheduled) or Day 1 and will remain in the hospital from Day 1 until discharge. All patients will receive SoC treatment, either with blinded candidate agent or matching blinded placebo. The SoC will be based on appropriate local written guidelines in place at a site at the time of treatment in the study; the SoC may change during the course of the study as new information becomes available about treating COVID-19. Dosing with the study treatment (as an add-on to SoC) will commence on Day 1. Patients will be assessed daily while hospitalized. If they are discharged from the hospital prior to Day 15, they will have study visits at Days 15 and 29 as an outpatient by telemedicine. The last day of primary assessments will be Day 29. An end-of-study visit will be conducted on Day 60 (±4 days) via telemedicine (unless the patient is still hospitalized in which case it would be conducted in person).

Sub-protocols will outline the scientific rationale, additional eligibility criteria (if necessary), treatment dose and regimen, statistical analysis populations, and other specifics unique to each candidate agent. The sub-protocols may define AEs of special interest and can include pharmacokinetic (PK) and/or pharmacodynamic assessments that are appropriate for the specific candidate agent. The endpoints specified in this Master Protocol will not be altered in the sub-protocols, but the sub-protocol may define additional endpoints. In order to enroll, a patient must meet all entry criteria for both the Master Protocol and at least one active sub-protocol.

The study will evaluate the candidate agents as an add-on to the SoC to assess safety and efficacy. Interim analyses may be performed for each candidate agent to evaluate futility for candidate agents.

Patients will be stratified at randomization by baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no).

Enrollment of patients will be continuous throughout the study for each candidate agent until the total number of planned patients for that agent is enrolled or until futility criteria is met at the interim analyses, or if the agent is considered unsafe.

In addition, centers may elect to participate in separate Investigator-initiated studies collecting additional data on patients (eg, PK analyses), as their resources permit.

4.2 Scientific Rationale for Study Design

There is a high unmet medical need for therapeutic agents available to treat COVID-19, an inflammatory disease caused by SARS-CoV-2, and there is an urgent public health need for rapid development of such interventions. This platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19 in hospitalized patients. Candidate agents may be added to and/or removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study are required to be hospitalized with confirmed active SARS-CoV-2 infection and require either ongoing medical care (Grade 5 on

the 8-point ordinal scale), supplemental oxygen (Grade 4), noninvasive ventilation or high-flow oxygen devices (Grade 3), or invasive mechanical ventilation or ECMO (Grade 2).

4.3 Justification for Dose

Justification for the dose of each candidate agent will be included in the corresponding sub-protocol.

4.4 End of Study Definition

For each sub-protocol, the end of the study for that candidate agent will be defined as the date on which the last patient randomized to that sub-protocol completes their last scheduled procedure as shown in the Schedule of Activities (SoA).

For the overall study, the end of the study will be defined as the date on which the last patient completes the last scheduled procedure for the final sub-protocol to be concluded.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Inclusion and exclusion criteria will be checked at screening and rechecked at baseline. The inclusion and exclusion criteria listed below may be supplemented by additional criteria stipulated in the sub-protocols that are specific to the target candidate being tested (eg, criteria related to safety concerns of the candidate agent or to prohibited medications). In order to enroll, a patient or legally authorized representative must sign an informed consent form (ICF) and meet all entry criteria for both the Master Protocol and at least one active sub-protocol.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply (as well as all criteria from the appropriate sub-protocol):

1. Adults (≥18 years of age) with active SARS-CoV-2 infection confirmed by laboratory tests and/or point-of-care tests (eg, commercial or public health assay, which is approved for emergency use). If no diagnostic test results are available that have been obtained during the previous 72 hours, then a test should be performed as part of the screening assessment (see Section 8.3).
2. A score of Grade 2 (hospitalized, on invasive mechanical ventilation or ECMO), Grade 3 (hospitalized, on noninvasive ventilation or high-flow oxygen devices), Grade 4 (hospitalized, requiring supplemental oxygen), or Grade 5 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]), as defined by an 8-point ordinal scale.
3. a) Male patients:

- A male patient must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 6 weeks (or longer if defined in the sub-protocol) after the last dose of study treatment and refrain from donating sperm during this period.

b) Female patients:

- A female patient is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

    i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.
    OR
    ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 6 weeks (or longer if defined in the sub-protocol) after the last dose of study treatment.

4. Ability to provide informed consent signed by the study patient or legally authorized representative.
5. Ability and willingness to participate in telephone/telemedicine follow-up visits if needed.
6. Randomized within 5 days of hospitalization.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply (or any of the criteria from the appropriate sub-protocol):

1. Patient with past medical/surgical history and/or any current condition for which, in the opinion of the Investigator, participation would be a safety risk or could affect the integrity of data.
2. Stage 4 severe chronic kidney disease or requiring dialysis.
3. Screening 12-lead electrocardiogram (ECG) with a measurable QTc interval according to Fridericia correction ≥500 ms.
4. Anticipated transfer to another hospital that is not a study center within 72 hours.
5. Patients who are currently pregnant or who are not willing to discontinue breastfeeding.
6. Patients participating in another clinical study of an investigational medicinal product or other unapproved (or investigational) treatment for COVID-19.
7. Active tuberculosis or a history of incompletely treated tuberculosis.
8. Active, uncontrolled systemic bacterial or fungal infection(s).
9. Where, in the opinion of the Investigator, progression to death is imminent and inevitable within the next 48 hours, irrespective of the provision of treatments.

5.3 Lifestyle Considerations

Any lifestyle considerations that are specific to the candidate agent will be defined in the corresponding sub-protocol.

Female patients are advised to avoid becoming pregnant during the study; treatment with candidate agent will be discontinued for patients who become pregnant. Similarly, male patients will be advised to avoid their partners becoming pregnant during the study.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information may be collected to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event (SAE).

6.0 STUDY INTERVENTIONS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a patient according to the study protocol. In this protocol, the term 'study treatment' is typically used to refer to either the candidate agent or placebo (and not SoC).

6.1 Study Intervention(s) Administered

This platform study will include multiple treatments (candidate agents) and matching placebos (each candidate agent will have its own matching placebo) from different pharmaceutical companies. Each candidate agent included within the study will have a sub-protocol that will provide details of that treatment (including placebo), including route and mode of administration, dose, dosage regimen, and duration of treatment. In lieu of matching placebos, candidate agent sub-protocols may utilize an unblinded pharmacist to prepare the study treatment.

These candidate agents may include, but will not be limited to, antivirals, vascular agents, or immunomodulatory agents; first-in-human agents will not be considered as candidate agents.

The SoC will be based on appropriate guidelines in place at a site at the time of treatment on the study. The SoC may change during the course of the study as new information becomes available about treating COVID-19.

6.2 Preparation/Handling/Storage/Accountability

Study treatment (candidate agent or placebo) will be shipped to the study center either directly from participating companies, from the Sponsor or candidate agent owner, or from other regional or local drug repositories. All other supplies will be provided by the study center.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive a study treatment and only authorized study center staff may supply or administer study treatments. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual for the study treatment.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatments using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

The study will randomize patients on an ongoing basis, in a double-blind manner, to receive either one of the active candidate agents plus SoC or to receive placebo plus SoC. Randomization will be performed using an Interactive Voice/Web Response System (IVRS/IWRS). The system will initially randomize to either an active candidate agent or generically to placebo plus SoC. If a patient is randomized to placebo plus SoC, the system will then further randomize the patient to a specific candidate agent's placebo from within the list of candidate agents available at the site and for which the patient was determined to be eligible. In either of these cases, the blinded team will be aware of the sub-protocol to which the patient has been randomized, but not whether it is the active agent or the agent's matching placebo. The system will limit randomization to those agents (or matching placebo) that are active for randomization, have not reached their total number of planned patients, have been approved by the site, and for which the patient matches the inclusion/exclusion criteria.

If candidate agents are added to and/or dropped from the study, randomization will proceed with an equal probability of assignment to each of the remaining candidate agents, except for situations where a patient does not meet the eligibility criteria for, and hence would be excluded from, one or more of the sub-protocols.

Study treatment will be dispensed at randomization or according to the sub-protocol SoA. Returned study treatment should not be re-dispensed to patients.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. The IVRS/IWRS will also be programmed with the ability for the safety team to perform a similar blind-breaking activity.

6.4 Study Treatment Compliance

For each study treatment, the prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 6.6. Any departures from the intended regimen must be recorded in the eCRFs.

Each dose of study treatment (candidate agent or placebo) will be administered by a member of the clinical research team who is qualified and licensed to administer the study product. Administration and date, time, and route will be entered into the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of, or during the two weeks prior to, enrollment (including screening) or receives during the study must be recorded in the eCRF. In addition, receipt of any COVID-19 vaccine, regardless of when the vaccine was received, must be recorded in the eCRF. The following data must be collected in the eCRF for all concomitant therapies, including any COVID-19 vaccine:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

If the local SoC per written policies or guidelines (ie, not just an individual clinician decision) includes use of off-label medications, then use of these medications during the study is permitted. Therapies taken for comorbid conditions, other than COVID-19, are allowed.

A list of excluded medications/therapy will be provided for each candidate agent in the corresponding sub-protocol.

6.6 Dose Modification

An Independent Data Monitoring Committee (IDMC) will actively monitor interim safety and efficacy data throughout the duration of the study to make recommendations about dose modifications, as well as early study closure or changes to the study treatment arms.

Details of permitted dose modifications for specific candidate agents will be detailed in the corresponding sub-protocol.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A patient may withdraw from study treatment at any time at his/her own request or may be withdrawn from study treatment at any time at the discretion of the Sponsor or Investigator for safety, behavioral, compliance, or administrative reasons. Specifically, a patient in this study may discontinue their assigned candidate agent (or placebo) for any of the following reasons:

- Patient (or their legally authorized representative) requests to discontinue study drug.
- Occurrence of any medical condition or circumstance that does not allow the patient to adhere to the requirements of the protocol or patient fails to comply with protocol requirements or study-related procedures.
- Any SAE, clinically significant AE, severe laboratory abnormality (including abnormal liver function test results, see below), intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
- Pregnancy recognized post start and prior to end of study treatment.

Unless the patient withdraws consent, those who discontinue study treatment early should remain in the study for further acquisition of endpoint measurements. The reason for patient discontinuation of study treatment should be documented in the eCRF.

Discontinuation of the study treatment for abnormal liver tests should be considered by the Investigator when a patient meets one of the following conditions, after consultation with the Medical Monitor:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN)
- ALT or AST >3 × ULN and either
  - total bilirubin level >2 × ULN, or
  - prothrombin time >1.5 × ULN

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request.

If the patient withdraws consent for disclosure of future information, the Sponsor or designee may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any residual remaining samples taken and not tested, and the Investigator must document this in the study center study

records. However, any laboratory or test data generated from samples that have already been processed and included in secondary translational research may not be recalled.

See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The specific SoA for a treatment arm, either active candidate agent or placebo, will be detailed in the corresponding sub-protocol.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (or does not participate in telephone/telemedicine follow-up visits) and is unable to be contacted by the study center.

The following actions must be taken if a patient fails to return to the study center for a required study visit:

- All efforts should be made to ascertain the vital status of the patient.
- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study. Efforts will be made to collect data from public sources to establish vital status.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Note: Given the nature of the disease and the condition of the patients, it may not always be possible to perform all planned assessments at all time points; however, all efforts should be made to perform assessments as long as it considered clinically safe to do so.

An example SoA is presented in Section 1.3. The specific SoA for a treatment arm, either active candidate agent or placebo will be detailed in the corresponding sub-protocol.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the CCI Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the corresponding sub-protocol for the candidate agent, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood work) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Clinical Severity Status 8-Point Ordinal Scale

For the purposes of this study, the condition of each potential patient in the study will be assessed using an 8-point category ordinal scale[8]:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive 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 limitations on activities

Clarifications regarding the ordinal scale scores are provided in Table 2 and Table 3. To be considered for inclusion in the study, patients must be Grade 2 to 5 on this scale at screening and at baseline.

Table 2 Clarification of the 8-point Ordinal Scale for Scores 2 Through 5

Ordinal Scale Score	General Description	Expanded Description
2	IMV or ECMO	ECMO or IMV, which includes closed systems, utilizing endotracheal intubation or tracheostomy, with ventilator assistance.
3	NIV, high-flow oxygen delivery (≥10 L/min)	NIV includes APAP, BiPAP, and CPAP. High-flow delivery systems include HFNC, non-rebreather face mask, and venturi mask where the oxygen flow rate is ≥10 L/min.
4	Low-flow oxygen delivery (<10 L/min)	Low-flow oxygen delivery systems include simple face mask and simple nasal cannula where the oxygen flow rate is <10 L/min.
5	No oxygen requirement	Not requiring supplemental oxygen but requiring in-hospital medical care for any active medical issues.

Abbreviations: APAP = automatic positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; IMV = invasive mechanical ventilation; min = minute; NIV = noninvasive ventilation.

A patient will be considered as fit-for-discharge if he/she achieves a score of 6, 7, or 8 on the ordinal scale (ie, as a minimum, the patient does not require ongoing hospitalized medical care) at least once on the study. Patients who achieve a 7 on the ordinal scale but are discharged to hospice care will not be considered as being fit-for-discharge.

Table 3 Clarification of the 8-point Ordinal Scale for Scores 6 Through 8

Ordinal Scale Score	General Description	Expanded Description
6	Fit-for-discharge but hospitalized	No longer requiring acute in-hospital medical care; clinically stable for discharge, may have ADL limitations, but is awaiting post-hospital/outpatient placement, or may have a delay in sourcing new or additional home care that makes discharge unadvisable.
7	Fit-for-discharge, not hospitalized with limitations in ADLs and/or oxygen needs	Not hospitalized. This category is reserved for patients with limitations in ADL and/or who require home oxygen.
8	Fit-for-discharge, not hospitalized and no limitations in ADL	Not hospitalized. This category describes patients with no limitations in ADL and/or those who have returned to baseline pre-COVID-19 performance.

Abbreviations: ADL = activities of daily living; COVID-19 = coronavirus disease 2019.

The primary endpoint will be time to confirmed clinical recovery through Day 29, ie, fit-for-discharge, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, without being rehospitalized through Day 29.

Incidence of patients achieving ≥2-point improvement from baseline on the ordinal scale or fit-for-discharge at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale will be a key secondary endpoint.

Distribution across categories on the 8-point ordinal scale at Days 8, 15, and 29, as well as the worst postbaseline score on 8-point ordinal scale from randomization to Day 29, the clinical recovery (based on patients who achieve a score of 6, 7, or 8) on Days 8, 15, and 29, and the sustained clinical recovery as confirmed by Day 60 will be secondary endpoints. 'Sustained' is defined as clinical recovery without readmission to a hospital by Day 60.

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[redacted]

8.1.2 Other Efficacy Assessments

The following will be evaluated as key secondary endpoints in addition to the key secondary endpoints described in Section 8.1.1:

- Incidence of oxygen-free recovery at Day 29, defined as patients who are alive, discharged, and not receiving supplemental oxygen.
- Incidence of all-cause mortality through Day 29.

The following will be evaluated as other secondary endpoints:

- The number of intensive care unit (ICU) days and invasive mechanical ventilator days from Day 1 through Day 29. This should include patients who are receiving ICU-level care, even though they might not physically be in an established ICU floor.

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[redacted]

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). The specific SoA for a treatment arm, either active candidate agent or placebo will be detailed in the corresponding sub-protocol.

8.2.1 Physical Examinations

A general physical examination will be performed at screening, including measurement of height and weight.

8.2.2 Vital Signs

Temperature, pulse rate, blood pressure, and respiratory rate will be assessed. Blood pressure and pulse measurements will be assessed with a completely automated device. SpO_2 will also be assessed. Manual techniques will be used only if an automated device is not available.

FiO_2, the fractional inspired oxygen, will also be recorded.

Measurements will be taken in line with standard practices for the study center.

Vital signs measurements will contribute to the NEWS2 score (see Section 8.1.2).

8.2.3 Clinical Safety Laboratory Assessments

Fasting is not required before collection of laboratory samples. See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Additional assessments, if required, will be defined in the sub-protocol, as will the sub-protocol SoA.

Additional tests may be performed at any time during the study as deemed necessary by the Investigator and/or appropriate designee, or as required by local regulations.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator and/or appropriate designee (for example, SAE or AE or dose modification), then the results must be recorded in the eCRF.

Reviewing and Recording Test Results

The Investigator and/or appropriate designee must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Repeating Testing After Clinically Significant Abnormal Findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Medical Monitor during study participation. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the candidate agent owner notified.

8.3 Viral Diagnosis

Either qualitative and/or quantitative polymerase chain reaction determination of SARS-CoV-2 or SARS-CoV-2 antigen testing in oropharyngeal/nasal swab will be performed at screening if no diagnostic test results are available that have been obtained during the previous 72 hours.

8.4 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs may be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment (see Section 7.0).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from provision of informed consent until the final follow-up visit, at the time points specified in the SoA (Section 1.3 and applicable sub-protocol).

All SAEs will be recorded and reported to CCI within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to CCI within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify CCI .

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAEs

Clinical sites must notify CCI Safety of any SAE, without regard to causality, within 24 hours after becoming aware of its occurrence. Any nonserious AE which worsens and eventually meets the criteria for an SAE must also be reported as a new SAE.

Information regarding SAEs will be transmitted to CCI Safety using the Serious Adverse Event Form within Electronic Data Capture (EDC), which must be completed by the clinical site within 24 hours of becoming aware of its occurrence. The SAE form in EDC should include a clearly written narrative describing signs, symptoms and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant information is available.

The initial and follow-up reports of an SAE should be made using the electronic data collection tool. If necessary, as a backup, reports can be made by e-mail or facsimile (fax). The contact details are:

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The CCI Medical Safety Advisor (or designee) must also be notified within 24 hours should any patient experience an SAE. Contact information for the SAE Coordinator will be provided on the SAE form/completion instructions.

Contact information for the candidate agent owner will be listed in the corresponding sub-protocol, should the sites need to contact the candidate agent owner to discuss any medical, safety related questions or SAEs.

An unlisted (unexpected) AE is one in which the nature or severity is not consistent with the applicable product reference safety information. For investigational product(s), the expectedness of an AE will be determined by whether or not it is listed in the reference safety information (eg, Investigator's Brochure). Investigators will be notified, and the reference safety information will be updated, if any pattern of AEs or laboratory abnormalities is found to be related to compound dosing during studies going forward.

The start date of an SAE reported on the Serious Adverse Event Form must be the same as the start date of the corresponding AE documented on the eCRF. If a change in severity is noted for the existing AE, it must be recorded. If a worsened AE meets the criteria for an SAE, the start date of the SAE must be the same as the start date of the worsened AE.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value is available;
- The event can be attributed to agents other than the study drugs or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. Any SAE reports will be reported by the Investigators (or designee) to their local IRB/IEC in accordance with local reporting requirements and reporting timelines.

Similarly, CCI will determine whether an SAE must be reported in an expedited manner to regulatory authorities, in accordance with regulatory requirements. If so, CCI will report the event to the regulatory authorities in accord with applicable reporting timelines.

Investigational New Drug (IND) safety reports should also be submitted as a cross-report to the relevant commercial INDs of the individual candidate agent owners.

CCI will submit a platform Development Safety Update Report (DSUR) for the Master Protocol. The platform DSUR will contain data for all compounds and will be presented in a tabular format throughout the document. CCI has the ability to redact the tabs in order to provide each candidate agent owner with their own required data while still protecting all other candidate agent owners' data.

CCI will inform the candidate agent owner of any important safety findings related to the candidate agent that arise during the conduct of this study. Similarly, the candidate agent owner will inform CCI of any important safety findings related to the candidate agent that they become aware of from other studies.

A joint safety team, with representatives from each candidate agent owner, will meet on a regular basis throughout the study to discuss important safety findings that may impact the study.

8.4.5 Pregnancy

All initial reports of pregnancy must be reported to CCI Safety (see Section 8.4.4) by the investigational staff within 24 hours of their knowledge of the event using the pregnancy reporting form. After the expected pregnancy end date, site will provide CCI Safety with the pregnancy outcome, delivery, and infant details for completion and reporting. Abnormal pregnancy outcomes are considered SAEs and must be reported using the Serious Adverse Event Form. Any patient who becomes pregnant during treatment must immediately discontinue treatment with the study treatment.

In addition, pregnancies in partners of male patients included in the study will be reported by the investigation staff within 24 hours of their knowledge of the event using the pregnancy reporting form.

8.4.6 Adverse Events of Special Interest

AEs of special interest will be specific to the target candidate agent and, as such, may be defined in the corresponding sub-protocol.

8.4.7 Disease-Related Events and/or Disease-Related Outcomes

Progression, signs, or symptoms of the disease being studied and clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease should be reported, as appropriate, as an AE or SAE.

8.5 Treatment of Overdose

In the event of an overdose of a candidate agent, the Investigator/treating physician should:

1. Contact the CCI Medical Monitor immediately.

2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities until the candidate agent can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6 Pharmacokinetics

Any PK assessments performed will be specific to the candidate agent and will be discussed in the corresponding sub-protocol, including a schedule for collection of samples of blood or other biological samples for analysis.

If a patient refuses blood collection for PK analysis, or it is not possible to collect samples for logistical reasons, this will not be considered a protocol violation as the PK analysis is not a primary or secondary objective of the protocol.

8.7 Pharmacodynamics

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8.8 Blood for Potential Future Research

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9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

A total of 350 patients are planned to be randomized to each candidate agent plus SoC. Simultaneously, patients will be randomized to placebo plus SoC throughout the course of the study. The subset of the placebo plus SoC group, regardless of which sub-protocol the placebo belongs, enrolled concurrently to any active agent with matching inclusion/exclusion criteria will serve as its comparator group. The primary efficacy endpoint to compare selected treatments plus SoC to placebo plus SoC will be the time to clinical recovery up to Day 29, ie, fit-for-discharge, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, without rehospitalization.

Assuming a median time to clinical recovery of 11 days for patients randomized to an active treatment group plus SoC compared with 15 days for those randomized to placebo plus SoC,[10] 350 patients are needed per arm in order to observe 490 clinical recovery events between the 2 treatment groups being compared at the primary analysis. This sample size will provide approximately 88% power to detect a hazard ratio (HR) of 1.364 for the occurrence of the clinical recovery events, when comparing each candidate agent plus SoC with placebo plus SoC, at a 1-sided significance level of 0.025.

This sample size will provide the following information about the key secondary endpoints: assuming the oxygen-free recovery rate at Day 29 is 65% for the placebo plus SoC group, a sample size of 350 patients per arm will provide approximately 80% power to detect a 9.7% absolute increase in the proportion of patients who have oxygen-free recovery at Day 29 among the active treatment group plus SoC group. Assuming 70% of patients randomized to placebo plus SoC achieve at least 2-point improvement from baseline on the 8-pt ordinal scale or being fit-for-discharge at Day 29, 350 patients per arm will provide approximately 80% power to

detect a 9.2% absolute increase in this proportion with a candidate agent plus SoC at Day 29. Assuming the all-cause mortality rate through Day 29 is 15% for the placebo plus SoC group, a sample size of 350 patients per arm will provide 80% power to detect an absolute reduction of 6.75% (8.25% rate for a candidate agent) in the mortality rate by Day 29 in the active treatment plus SoC group. Assuming a mortality rate of 15% for the placebo plus SoC group and 19% for a candidate agent plus SoC (ie, an adverse treatment effect of 4%), with a sample size of 350 per arm, the chance to observe a decrease in the mortality rate of at least 1% with a candidate agent plus SoC compared to placebo plus SoC is approximately 4%. The sample size calculation was performed using EAST 6.5.

For a sub-protocol where the primary analysis population is a subset of the randomized population, the sample size may be adjusted as applicable to power the designated primary analysis population as appropriate. More details will be presented in the sub-protocol SAP.

Each candidate agent will be evaluated for futility at up to 2 interim analyses. These interim analyses will be planned at information fractions of approximately 25% and 55% of expected number of recoveries, ie, after approximately 123 and 270 patients have met the primary endpoint of clinical recovery on a particular candidate agent plus SoC and placebo plus SoC, respectively. However, the timing of the interim analyses may be adjusted due to operational considerations, eg, actual enrollment rate.

For the interim analyses, a Pocock beta spending function will be used for non-binding futility boundary specification. This strategy will allow for ineffective agents to be identified early for discontinuation of further evaluation. Assuming no treatment effect for a candidate agent plus SoC compared with placebo plus SoC, there is a 49.7% chance that enrollment to this agent is stopped at the first interim analysis and 34.6% chance at the second interim analysis. Under the scenario that treatment has a negative effect on outcomes (Table 7 in Appendix 7) these probabilities become 72.3% and 24.7%, respectively.

The primary analysis for a candidate agent will occur after 350 patients have been randomized to an active agent plus SoC and have had the opportunity to complete the Day 29 visit, when approximately 490 clinical recovery events are expected to have been observed, unless an agent is stopped early for futility. The final analysis for a candidate agent will occur after all patients randomized to that agent plus SoC and the concurrent placebo plus SoC controls have had the opportunity to complete the Day 60 visit.

Appendix 7 presents a summary of futility incremental probabilities at the first interim, second interim, and the primary analyses together with Pocock futility boundaries in the scenario of 88.3% estimated power when the analyses occur at information fractions of 25% and 55% of expected number of recoveries, respectively.

Details will be provided in the IDMC charter and SAP.

9.2 Populations for Analyses

For purposes of analysis, the analysis sets in Table 4 are defined. Specific analysis sets may be defined in sub-protocols or their corresponding SAPs.

Table 4 Analysis Sets for the Master Protocol

Analysis Set	Description
Full Analysis Set	All patients who are randomized.
Safety Set	All patients who are randomized and take at least one dose of study treatment or placebo.

9.3 Statistical Analyses

The SAPs (for the Master Protocol and for the sub-protocols) will describe the patient analysis sets to be included in the analyses and procedures for accounting for missing, unused, and spurious data. General principles will be specified in Master Protocol SAP, while specific populations and method of handling multiplicity (eg, testing sequences) might be given in sub-protocols and further detailed in sub-protocol SAPs.

Efficacy and safety results will be summarized by scheduled times for the respective analysis sets, where appropriate.

9.3.1 Primary Efficacy Endpoint Analyses

The time to confirmed clinical recovery through Day 29, as defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale of clinical severity status, ie, fit-for-discharge, without being rehospitalized through Day 29, will be compared between the selected candidate agent plus SoC and contemporaneous placebo plus SoC, using a stratified log-rank test, stratifying for baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no), with patients who have died prior to or on Day 29 censored at Day 29. Patients who score a 7 on the 8-point ordinal scale but are discharged to hospice care will not be considered as 'fit-for-discharge.' The p-value associated with the stratified log-rank test statistic at the time of the primary analysis will be compared at the 2-sided 0.05 alpha level. The p-value will also be compared with the specified boundaries at the interim analyses for futility in order to serve as guidance for the IDMC to make recommendations based on the totality of available information at the time of the interim analyses. The HR for the treatment arm plus SoC versus placebo plus SoC will be estimated using a Cox regression, adjusting for randomization stratification factors, with deaths censored at Day 29.

9.3.2 Key Secondary Endpoint Analyses

The key secondary endpoint of incidence of oxygen-free recovery at Day 29, defined as patients who are alive, discharged, and not receiving supplemental oxygen at Day 29, will be analyzed

using a logistic regression model with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

The key secondary endpoint of incidence of patients achieving ≥2-point improvement from baseline or being fit-for-discharge on the ordinal scale at Day 29, with fit-for-discharge defined as categories 6, 7, and 8 on the 8-point ordinal scale at Day 29, will be analyzed using logistic regression with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

The key secondary endpoint of the incidence of all-cause mortality through Day 29 will be analyzed using a logistic regression with baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) included as covariates.

A hierarchical testing procedure will be used to control the family-wise type I error over the primary hypothesis and three key secondary hypotheses. With this approach, when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The hierarchical testing procedure will be implemented in the order of the primary endpoint followed by the three key secondary endpoints in the following order: oxygen-free recovery at Day 29, at least a 2-point improvement from baseline on the 8-point ordinal scale or being fit-for-discharge at Day 29, and all-cause mortality through Day 29.

9.3.3 Other Endpoint Analyses

For the other secondary endpoints, a binary endpoint will be analyzed by logistic regression including baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no) as covariates. For ordinal other secondary endpoints, the number and percentage of patients in each category will be provided for each treatment arm and will be analyzed using a proportional odds model, including the baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity (yes or no) and remdesivir use at baseline (yes or no) as stratification variables.

CCI [redacted]

9.3.4 Missing Data

All patients recruited into the study will be accounted for, including those who did not complete the study along with the reasons for withdrawal. Patients who withdraw from the study will have the reason(s) for withdrawal collected in the eCRF. For the key secondary endpoint of oxygen-free recovery at Day 29, patients with missing data preventing definition of status regarding oxygen-free recovery at Day 29 will not be considered as having met criteria defining the endpoint. Details will be presented in the SAP.

9.4 Review Committees

9.4.1 Joint Steering Committee

A Joint Steering Committee (JSC) will evaluate the recommendations to make decisions on the candidate agents within the study, and it will provide guidance, advice, and recommendations to the program on relevant clinical issues related to the strategy, implementation, and conduct of the study.

9.4.2 Independent Data Monitoring Committee

An IDMC will monitor ongoing data to ensure patient well-being and safety as well as study integrity. The IDMC will be asked to make recommendations to the JSC regarding early termination or modification of the evaluation of a candidate agent. More details will be provided in the IDMC charter.

A data safety review by the IDMC may be conducted regularly, whereas whether the interim analyses would be conducted or not for a certain agent will be determined by the number of observed occurrences of clinical recovery in that particular experimental arm and contemporaneous placebo + SoC.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
21 CFR	Code of Federal Regulations Title 21
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
COVID-19	Coronavirus disease 2019
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic Data Capture
FiO_2	Fraction of inspired oxygen
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HR	Hazard ratio
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JSC	Joint Steering Committee
CCI	[redacted]
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities

Abbreviation	Definition
SoC	Standard of care
SpO_2	Oxygen saturation
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Protocol Compliance

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice (GCP). Prospective, planned deviations or waivers to the protocol are not permitted; eg, it is not acceptable to enroll a patient if they do not meet the eligibility criteria or restrictions specified in the protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and CCI immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the Sponsor. Frequent non-compliances could potentially be classified as a serious breach.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the Master Protocol and sub-protocols and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines.
  - Applicable laws and regulations.
- The Master Protocol, sub-protocol, protocol amendments, ICF, Investigator Brochures, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- In regions where more than one sub-protocol has received local regulatory and IRB/IEC approval, it is required that participating sites are activated for enrollment for all approved sub-protocols.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

  - Providing oversight of the conduct of the study at the study center and adherence to requirements of the Code of Federal Regulations Title 21 (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or designee CCI (Appendix 8). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor or designee CCI with sufficient, accurate financial information as requested to allow the Sponsor or designee CCI to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients in this study. The terms of the insurance will be kept in the study files.

Due to the coronavirus public health crisis, in the US the federal government has a program that may provide compensation to the patient or their family if the patient experiences serious physical injuries or death as a result of participating in this clinical trial covered by the Public Readiness and Emergency Preparedness Act. More information regarding this Countermeasures Injury Compensation Program is available at https://www.hrsa.gov/cicp/index.html or by calling 1-855-266-2427.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that informed consent was obtained before the patient was entered in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Data Protection

Patients will be assigned a unique identifier by CCI . Any patient records or datasets that are transferred to the Sponsor, designee CCI , or any candidate agent owner will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

The trial will be overseen by a JSC that has decision-making rights on critical decisions that impact the platform trial. The JSC, at a minimum, will be composed of a senior representative of each company participating in the trial.

The administrative structure will be documented in more detail in the Trial Master File.

Medical Monitor

The CCI (Medical Monitor) is available for 24 hours a day/7 days a week urgent contact.

The following additional numbers are available for urgent contact:

CCI

Dissemination of Clinical Study Data

The results of the study should be reported within one year from the end of the overall clinical study. Irrespective of the outcome, the Sponsor will submit to US National Institutes of Health's website www.ClinicalTrials.gov and other publicly-accessible sites within one year from the end of the overall clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

All patient data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee CCI electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee CCI is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the eCRF completion guidelines.

Study and Study Center Closure

The Sponsor reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

To coordinate dissemination of data from this study, the Sponsor may facilitate the formation of a Publication Committee, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other Investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the

content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the Publication Committee for review. The Clinical Trial Agreement among the institution, Investigator, and the Consortium will detail the procedures for, and timing of, the Publication Committee's review of publications.

Appendix 3 Clinical Laboratory Tests

The minimum tests to be performed are detailed in Table 5. Any additional tests that are specific for the candidate agent will be detailed in the corresponding sub-protocol. Clinical laboratory tests will be performed at a local laboratory.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.0 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Changes to some laboratory parameters are anticipated for any patients moving on to ECMO therapy.

Investigators must document their review of each laboratory safety report.

Table 5 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count Hemoglobin White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	D-dimer test Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International Normalized Ratio (INR) C-reactive protein Ferritin Lactate dehydrogenase (LDH) Procalcitonin
Clinical Chemistry	Potassium Sodium Calcium Magnesium Phosphate Bicarbonate Creatinine Glucose
Liver Function Tests	Alkaline phosphatase Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT)
Cardiac Panel	Creatine kinase (MB fraction) Triglycerides Troponin

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

For completeness, the full guidance for AE reporting is presented in this appendix.

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to CCI in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by CCI. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to CCI.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following Common Terminology Criteria for Adverse Events grades:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- 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 (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (Grade 3 and higher).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as related or unrelated.
  - "Related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship for the individual case.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to CCI. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to CCI.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by CCI to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide CCI with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to CCI within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to CCI will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Safety Advisor/SAE Coordinator by telephone.

SAE Reporting via Paper Case Report Form

- Facsimile transmission of the SAE paper case report form is the preferred method to transmit this information to the Medical Safety Advisor or the SAE Coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male patients

- Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- In addition, male patients must refrain from donating sperm for the duration of the study and for 6 weeks (or longer if defined in the sub-protocol) after the last dose of study treatment.

- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 6 weeks (or longer if defined in the sub-protocol) after the last dose of study treatment.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system. Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 6 weeks (or longer if defined in the sub-protocol) after the last dose of study treatment.

Pregnancy Testing:

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test.

Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Study treatment will be discontinued for patients who become pregnant.

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to CCI within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to CCI. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to CCI as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.

CCI

Appendix 7 Summary of Futility Probabilities and Boundaries

Table 6 Summary of Futility Probabilities and Boundaries with 88.3% Power Using Pocock Futility Boundaries

Analysis	Total Number of Events (Information Fraction)	Boundary of Futility, Non-binding (HR)	Boundary of Futility, Non-binding (p-value)	Incremental Probability to Declare Futility Under the Null (HR=1)
First Interim	123 (25%)	≤0.998	0.503	0.497
Second Interim	270 (55%)	≤1.121	0.175	0.346

Abbreviation: HR=hazard ratio.
Assume 1-sided α of 0.025.
Interim analysis using Pocock futility boundaries at 25% and 55% information fraction.
HR boundaries are translated from p-values. Dependent of relative timing and will be re-calculated for Independent Data Monitoring Committee.

Table 7 Summary of Futility Probabilities and Boundaries with 88.3% Power Using Pocock Futility Boundaries for the Negative Treatment Effect Scenario (HR=0.9)

Analysis	Total Number of Events (Information Fraction)	Boundary of Futility, Non-binding (HR)	Boundary of Futility, Non-binding (p-value)	Incremental Probability to Declare Futility Under the Negative Treatment Effect Scenario (HR=0.9)
First Interim	123 (25%)	≤0.998	0.503	0.723
Second Interim	270 (55%)	≤1.121	0.175	0.247

Abbreviation: HR=hazard ratio.
Assume 1-sided α of 0.025.
Interim analysis using Pocock futility boundaries at 25% and 55% information fraction.
HR boundaries are translated from p-values. Dependent of relative timing and will be re-calculated for Independent Data Monitoring Committee.

Appendix 8 Signature of Investigator

PROTOCOL TITLE: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

PROTOCOL NO: COV-01

VERSION: Protocol Amendment 4

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO/Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

TITLE PAGE

Master Protocol Title: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

Sub-protocol Number: COV-01-001

Sub-protocol for Candidate Agent: Lanadelumab-IV

Short Title: COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY)

Study Phase: 3

Candidate Agent Owner: Takeda Development Center Americas

Legal Registered Address: 95 Hayden Avenue, Lexington, MA 02421, USA

Regulatory Agency Identifying Number(s): **IND 150485**
EudraCT 2020-002594-10

Date of Sub-protocol: 26 October 2020

Version: 1.2

Candidate Agent Owner Contact:

PPD

Candidate Agent Owner (Takeda) Signatory:

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

PPD

PPD

Takeda Development Center Americas

Date

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

PROTOCOL VERSION SUMMARY

Protocol Version 1.2

Protocol Version 1.2 (dated 26 October 2020) replaces the final Version 1.1 protocol (dated 20 October 2020). The version incorporates the following main changes:

- In the Schedule of Activities:
  - Clarifies procedures for obtaining/recording patient height and weight.
  - Removes the optional clinical safety laboratory assessments (hematology, clinical chemistry, and liver function tests) on Days 5, 11, and 18.

Protocol Version 1.1

Protocol Version 1.1 (dated 20 October 2020) replaces the final Version 1.0 protocol (dated 06 October 2020). The version incorporates the following main changes:

- Adds C-reactive protein, lactate dehydrogenase, ferritin, fibrinogen, and D-dimer to the list of pharmacodynamic assessments.
- Clarifies timing of sample collection for pharmacokinetic and pharmacodynamic assessments.

1.0 SUB-PROTOCOL SUMMARY

1.1 Overview of Sub-protocol

Lanadelumab (TAKHZYRO™, TAK-743, formerly SHP643 or DX-2930) is currently approved for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. It is a recombinant, fully human, immunoglobulin G1, kappa light chain, monoclonal antibody and is a highly potent and a specific inhibitor of plasma kallikrein (pKal). pKal is a protease that cleaves high molecular weight kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin. Bradykinin is a potent proinflammatory and vasodilative nonameric peptide responsible for the characteristic symptoms of localized swelling, pain, and inflammation that contributes to several of the deleterious consequences also seen in acute respiratory distress syndrome (ARDS). Blocking bradykinin production with a pKal inhibitor could allow for control over bradykinin production during serious and prolonged coronavirus disease 2019 (COVID-19) illness. One of the most severe complications of COVID-19 is ARDS, a life-threatening condition characterized by an acute onset of lung edema, severe hypoxemia, and loss of pulmonary compliance (Wu et al., 2020). Patients with COVID-19 who develop ARDS have an increased risk of death with a mortality rate exceeding 50% (Wu et al., 2020). While the molecular mechanisms inciting ARDS are not well-elucidated, there is evidence of activation of the kallikrein-kinin system (KKS), also known as the contact activation system, in lung injury (Hess et al., 2017). As a highly potent and specific inhibitor of pKal, lanadelumab could provide persistent control over bradykinin production during serious COVID-19 illness and reduce/prevent ARDS.

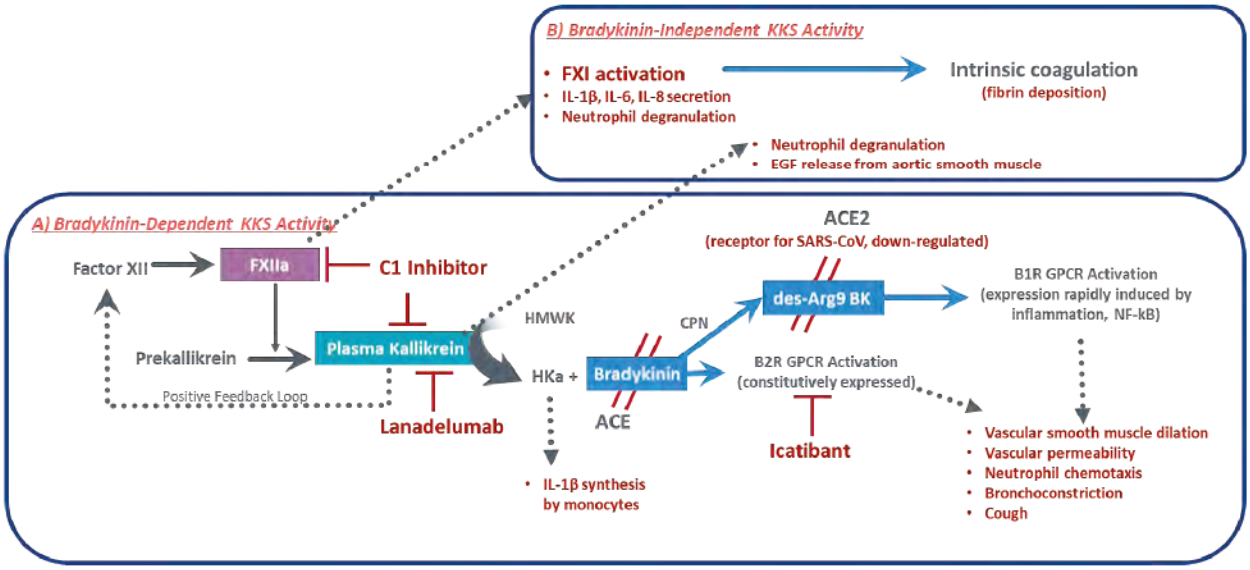
ARDS is characterized as a systemic inflammatory process whereby damage to the endothelium in the pulmonary vasculature results in the influx of immune cells, accumulation of protein-rich edema fluid within the interstitium and alveolus, and secretion of inflammatory cytokines contributing to further disruption of endothelial-alveolar barrier (Thompson, 2017). Activation of the KKS (ie, contact system) in ARDS may occur as a result of endothelial injury and barrier disruption (eg, subendothelial collagen, apoptotic cells, or other negatively charged substances), including virally infected endothelial cells (Taylor et al., 2013).

Once activated, the KKS can contribute to the pathogenesis of ARDS via 2 synergizing mechanisms (Johnson and Matthay, 2010; Wachtfogel et al., 1983; Abdallah et al., 2010; Toossi et al., 1992; Hess et al., 2017; Wachtfogel et al., 1986; Khan et al., 2006; Qadri and Bader, 2018):

- The cleavage of HMWK to produce bradykinin, a potent vasodilator and cause of edema; and
- The activation of coagulation factor XII (FXII) through a positive feedback loop which in turn leads to the activation of inflammatory cells, the production of proinflammatory cytokines, and initiation of the intrinsic coagulation pathway.

Plasma and bronchoalveolar lavage fluid from patients with ARDS indicate excess generation of coagulation factor XIIa, pKal activity, and bradykinin via contact system activation (Hess et al., 2017; Velasco et al., 1986; Carvalho et al., 1988). This suggests there may be a treatment opportunity by intervening early with modulators of the KKS (Figure 1) in patients with pneumonia from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) before progressing to ARDS requiring intensive respiratory support and invasive mechanical ventilation. Targeting the KKS has been recently proposed as a therapeutic strategy for COVID-19 patients in respiratory distress (van de Veerdonk et al., 2020). Treatment for ARDS for the severely affected portion of the COVID-19 patients will play an important role in decreasing the mortality of the disease (Zhou et al, 2020).

Figure 1 Potential Role of the Kallikrein-kinin System in Lung Inflammation and Hypercoagulability in Coronavirus Disease 2019



ACE=angiotensin-converting enzyme; ACE2=angiotensin-converting enzyme 2; B1R=bradykinin B1 receptor; B2R=bradykinin B2 receptor; C=component; CPN=carboxypeptidase N; des-Arg9 BK=bradykinin metabolite; EGF=epidermal growth factor; F=coagulation factor; GPCR=G-protein coupled receptor; HKa=kallikrein-cleaved HMWK; HMWK=high molecular weight kininogen IL=interleukin; KKS=kallikrein-kinin system; NF-κB=nuclear factor kappa B; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

1.2 Schedule of Activities

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
ELIGIBILITY						
Informed consent	X					
Demographics	X					
Relevant medical history[b]	X					
Review of SARS-CoV-2 diagnostic tests (obtained during the previous 72 hours, if available)	X					
SARS-CoV-2 diagnostic test[c]	X					
Inclusion and exclusion criteria	X	X				
12-lead electrocardiogram	X		***Date of discharge only***			
STUDY INTERVENTION						
Randomization		X				
Administration of Study Drug[d]		***X***	***Day 4***			
Treatment with SoC		SoC will be based on the practices of the study center				
STUDY PROCEDURES						
Physical examination (including height, weight)[e]	X					
Vital signs, including body temperature, pulse rate, blood pressure, respiratory rate, SpO_2, FiO_2[f]		X[g]	X	X[h]	X[h]	
CCI						
Ordinal scale		X[g]	X	X	X	X

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
Clinical assessments[i]		X[g]	X	X	X	X[j]
Assessment of floor status (ICU yes/no)		X	X[h]	X[h]	X[h]	
Assessment of rehospitalization for discharged patients[k]				X	X	X
Concomitant medication review (including use of vasopressors)	X	X[g]	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X
SAFETY LABORATORY						
Clinical safety laboratory assessments	X[l,m]	X[g,n,o]	Days 3[p], 8[n], 22[n], and at discharge[n,q] All other days while in hospital[r]	X[n,s]	X[n]	
Pregnancy test for females of childbearing potential	X[l]					
RESEARCH LABORATORY						
CCI [redacted]						
PK[t]		***X***	***Days 4, 7***	***X***	***X***	
PD[t]		***X***	***Days 4, 7***	***X***	***X***	
Plasma antidrug antibody sample[u]		***X***		***X***	***X***	

Abbreviations: Ang2=angiopoietin 2; ARDS=acute respiratory distress syndrome; cHMWK=cleaved high molecular weight kininogen; COVID-19=coronavirus disease 2019; CRP=C-reactive protein; eCRF=electronic case report form; FDP=fibrin degradation products; FiO_2=fraction of inspired oxygen; ICU=intensive care unit; IFN= interferon; IL=interleukin; IV=intravenous; LDH=lactate dehydrogenase; CCI [redacted]; PAI-1=plasminogen-activator inhibitor-1; PD=pharmacodynamic; PK=pharmacokinetic; pKal= plasma kallikrein; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoC=standard of care; SpO_2=oxygen saturation; TNF=tumor necrosis factor.

Note: Additional assessments for this sub-protocol are highlighted in bold and italics.

[a] These visits will be performed even if a patient has already been discharged. If discharged prior to scheduled visit, these visits will be conducted via telemedicine. For visits conducted by telephone, it may not be possible to perform some scheduled assessments (eg, vital signs). The Day 29 assessments will also be performed, where possible, for patients who discontinue the study prematurely.

[b] Medical history includes estimated date and time of first COVID-19 related symptoms and co-morbidities (eg, respiratory [including date of diagnosis of ARDS, if present], cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, renal).

[c] Oropharyngeal/nasal swab for polymerase chain reaction determination of SARS-CoV-2 or for SARS-CoV-2 antigen testing. Only to be performed if no diagnostic test results are available that have been obtained during the previous 72 hours.

[d] ***Study drug must be infused over a period of 60 minutes ± 15 minutes. Study drug administration start and stop times must be recorded in source documents and the eCRF. The clock time of the second infusion should be approximately the same as the first infusion.***

[e] If height and/or weight cannot be obtained at the Screening Visit (Day -1 or Day 1), these parameters can be recorded as a combination of patient-reported data and data obtained from recent medical records (ie, at hospital admission).

[f] For patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation only, provide FiO_2 requirement.

[g] Baseline assessments should be performed prior to study drug administration.

[h] To be assessed only while hospitalized.

[i] Includes oxygen requirement (ie, mode of delivery/liters of oxygen flow, FiO_2 requirement), stop date of oxygen for patients who were discharged on home oxygen, extracorporeal membrane oxygenation support, noninvasive or invasive ventilator requirement, including start and stop of low- or high-flow oxygen supply or of any form of ventilation, and need for renal replacement therapy. Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.

[j] Only stop date of oxygen for patients who were discharged on home oxygen.

[k] Information recorded is yes/no, hospitalization date, discharge date.

[l] Laboratory tests performed within the 48 hours prior to enrolment will be accepted for determination of eligibility.

[m] Hematology and clinical chemistry.

[n] Hematology, clinical chemistry, liver function tests, cardiac panel, and coagulation.

[o] Any laboratory tests performed as part of routine clinical care can be used for safety laboratory testing.

[p] Hematology, clinical chemistry, and liver function tests.

[q] If not done or entered into the eCRF within previous day.

[r] Hematology, clinical chemistry, and liver function tests will be collected on the eCRF, if available, while the patient is in hospital.

[s] This assessment will be performed on Day 15 or date of discharge, if earlier.

[t] ***Samples for PK/PD assessments will be collected temporally as close as possible to Hour 0 (start of study drug infusion/dosing) within 60 minutes before the infusion as well as at the end of the infusion on Day 1 (within 30 minutes post infusion). If feasible, samples for PK and PD will be collected at Days 4, 7, 15, and 29 (or hospital discharge, if earlier) at any time during the day. Start and end of study drug infusion times (day, hour, minute) for each dose should be accurately recorded per 24-hour clock. All PK/PD sampling times (day, hour, minute) should be accurately recorded per 24-hour clock. No sample collection is required after discharge.*** CCI [redacted]

[u] ***Antidrug antibody samples will be collected at Day 1 (pre-infusion within 30 minutes before the infusion) and at Days 15 and 29 (or hospital discharge, if earlier).***

1.3 End of Study Definition for Sub-protocol

The Master Protocol defines the end of study for the overall platform study.

For this specific sub-protocol, the end of the study will be defined as the date on which the last patient randomized to this sub-protocol completes the last scheduled procedure as shown in the Schedule of Activities (SoA; Section 1.2).

2.0 BACKGROUND/RATIONALE IN SUPPORT OF LANADELUMAB-IV IN COVID-19

Since the start of the COVID-19 pandemic, the Candidate Agent Owner (Takeda) has received anecdotal reports from physicians in Brazil, Italy, and the Netherlands who have produced positive clinical outcomes in patients with COVID-19 by treating with repeat doses of icatibant. A case-control study reporting these findings from the Netherlands has been recently published (van de Veerdonk et al., 2020). Icatibant is a competitive antagonist selective for the bradykinin receptor B2, with an affinity similar to bradykinin, that is currently approved for the treatment of acute attacks of HAE in adults 18 years of age and older. Icatibant inhibits bradykinin from binding to the B2 receptor and thereby treats the clinical symptoms of an acute, episodic attack of HAE (Firazyr, 2015).

The clinical observation that COVID-19 can lead to fluid extravasation and accumulation within the lungs has led some treating physicians in Europe to utilize icatibant in critically ill patients. Preliminary observations (along with a separate ongoing investigator-sponsored study) indicate positive outcomes with icatibant, suggesting that sustained inhibition of bradykinin signaling may provide clinical benefit throughout the course of COVID-19 by preventing proinflammatory effects and fluid extravasation and accumulation within the lungs. As icatibant has a short halflife ($t_{½}$) of approximately 1.4 hours after a single subcutaneous 30 mg dose (Firazyr, 2015), a medication with a significantly longer $t_{½}$ which modulates the KKS and reduces the production of bradykinin may impart additional therapeutic benefit. In contrast to icatibant, lanadelumab has a longer $t_{½}$ of approximately 14 days (Takhyzro, 2018), which Takeda hypothesizes should allow for superior control over bradykinin production during serious and prolonged COVID-19 illness. In addition, given that lanadelumab is a pKal inhibitor, it is reasonable to hypothesize that pKal inhibition may help to reduce inflammation and coagulation driven by FXII, which is activated by pKal through a positive feedback loop (Kenniston et al., 2014). Additionally, it has the advantage of reducing activation of the B1 receptor by des-Arg9 BK, a bradykinin metabolite. Bradykinin B1 receptor has been found to be upregulated in response to tissue injury or inflammation (Passos et al., 2004).

It is believed that the validated lanadelumab mechanism of action, coupled with the available literature and anecdotal reports of icatibant use in COVID-19, provide a reasonable rationale for evaluating the efficacy and safety of lanadelumab in patients hospitalized with COVID-19.

2.1 Benefit/Risk Assessment

Based on the mechanism of action of lanadelumab, there is strong scientific rationale and high unmet medical need to evaluate the use of lanadelumab as a therapy for KKS-mediated inflammation associated with COVID-19.

ARDS is a life-threatening condition characterized by an acute onset, lung edema formation, severe hypoxemia, and loss of pulmonary compliance (Johnson and Matthay, 2010). Lung trauma, including viral infection with SARS-CoV-2 infection, can lead to ARDS, which is associated with severe inflammatory (influx of inflammatory cells and cytokine production) and procoagulant activity in the airways that can result in tissue and organ damage (Johnson and Matthay, 2010; Wu et al., 2020).

There exists a serious unmet medical need in patients hospitalized with COVID-19 pneumonia. Therefore, the main goal in managing patients hospitalized with COVID-19 pneumonia is to provide supportive care and monitor for complications including ARDS. Treatment of progressive ARDS is primarily supportive and includes invasive mechanical ventilation. The best strategy to improve patient outcomes is to reduce or prevent ARDS. This could not only improve patient outcomes, but also reduce intensive care management which may strain already limited healthcare resources.

Clinical evidence supports the need for early intervention in patients hospitalized with COVID-19 pneumonia. Studies of Chinese patients hospitalized for COVID-19 show that development of ARDS can occur within a median time of 2 days from the date of admission (Huang et al., 2020; Wu et al., 2020). Therefore, lanadelumab administered intravenously (IV) soon after hospital admission could benefit patients with respiratory symptoms and reduce/prevent ARDS; thereby avoiding the need for invasive mechanical ventilation.

The overall risk in this patient population is outweighed by the potential benefits of lanadelumab. Therefore, the benefit-risk appears to be favorable and supports treatment with IV lanadelumab (Lanadelumab-IV) in this patient population. Details on the use of the IV route of administration is discussed in Section 2.2.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of lanadelumab may be found in the Investigator's Brochure and Package Insert.

2.2 Dose Justification for Lanadelumab-IV

The 300 mg dose via IV administration is chosen for this trial based on the following rationale:

Previously reported measurements of prekallikrein consumption in plasma indicate that the extent of ongoing KKS activation in ARDS (estimated on the basis of prekallikrein consumption to generate between 170 and 300 nM pKal in the plasma) may be greater than in patients with HAE (estimated pKal: 20 to 186 nM) (Velasco et al., 1986; Carvalho et al., 1988; Schapira et al., 1983; Cugno, 1988; Sexton et al., 2017). As lanadelumab is a tight binding inhibitor, excess levels of pKal activity are expected to be controlled by approximately stoichiometric drug concentrations in plasma. The pharmacokinetic (PK) and pharmacodynamic (PD) properties of lanadelumab have been well characterized in patients with HAE following

subcutaneous (SC) administration with a population PK/PD modeling and simulation approach (using cHMWK as an indirect inhibition marker). Following SC administration of 300 mg of lanadelumab every 2 weeks (approved dosage for HAE indication), the time to maximum concentration (T_{max}) was 4 days or later with maximum concentration (C_{max}) of approximately 34 µg/mL, which may not meet the treatment needs in patients with progressing COVID-19 illness; therefore, IV administration is proposed.

IV administration will provide much earlier T_{max} (approximately 1 hour for 60 minutes of infusion) as compared to SC administration. Since high variability in the time course and severity of COVID-19 pneumonia has been reported, a 300 mg dose on Day 1 with an additional dose administered after 3 days (ie, on Day 4) are considered to meet such exposure requirements based on the clinical pharmacology properties of lanadelumab. To support the safety evaluation, exposure to Lanadelumab-IV was predicted by simulation using a 2-compartment IV model with PK parameters estimated by fitting the model to mean values of lanadelumab concentrations in HAE clinical studies, for a single 300 mg IV infusion, and 300 mg IV infusion on Day 1 and Day 4 (Table 1). Although Takeda has not tested the IV route of administration in the HAE clinical trials, the exposure (predicted C_{max} and area under the concentration-time curve) to lanadelumab is comparable to the exposure observed in the clinical package; the sufficient safety margins for the proposed IV dosing regimen by the nonclinical HAE package are provided (Table 1) using No Observed Adverse Effect Level exposure observed in both Good Laboratory Practice (GLP) and non-GLP monkey toxicity studies.

Thus, the IV route of administration is proposed for the study in patients hospitalized with COVID-19 pneumonia. One dose will be administered on Day 1, and a second dose will be administered on Day 4. Two Phase 1 studies utilizing lanadelumab via IV administration are currently ongoing. TAK-743-1002, a Phase1b study in patients with COVID-19, has not yet enrolled. However, TAK-743-1003, a Phase 1a healthy volunteer study, has completed enrollment and dosing. Preliminary, blinded interim safety data available at the time of this subprotocol finalization have shown no safety signals.

Table 1 Predicted Clinical Exposure Margins Compared to Observed Exposure (NOAEL) in Cynomolgus Monkeys

Cynomolgus Monkey Exposure (NOAEL)		GLP Toxicity Repeat-Dose IV Study (Day 21 to 28)	Non-GLP Tolerability Single-Dose IV Study (Day 0 to 28)
AUC_{last} (µg*hr/mL)		123000	137500
C_{max} (µg*mL)		1640	1155
Human 300 mg[a]		**Safety Margin**	
AUC_{0-672} (µg*hr/mL)	17281	7.1	8.0
C_{max} (µg*mL)	94.1	17	12
Human 2×300 mg[b]		**Safety Margin**	
AUC_{0-672} (µg*hr/mL)	33532	3.7	4.1
C_{max} (µg*mL)	130	13	8.9

AUC_{0-672}=area under the plasma concentration-time curve from time 0 to 672; AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last concentration measured; C_{max}=maximum plasma concentration; GLP=Good Laboratory Practice; IV=intravenous(ly); NOAEL=No Observed Adverse Effect Level.

[a] Infused over 60 minutes on Day 1.

[b] Infused over 60 minutes on Days 1 and 4 (individual doses separated by 3 days).

3.0 STUDY POPULATION

3.1 Enrolment and Screening

Refer to the Master Protocol for enrolment and screening procedures.

3.2 Eligibility Criteria

Overall inclusion and exclusion criteria are presented in Sections 5.1 and 5.2 of the Master Protocol, respectively. Patients must meet all inclusion criteria and no exclusion criteria for the Master Protocol to be considered for inclusion in this COV-01-001 sub-protocol.

The following sections detail variations to those criteria that are specific to this sub-protocol.

3.2.1 Inclusion Criteria

No additional criteria.

3.2.2 Exclusion Criteria

Additional exclusion criteria that are specific to the sub-protocol are as follows:

X1. Known or suspected hypersensitivity to lanadelumab or any of its excipients.

X2. Previous (within 3 months prior to baseline) or current use of immunomodulators (eg, methotrexate, azathioprine, 6-mercaptopurine, tumor necrosis factor [TNF] α inhibitor, Janus kinase [JAK] inhibitor, alpha-integrin inhibitor).

X3. Known or suspected venous thromboembolism.

X4. Previous (within 3 months [or 5 half-lives, whichever is greater] of screening) or current use of pKal inhibitor or bradykinin receptor blocker.

3.3 Primary Analysis Population

The analyses on the primary and key secondary efficacy endpoints, as defined in the Master Protocol, will be performed in the Primary Analysis Population for this sub-protocol.

The Primary Analysis Population for this sub-protocol will consist of randomized patients with a baseline clinical severity status of Grade 3 to 5 on the 8-point ordinal scale of clinical severity.

Consistent with Section 9.1 of the Master Protocol, the planned sample size for this sub-protocol, a total of 490 events between the lanadelumab plus standard of care group and placebo plus standard of care group, as well as the target randomized population of 350 patients per group to achieve these events, are both applicable to the Primary Analysis Population made of patients of Grade 3 to 5 at baseline. Patients of baseline Grade 2 are enrolled in addition to these totals.

3.4 Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

The reason for and date of discontinuation from study treatment and/or from study participation will be collected for all randomized patients who prematurely discontinue study treatment or participation.

3.4.1 Discontinuation of Study Treatment

A patient in this study may discontinue the study treatment per the criteria listed in Section 7 of the Master Protocol.

3.4.2 Patient Discontinuation/Withdrawal from the Study

In addition to the criteria listed in the Master Protocol, a patient in this study may withdraw from the study for any of the reasons detailed below:

- Candidate Agent Owner or its designee stops the patient's participation in this sub-protocol or Candidate Agent Owner stops the sub-protocol for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

4.0 STUDY ASSESSMENTS AND PROCEDURES

In addition to the study assessments and procedures described in Section 8.0 of the Master Protocol, assessments specific to this COV-01-001 sub-protocol will be performed as described in the following sections. The SoA for this sub-protocol is presented in Section 1.2.

4.1 Safety Assessments

- Treatment-emergent AEs, including serious AEs (SAEs) and AEs of special interest (AESI; Section 4.1.1.2)

4.1.1 Adverse Events

4.1.1.1 Adverse Events from Approved Indications

The safety and tolerability of lanadelumab have been well characterized in HAE patients following SC administration.

Lanadelumab was approved by the US Food and Drug Administration on 23 August 2018 for prophylaxis to prevent attacks of HAE in patients aged 12 years and older. The safety, tolerability, efficacy and PK and PD results from these studies to date demonstrate that lanadelumab is safe and efficacious in HAE patients and have served as the basis of submissions for global expansion.

Per the reference labeling US Prescribing Information, the most common adverse reactions are injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea. Other adverse reactions that occurred at a higher incidence in lanadelumab-treated patients compared to placebo include hypersensitivity, increased aspartate transaminase, and increased alanine transaminase.

Hypersensitivity is an important identified risk and is discussed in the warnings and precautions of the reference labelling. Immunogenicity and liver toxicity (European Union-specific) are important potential risks for lanadelumab and are monitored closely. Based on the review of the safety data from the completed and ongoing clinical trials, the known cumulative exposure and continuous pharmacovigilance monitoring for the risks, the benefit-risk continues to be favorable. Always refer to the latest version of the lanadelumab Investigator's Brochure for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of lanadelumab.

4.1.1.2 Adverse Events of Special Interest

AESI will be captured and monitored during this study. Investigators will report all AESI to CCI, regardless of causality, using the same timelines as described for SAE reporting (ie, within 24 hours of awareness). This information will be further distributed to the Sponsor (Amgen) and Candidate Agent Owner (Takeda).

The following are defined as AESI for Lanadelumab-IV in this protocol:

- Hypersensitivity reactions; and
- Events of disordered coagulation.

Predefined AESI in registrational clinical studies of lanadelumab in HAE patients were hypersensitivity reactions and disordered coagulation (bleeding events or hypercoagulable events). The incidence of hypersensitivity in the lanadelumab-treated population was low with no events of anaphylaxis reported and no antidrug antibodies (ADA) detected in these patients. The incidence of disordered coagulation was similarly low with no cases of related bleeding or hypercoagulable events.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration.

Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although activated partial thromboplastin time prolongation due to pKal inhibition is an artifactual in vitro phenomenon attributed to an interaction with the laboratory test, as a precautionary measure in evaluating the safety of Lanadelumab-IV, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (Appendix 2) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

4.1.1.3 Safety Reporting

All SAEs, AESI, and overdoses will be recorded and reported to CCI Safety within 24 hours after becoming aware of its occurrence. The initial and follow-up reports should be made using the Electronic Data Capture tool. If necessary, as a backup, reports can be made by e-mail or facsimile (fax). The contact details are:

CCI [redacted]

The CCI [redacted] Medical Safety Advisor (or designee) must also be notified within 24 hours should any patient experience an SAE. Contact information for the SAE Coordinator will be provided on the SAE form/completion instructions.

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

4.1.2 Clinical Safety Laboratory Assessments

Blood samples will be collected for safety assessments during hospitalization, in accordance with the SoA (Section 1.2) and Appendix 2. Safety parameters will be the same as those included in the Master Protocol, with the addition of fibrin degradation products.

4.2 Pharmacokinetic Assessments

Plasma samples for PK analysis will be collected temporally as close as possible to Hour 0 (start of study drug infusion/dosing) within 60 minutes before the infusion as well as at the end of the infusion on Day 1 (within 30 minutes post infusion). If feasible, plasma samples for PK analysis will also be collected on Days 4, 7, 15, and 29 (or hospital discharge, if earlier) at any time during the day (Section 1.2). All PK sampling times (day, hour, minute) should be accurately recorded per 24-hour clock. No sample collection is required after discharge. PK samples are to be shipped to the study central laboratory and routed to a specialty laboratory for analysis.

CCI [redacted]

4.3 Pharmacodynamic Assessments

Blood and plasma samples for PD analyses will be collected temporally as close as possible to Hour 0 (start of study drug infusion/dosing) within 60 minutes before the infusion as well as at the end of the infusion on Day 1 (within 30 minutes post infusion). If feasible, samples for PD analyses will also be collected on Days 4, 7, 15, and 29 (or hospital discharge, if earlier) at any time during the day (Section 1.2). All PD sampling times (day, hour, minute) should be accurately recorded per 24-hour clock. No sample collection is required after discharge. CCI [redacted] Samples will be shipped to the study central laboratory and routed to a specialty laboratory for analysis. CCI [redacted]

4.4 Plasma Anti-Drug Antibody Testing

Plasma samples for determination of the presence or absence of neutralizing or non-neutralizing ADA will be collected at Day 1 (pre-infusion) and at Days 15 and 29 (or hospital discharge, if earlier) (Section 1.2). Additional testing may be required in patients who have positive ADA. All sampling times (day, hour, minute) should be accurately recorded per 24-hour clock. Samples will be shipped to the study central laboratory and routed to a specialty laboratory for analysis. CCI [redacted]

4.5 Future Biomedical Research

CCI [redacted]

5.0 STUDY TREATMENT

5.1 Treatment Plan

Patients eligible for treatment will receive either IV administration of lanadelumab diluted in 100 mL sterile 0.9% sodium chloride solution or placebo in a double-blind manner. Study treatment will be administered along with standard of care in line with institutional practice.

Lanadelumab will be supplied by Takeda prepackaged in a study kit. Each study kit will contain one (1) vial of lanadelumab 300 mg/vial liquid form. The comparator product is matching placebo (normal saline [NS], 0.9% sodium chloride) for infusion (provided by the site). Further details are provided in the Pharmacy Manual.

Unblinded pharmacy personnel will be responsible for providing the study drug(s) to the blinded study personnel for dosing as per the randomization scheme.

5.2 Study Drug Administration

Based on the mechanism of action, PK/PD extrapolations, prior experience with lanadelumab in clinical trials, and supportive safety profile based on the existing clinical package, the recommended double-blind dose is an infusion of lanadelumab 300 mg or placebo IV, 1 dose on Day 1 and a second dose on Day 4.

The infusion of lanadelumab or placebo must be administered over a period of 60 minutes ± 15 minutes and must use an infusion set with an in line, sterile, non-pyrogenic, low protein-binding filter (pore size of 0.2 µm or less). Infusion should begin within 3 hours of preparation. Refer to the Pharmacy Manual for a list of infusion sets and infusion pumps acceptable for use with lanadelumab.

The times of the beginning and the end of infusion will be recorded. Dosing interruptions will be recorded.

5.3 Preparation/Handling/Storage/Accountability

Storage and handling

- Store vials refrigerated at 36°F to 46°F (2°C to 8°C).
- Do not freeze.
- Do not shake.
- Keep the vial in the original carton in order to protect the vial from light.

Preparation

- Lanadelumab-IV will be supplied as a clear to slightly opalescent, colorless to slightly yellow solution. Do not use any vial that appears discolored or contains visible particles. Avoid vigorous agitation of the vial.

- Take the Lanadelumab-IV vial out of the refrigerator 15 minutes before injecting to allow it to equilibrate to room temperature.
- Using aseptic technique, withdraw 2 mL of Lanadelumab-IV from the vial using an 18-gauge needle.
- Following local process, add the Lanadelumab-IV to 100 mL sterile 0.9% sodium chloride infusion bag and infuse over a period of 60 minutes ± 15 minutes on Day 1, followed by a second dose on Day 4.
- For patients assigned to placebo, administer NS via IV infusion over a period of 60 minutes ± 15 minutes on Day 1, followed by a second administration on Day 4.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment, and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment can be found in the Pharmacy Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

5.4 Dose Modifications and Toxicity Management

No dedicated clinical study of lanadelumab has been conducted in patients with renal or hepatic impairment. CCI [redacted]

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the CCI [redacted] Medical Monitor based on the clinical evaluation of the patient.

5.5 Treatment of Overdose

There have been no reports of overdose with lanadelumab.

For this study, any dose of study drug greater than 300 mg in less than a 72-hour time period will be considered an overdose. Investigators should report all overdose events to CCI using the same timelines as described for SAE reporting (ie, within 24 hours of awareness). This information will be further distributed to Takeda.

Takeda does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the CCI Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the electronic case report form.
4. Hold administration of the next dose (if applicable) until further instructions are received from the CCI Medical Monitor.

5.6 Concomitant Medications

No dedicated drug interaction studies have been conducted with lanadelumab.

The use of immunomodulators (eg, methotrexate, azathioprine, 6-mercaptopurine, TNFα inhibitor, JAK inhibitor, alpha-integrin inhibitor) are prohibited during participation in the study.

5.6.1 Rescue Medication

Not applicable to this sub-protocol.

5.7 Study Drug Information

Lanadelumab is currently marketed under the TAKHZYRO tradename as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution currently approved in a single-dose glass vial for SC injection only; injection: 300 mg/2 mL (150 mg/mL) solution.

Takeda intends to use currently approved TAKHZYRO vials to be diluted in 100-mL sterile 0.9% sodium chloride solution bags for IV administration (Luo et al, 2020).

The Lanadelumab-IV and placebo solutions will be administered in the same manner (Section 5.3). The placebo solution will match the active solution in appearance.

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7.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ARDS	acute respiratory distress syndrome
cHMWK	cleaved high molecular weight kininogen
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
des-Arg9 BK	bradykinin metabolite
FXII	coagulation factor XII
GLP	Good Laboratory Practice
HAE	hereditary angioedema
HMWK	high molecular weight kininogen
IEC	Independent Ethics Committee
IL	interleukin
IRB	Institutional Review Board
IV	intravenous(ly)
JAK	Janus kinase
KKS	kallikrein-kinin system
NS	normal saline
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
pKal	plasma kallikrein
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous(ly)
$t_{½}$	half-life
T_{max}	time to maximum concentration
TNF	tumor necrosis factor

Appendix 2 Clinical Laboratory Tests

The minimum tests to be performed are detailed in Table 2, with any additional tests specific for the candidate agent highlighted in bold italics. Clinical laboratory tests will be performed at a local laboratory.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in the Master Protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Changes to some laboratory parameters are anticipated for any patients moving on to extracorporeal membrane oxygenation therapy.

Investigators must document their review of each laboratory safety report.

Table 2 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count Hemoglobin White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	D-dimer test Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International Normalized Ratio (INR) C-reactive protein Ferritin Lactate dehydrogenase (LDH) Procalcitonin ***Fibrin degradation products***
Clinical Chemistry	Potassium Sodium Calcium Magnesium Phosphate Bicarbonate Creatinine Glucose
Liver Function Tests	Alkaline phosphatase Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT)
Cardiac Panel	Creatine kinase (myocardial band [MB] fraction) Triglycerides Troponin

Note: Additional assessments for this sub-protocol are highlighted in bold and italics.

Appendix 3 Signature of Investigator

PROTOCOL TITLE: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

SUB-PROTOCOL NO: COV-01-001

SUB-PROTOCOL FOR CANDIDATE AGENT: Lanadelumab-IV

VERSION: 1.2

This sub-protocol is a confidential communication of the Sponsor (Amgen) and Candidate Agent Owner (Takeda). I confirm that I have read this sub-protocol, I understand it, and I will work according to this sub-protocol, in conjunction with the Master Protocol for the overall platform study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO/Candidate Agent Owner (Takeda).

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

TITLE PAGE

Master Protocol Title: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

Sub-protocol Number: COV-01-004

Sub-protocol for Candidate Agent APREMILAST

Short Title: COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY)

Study Phase: 3

Sponsor Name: Amgen, Inc.

Legal Registered Address: **1 Amgen Center Drive**
Thousand Oaks, CA 91320, US

Regulatory Agency Identifying Number(s): **IND 150485**
EudraCT 2020-002594-10

The Sponsor is conducting this study to determine whether apremilast can safely and effectively be used to treat COVID-19 in accordance with the United States Secretary of the Department of Health and Human Services' (HHS's) Declaration under the Public Readiness and Emergency Preparedness (PREP) Act for medical countermeasures against COVID-19 (COVID-19 Declaration) effective 04 February 2020. The purpose of this study is to test whether apremilast results in clinical benefit in patients hospitalized with COVID-19. This study is authorized to proceed under an approved Investigational New Drug (IND) application in accordance with the public health and medical response of Food and Drug Administration (FDA), an Authority Having Jurisdiction as described under the PREP Act, to prescribe, administer, deliver, distribute or dispense this Covered Countermeasure as defined by and following the United States HHS's COVID-19 Declaration.

Date of Sub-protocol: 14 April 2021

Version: 4.0

Candidate Agent Owner Contact:

PPD

Candidate Agent Owner:

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

PPD

April 16, 2021

PPD

Date

Amgen, Inc

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY

Protocol Amendment 3 (Version 4.0)

Protocol Amendment 3 (Version 4.0; dated 14 April 2021) replaces the final Protocol Version 3.1 (dated 26 October 2020). The amendment incorporates the following main changes:

- Provides updated apremilast clinical trial data.
- Includes text relative to discontinuation of study treatment and patient discontinuation/withdrawal.
- CCI [redacted]
- To align with the Master Protocol, removes statement that "concomitant treatments will be recorded throughout the study from time of enrollment (including screening) until the End of Study Visit."

Protocol Version 3.1

Protocol Version 3.1 (dated 26 October 2020) replaced the final Protocol Amendment 2 (Version 3.0; dated 08 October 2020). The version incorporated the following main changes:

- In the Schedule of Activities:
  - Clarified procedures for obtaining/recording patient height and weight.
  - Removed the optional clinical safety laboratory assessments (hematology, clinical chemistry, and liver function tests) on Days 5, 11, and 18.

Protocol Amendment 2 (Version 3.0)

Protocol Amendment 2 (dated 08 October 2020) replaced Protocol Amendment 1 (dated 27 August 2020).

The amendment incorporated the following changes:

- Provided Candidate Agent Owner contact information.
- In the Schedule of Activities:
  - Clarified that medical history includes the date of diagnosis of acute respiratory distress syndrome, if present.
  - Clarified that for patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation ***only***, provide FiO2 requirement.
  - Clarified that on Day 1, the National Early Warning Score 2 is to be assessed prior to study drug administration.

  - Added that clinical safety laboratory assessments are to be completed 'all other days while in hospital' and these data are to be collected on the electronic case report form.
- Clarified procedures for the treatment of overdose.

Protocol Amendment 1 (Version 2.0)

Protocol Amendment 1 (dated 27 August 2020) replaced the final Version 1.0 protocol (dated 24 June 2020).

The amendment incorporated the following changes:

- The study design was modified to be a double-blind, placebo-controlled platform study.
  - Schedule of Activities table was updated.
  - Where appropriate, reference to placebo was added (ie, apremilast or placebo).
- Schedule of Activities table was updated to specify that study treatment will be administered as twice daily dosing from Day 1 to Day 14 or until hospital discharge, whichever occurs first.

1.0 SUB-PROTOCOL SUMMARY

1.1 Overview of Sub-protocol

This sub-protocol is designed to assess the efficacy and safety of apremilast plus standard of care (SoC) in patients hospitalized for coronavirus disease 2019 (COVID-19).

This study will evaluate whether apremilast plus SoC could be a useful therapeutic in the current management landscape where patients are hospitalized for progressive respiratory signs and symptoms due to COVID-19.

Twice daily (BID) apremilast 30 mg is the same dose approved for treatment of psoriatic arthritis (PsA), plaque psoriasis (PsO), and oral ulcers associated with Behçet's disease (BD).

1.2 Schedule of Activities

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
ELIGIBILITY						
Informed consent	X					
Demographics	X					
Relevant medical history[b]	X					
Review of SARS-CoV-2 diagnostic tests (obtained during the previous 72 hours, if available)	X					
SARS-CoV-2 diagnostic test[c]	X					
Inclusion and exclusion criteria	X	X				
12-lead electrocardiogram	X					
STUDY INTERVENTION						
Randomization		X				
Administration of study treatment ***BID***		***Daily from Day 1 to Day 14 or until hospital discharge, whichever occurs first***				
Treatment with SoC		SoC will be based on the practices of the study center				
STUDY PROCEDURES						
Physical examination (including height and weight)[d]	X					
Vital signs, including body temperature, pulse rate, blood pressure, respiratory rate, SpO_2, FiO_2[e]		X[f]	X	X[g]	X[g]	
CCI [redacted]						

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days) (End of Study)**
Ordinal scale		X[f]	X	X	X	X
Clinical assessments[h]		X[f]	X	X	X	X[i]
Assessment of floor status (ICU yes/no)		X	X[g]	X[g]	X[g]	
Assessment of rehospitalization for discharged patients[j]				X	X	X
Concomitant medication review (including use of vasopressors)	X	X[f]	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X
SAFETY LABORATORY						
Clinical safety laboratory assessments	X[k,l]	X[f,m,n]	Days 3[o], 8[m], 22[m], and at discharge[m,p] All other days while in hospital[q]	X[m,r]	X[m]	
Pregnancy test for females of childbearing potential	X[k]					
RESEARCH LABORATORY						
Blood for pharmacokinetic assessment			**Day 8**	**X**		
CCI						

Abbreviations: ARDS=acute respiratory distress syndrome; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; FiO_2=fraction of inspired oxygen; ICU=intensive care unit; CCI ; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; SoC=standard of care; SpO_2=oxygen saturation.

Note: Additional assessments, if required, will be defined in the sub-protocol.

[a] These visits will be performed even if a patient has already been discharged. If discharged prior to scheduled visit, these visits will be conducted via telemedicine. For visits conducted by telephone, it may not be possible to perform some scheduled assessments (eg, vital signs). The Day 29 assessments will also be performed, where possible, for patients who discontinue the study prematurely.

[b] Medical history includes estimated date and time of first COVID-19 related symptoms and co-morbidities (eg, respiratory [including date of diagnosis of ARDS, if present], cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, renal).

[c] Oropharyngeal/nasal swab for polymerase chain reaction determination of SARS-CoV-2 or for SARS-CoV-2 antigen testing. Only to be performed if no diagnostic test results are available that have been obtained during the previous 72 hours.

[d] If height and/or weight cannot be obtained at the Screening Visit (Day -1 or Day 1), these parameters can be recorded as a combination of patient-reported data and data obtained from recent medical records (ie, at hospital admission).

[e] For patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation only, provide FiO_2 requirement.

[f] Baseline assessments should be performed prior to study drug administration.

[g] To be assessed only while hospitalized.

[h] Includes oxygen requirement (ie, mode of delivery/liters of oxygen flow, FiO_2 requirement), stop date of oxygen for patients who were discharged on home oxygen, extracorporeal membrane oxygenation support, noninvasive or invasive ventilator requirement, including start and stop of low- or high-flow oxygen supply or of any form of ventilation, and need for renal replacement therapy. Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.

[i] Only stop date of oxygen for patients who were discharged on home oxygen.

[j] Information recorded is yes/no, hospitalization date, discharge date.

[k] Laboratory tests performed within the 48 hours prior to enrollment will be accepted for determination of eligibility.

[l] Hematology and clinical chemistry.

[m] Hematology, clinical chemistry, liver function tests, cardiac panel, and coagulation.

[n] Any laboratory tests performed as part of routine clinical care can be used for safety laboratory testing.

[o] Hematology, clinical chemistry, and liver function tests.

[p] If not done or entered into the eCRF within previous day.

[q] Hematology, clinical chemistry, and liver function tests will be collected on the eCRF, if available, while the patient is in hospital.

[r] This assessment will be performed on Day 15 or date of discharge, if earlier.

1.3 End of Study Definition for Sub-protocol

The Master Protocol defines the end of study for the overall platform study.

For this specific sub-protocol, the end of the study will be defined as the date on which the last patient included within this sub-protocol is assessed or receives an intervention for evaluation in the sub-protocol (ie, last patient last visit), including any additional parts in the sub-protocol (eg, safety follow-up), as applicable.

An individual patient is considered to have completed the study if he/she has had the opportunity to complete the End of Study Visit (Day 60) as shown in the Schedule of Activities (Section 1.2).

2.0 BACKGROUND/RATIONALE IN SUPPORT OF APREMILAST IN COVID-19

Since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (causing COVID-19) in December 2019, this rapidly evolving pandemic has infected 23,964,800 people and has claimed 820,989 lives globally (John Hopkins COVID-19 data source, as of 26 August 2020). Compared to the typical, annual influenza epidemic, COVID-19 is associated with a mortality rate that is 10-fold higher, with a disproportionately higher rate of death among the elderly and individuals with underlying comorbidities (Wu and McGoogan, 2020). Although the vast majority of patients appear asymptomatic, or present with mild symptoms, experience from China has revealed that 14% of patients present with severe disease and 5% have a critical presentation associated with respiratory failure, shock, or multi-organ system dysfunction (Wu and McGoogan, 2020). The morbidity and mortality associated with this illness has been significant; in the United States, 19% of COVID-19 patients with known disposition have required hospitalization, with 6% of all patients requiring intensive care unit (ICU) admission (United States Centers for Disease Control [US CDC], 2020b). The clinical course in severe cases of COVID-19 infection is characterized by a hyperinflammatory immune response and often a rapid progression to acute respiratory distress syndrome (ARDS), resulting in a high ICU mortality rate, ranging from 39% to 72% (United States Centers for Disease Control [US CDC], 2020a). These high ICU mortality rates from China were also observed in Italy, where the ICU mortality was 26% with worse outcomes observed for older patients (≥ 64 years of age, 36%) compared to younger patients (≤ 63 years of age, 15%) (Grasselli et al, 2020).

There is an unmet medical need for effective therapies for COVID-19. Clinical management of the disease has been limited solely to supportive measures, with frequent off-label use of unproven or experimental therapies. Therefore, there is a significant high unmet need for an effective therapy for management of COVID-19. Additionally, recent data from COVID-19 infections have demonstrated an increase in proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor alpha (TNFα), with higher levels being observed in patients with more severe disease (Wu and Chen et al, 2020; Huang et al, 2020). Characterization of the disease to date has identified this inappropriate hyperinflammatory immune response as a key driver leading to the clinical decompensation observed in COVID-19 patients; thus, a therapeutic that mitigates this immune response might be able to alter the clinical disease course.

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that has been approved in adult patients for treatment of PsA, PsO, and BD. Phosphodiesterase 4 is expressed in both the innate and adaptive cellular components of the immune system. Inhibition of PDE4 results in elevation of intracellular cyclic adenosine monophosphate (cAMP) levels, down regulating inflammatory responses through reduced expression of TNFα, IL-23, and other proinflammatory cytokines (Schafer et al, 2014). In addition, inhibition of PDE4 also increases anti-inflammatory cytokines

such as IL-10 (Eigler, 1998). In clinical studies of PsA and PsO, compared to placebo, treatment with apremilast had a significant impact on changes in plasma cytokines, including reduction of inflammatory cytokines TNFα, IL-8, IL-6, IL-17, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), and increase of anti-inflammatory mediators IL-10 and IL-1RA (Schafer et al, 2015; Apremilast Investigator's Brochure).

Since apremilast reduces proinflammatory cytokines, such as IL-6 and TNFα expression, in other inflammatory states, it is hypothesized that apremilast can suppress the hyperinflammatory response associated with COVID-19 and prevent progression of the morbid clinical course. Finally, ibudilast, another PDE4 inhibitor, inhibited TNFα and IL-2 in a lipopolysaccharide-stimulation mouse model of neonatal ARDS, and reduced pulmonary injury in this context (Yang et al, 2020), providing further preclinical rationale in support of evaluating apremilast in treatment of COVID-19 in hospitalized patients.

A detailed description of the chemistry, pharmacology, and safety of apremilast is provided in the Investigator's Brochure.

2.1 Benefit/Risk Assessment

Apremilast has not been evaluated in patients with COVID-19. However, there is some evidence from nonclinical studies that apremilast and another PDE4 inhibitor, ibudilast, may improve pulmonary manifestations in patients with COVID-19. Apremilast is generally well-tolerated and does not have an increased risk of serious infections or other identified risks that could preclude its use in this patient population.

As of 20 March 2021, apremilast had been administered at daily doses ranging from 10 to 105 mg/day to more than 9,000 patients in completed and ongoing clinical studies, approximately 7,235 of whom received apremilast in 30 Phase 2, Phase 3, and Phase 4 studies in multiple indications including PsA, PsO, and BD.

In pivotal Phase 3 studies, BID apremilast 30 mg resulted in statistically significant and clinically meaningful improvements in the signs and symptoms of PsA, PsO, and BD. The most commonly observed treatment-emergent adverse events (ie, those reported in > 5% of patients) have been diarrhea, nausea, headache (including tension headache), upper respiratory tract infections, and nasopharyngitis. The majority of treatment-emergent adverse events of diarrhea, nausea, and headache, occurred within the first 2 weeks of treatment and most resolved within 4 weeks. The majority of reported treatment-emergent adverse events were mild or moderate in severity and resolved while patients continued apremilast treatment. The incidence of serious adverse events was low and comparable between apremilast and placebo treatment groups in the placebo-controlled periods and was not driven by any single preferred term or any specific individual organ toxicity. There was no evidence of an increased risk of serious or opportunistic infections in the Phase 3 studies. The safety profile of apremilast is comparable across its approved indications in PsA, PsO, and BD.

As of 20 March 2021, a total of approximately 10,000 patients have been enrolled in clinical studies in which 9,312 patients have received apremilast; worldwide exposure to commercial apremilast is approximately 736,035 unique patients with a cumulative exposure of 376,044 patient years. In the US, a total of 457,379 patients have been exposed to apremilast since it was approved in March 2014. The safety profile of apremilast in the postmarketing setting remains similar to that observed in the registrational clinical program. The most frequently reported adverse events have been gastrointestinal (diarrhea, nausea, vomiting, abdominal discomfort) and nervous system disorders (headache). The benefit-risk balance of apremilast remains favorable for the approved indications.

In the approved indications, apremilast is initially titrated from 10 mg once daily (QD) to 30 mg BID over the first 5 days of therapy, which is intended to reduce the gastrointestinal symptoms associated with initial therapy. During the initial Phase 1 studies, more patients reported gastrointestinal adverse events at the initiation of apremilast. In general, these events were mild to moderate in severity and did not lead to discontinuation. As a result, a titration regimen was implemented. For this study, as the potential effect of apremilast in the inflammatory cascade is expected to be during the first days of therapy, no titration regimen will be used. It is not expected that the initiation of apremilast without titration will change the risk benefit. Patients will be closely monitored during the 14-day treatment period.

Although risks of treatment with apremilast are known, the benefits for patients with COVID-19 are potential and the absence of effective treatments of COVID-19 complications during this pandemic, warrant investigations such as this study.

The above benefit-risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure or product labeling for further data on apremilast.

2.2 Dose Justification for Apremilast

The apremilast dose to be evaluated in this study is 30 mg BID, the same dose approved for treatment of PsA, PsO, and BD. Inhibition of PDE4 results in the down-regulation of proinflammatory cytokines. In clinical studies of PsA and PsO, compared to placebo, treatment with BID apremilast 30 mg resulted in significant suppression on a range of serum cytokines, including IL-8, MCP-1, MIP-1β, TNFα, IL-6, ferritin, and IL-2 (Schafer et al, 2015). Apremilast pharmacokinetics are not expected to differ between COVID-19 patients and other patient populations and it is expected that apremilast systemic exposures attained with 30 mg BID in the approved indications will also be effective in modulating the increases in proinflammatory cytokines observed in COVID-19 infections and thus help prevent progression of the morbid clinical course (Chen et al, 2020; Huang et al, 2020).

In vitro studies have shown that the half-maximal concentration (IC_{50}) needed to inhibit PDE4 is 0.074 μM and for cytokines including TNFα, interferon gamma (IFN-γ), and IL-12p70 is 0.11, 0.013, and 0.12 μM, respectively (Schett et al, 2010). At the approved dose of 30 mg BID, the

exposures in patients with PsA is approximately 550 ng/mL (1 μM) at steady-state (Study CC-10004-PK-010). These exposures are well above the IC_{50} values required for inhibition of cytokines as well as chemokines.

In a Phase 1 study in healthy subjects (Study CC-10004-PK-007), multiple doses of apremilast were evaluated as QD or BID dosing for 14 days (doses ranging from 40 mg QD to 80 mg QD and 40 mg BID). During the 14 days of dose administration, nausea occurred more frequently during the first week of dosing, and less frequently thereafter. In addition, this study evaluated the frequency of gastrointestinal related adverse events with and without dose titration for 40 mg QD for 14 days. The proportion of subjects who reported nausea was lower in the dose group with titration (44%) compared to the dose group without (78%). Overall, the dose titration group had fewer total number of adverse events reported (34 adverse events with dose titration versus 72 adverse events reported by the group without titration).

Twice daily apremilast 30 mg without titration has been evaluated in 3 Phase 1 studies in healthy subjects and subjects with PsA (N = 106 subjects) for a duration of 4 to 10 days (Studies CC-10004-PK-008, CC-10004-PK-010, and CC-10004-CP-020). This regimen without titration was well-tolerated and there were no discontinuations reported due to gastrointestinal-related adverse events following start of therapy. The most common adverse event observed was headache, followed by nausea, and vomiting, which were mostly mild in severity.

In the setting of COVID-19, in which progression of the clinical course occurs rapidly, apremilast will not be initially titrated since rapid attainment of steady-state exposures to maximize the chance of clinical efficacy is more important than mitigating the incidence of generally mild gastrointestinal symptoms that were largely well-tolerated in studies without titration.

3.0 STUDY POPULATION

3.1 Enrollment and Screening

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained.

3.2 Eligibility Criteria

Overall inclusion and exclusion criteria are presented in Sections 5.1 and 5.2 of the Master Protocol, respectively. Patients must meet all inclusion criteria and no exclusion criteria for the Master Protocol to be considered for inclusion in the COV-01-004 sub-protocol. The following sections detail variations to those criteria that are specific to this sub-protocol.

3.2.1 Inclusion Criteria

No additional inclusion criteria are specific for the sub-protocol.

3.2.2 Exclusion Criteria

Additional exclusion criteria that are specific to the sub-protocol are as follows:

Prior/Concomitant Therapy

X1. Current treatment with apremilast, or another agent of similar mechanism of action, for any indication within 1 week prior to first dose of investigational product.

X2. Concurrent use at screening or randomization of cytochrome P450 (CYP)3A inducers (eg, rifampin, phenobarbital, carbamazepine) within 1 week prior to first dose of investigational product.

Other Exclusions

X3. Known hypersensitivity to apremilast or any excipients in formulation.

3.3 Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

The reason for and date of discontinuation from study treatment and/or from study participation will be collected for all randomized patients who prematurely discontinue study treatment or participation. A patient may discontinue study treatment or withdraw from the study per the criteria listed in Section 7 of the Master Protocol.

4.0 ADDITIONAL SUB-PROTOCOL STUDY ASSESSMENTS AND PROCEDURES

In addition to the study assessments and procedures described in Section 8.0 of the Master Protocol, assessments specific to the COV-01-004 sub-protocol will be performed as described in the following sections. The Schedule of Activities for this sub-protocol is presented in Section 1.2.

4.1 Pharmacokinetic Assessments

Blood will be collected on Days 8 and 15 for assessment of apremilast concentrations. The date and time of the pharmacokinetic sample collection will be documented on the electronic case report form (eCRF).

4.2 Pharmacodynamic Assessments

CCI [redacted]

5.0 SUB-PROTOCOL STUDY TREATMENT

5.1 Treatment Plan

Patients will receive BID either apremilast 30 mg or placebo in a double-blind manner plus SoC for 14 days or until hospital discharge, death, or discontinuation of investigational product, whichever occurs first.

5.2 Study Drug Administration

The tablet formulation of apremilast or placebo will be provided in a double-blind manner in bottles throughout the entire study.

Double-blind treatment (apremilast or placebo) will be taken orally BID, with doses approximately 12 hours apart, without restriction of food or drink.

The quantity of tablets, type of administration (intact or disintegrated tablets), date/time of each dose, and box number of study treatment are to be recorded on the patient's eCRF.

5.3 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

5.4 Dose Modifications and Toxicity Management

The reason for dose change of study treatment is to be recorded on the patient's eCRF.

The dose of apremilast or placebo is to be reduced as follows:

- Study treatment administration should be reduced to QD in patients with creatinine clearance of < 30 mL/min (estimated by the Cockcroft-Gault equation).
- If gastrointestinal adverse events associated with the start of therapy are not mitigated with antiemetics and/or antidiarrheals, study treatment dosing may be reduced to QD for 1 to 3 days. Thereafter, the dose should be increased to 30 mg BID.
- Study treatment is to be withheld if a patient requires renal replacement therapy, such as hemodialysis. Treatment may be resumed the next day if renal replacement therapy is no longer needed, if prior to Day 14. If dosing is resumed, daily dose will be based on the patient's creatinine clearance.

5.5 Treatment of Overdose

Overdose for this protocol, on a per dose basis, is defined as any amount over the protocol-specified dose of apremilast or placebo (30 mg BID) given to a patient, regardless of any associated adverse events or sequelae. On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the CCI Medical Monitor immediately.
2. Closely monitor the patient for any adverse event/serious adverse event and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the CCI Medical Monitor based on the clinical evaluation of the patient.

5.6 Concomitant Medications

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for excluded medications.

The following medications are prohibited:

- CYP3A inducers (ie, rifampicin, phenobarbital, carbamazepine), see Appendix 2
- Concurrent use of a PDE4 antagonist

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, emphasis is placed on collection of the following concomitant medications:

- vasopressors (eg, dopamine, epinephrine)
- antidiarrheals
- antiemetics
- anticoagulants (eg, heparin, lovenox)
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAIDs)
- antipyretics other than NSAIDs
- antivirals (eg, hydroxychloroquine, lopinavir, ritonavir)
- antifungals
- antibacterial
- antimycobacterials
- antiprotozoans
- immune mediating therapies (eg, INF-β, convalescent serum, immunomodulators taken for underlying comorbid medical conditions)
- angiotensin converting enzymes
- angiotensin receptor inhibitors/blockers
- CYP3A inducers (eg, rifampicin)
- PDE4 antagonists

For concomitant medications, collect name of medication, reason for use, dates of administration (including start and end dates), and dosage information (including dose, unit, and frequency).

5.6.1 Rescue Medicine

Not applicable.

5.7 Study Drug Information

The chemical name of apremilast is acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl].

The 30 mg tablet formulation of apremilast will be provided in bottles throughout the study. Apremilast will be shipped to the site from regional or local drug repositories. All other supplies will be provided by the site.

The placebo will be administered as tablets ready for oral administration matching the active tablets in color, size, and shape.

Apremilast or matching placebo will be taken orally BID, with doses approximately 12 hours apart, without restriction of food or drink.

CCI [redacted]

The quantity of tablets, type of administration (intact or disintegrated tablet), date/time of each dose, and box number of study treatment are to be recorded on the patient's eCRF.

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7.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Explanation
ARDS	acute respiratory distress syndrome
BD	Behçet's disease
BID	twice daily
cAMP	cyclic adenosine monophosphate
eCRF	electronic case report form
FIO_2	fraction of inspired oxygen
IC_{50}	half-maximal concentration
ICU	intensive care unit
IFN-γ	interferon gamma
IL	Interleukin
IPPA	Investigational Product Preparation and Administration
MCP-1	monocyte chemoattractant protein-1
MIP-1β	macrophage inflammatory protein-1 beta
CCI	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
O_2	oxygen
PCR	polymerase chain reaction
PDE4	phosphodiesterase 4
PsA	psoriatic arthritis
PsO	plaque psoriasis
QD	once daily
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoC	standard of care
TNFα	tumor necrosis factor alpha

Appendix 2 CYP3A Inducers

	Strong inducers	Moderate inducers	Weak inducers
CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, phenobarbital, primidone	armodafinil, modafinil, rufinamid

Abbreviations: CYP3A=cytochrome P450 A

Note: Strong, moderate, and weak inducers are drugs that decreases the area under the concentration time curve of sensitive index substrates of a given metabolic pathway by ≥ 80%, ≥ 50% to < 80%, and ≥ 20% to < 50%, respectively.

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

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3. Accessed 09 April 2021.

Appendix 3 Signature of Investigator

PROTOCOL TITLE: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

SUB-PROTOCOL NO: COV-01-004

SUB-PROTOCOL FOR CANDIDATE AGENT APREMILAST

VERSION: 4.0

This sub-protocol is a confidential communication of the Sponsor. I confirm that I have read this sub-protocol, I understand it, and I will work according to this sub-protocol, in conjunction with the Master Protocol for the overall platform study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO/Sponsor.

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

TITLE PAGE

Master Protocol Title: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

Sub-protocol Number: COV-01-005

Sub-protocol for Candidate Agent: Zilucoplan

Short Title: COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY)

Study Phase: 3

Candidate Agent Owner: **UCB Biopharma SRL**

Legal Registered Address: **Allée de la Recherche 60**
1070 Brussels, Belgium

Regulatory Agency Identifying Number(s): **IND 150485**
EudraCT 2020-002594-10

Date of Sub-protocol: 03 November 2020

Version: 1.2

Candidate Agent Owner Contact:

PPD

Translational Medicine, UK Satellite Hub
UCB Biopharma SRL
PPD

Candidate Agent Owner (UCB Biopharma SRL) Signatory:

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

PPD

03 NOV 2020

Date

Translational Medicine, UK Satellite Hub
UCB Biopharma SRL

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

PROTOCOL VERSION SUMMARY

Protocol Version 1.2

Protocol Version 1.2 (dated 03 November 2020) replaces the final Version 1.1 protocol (dated 26 October 2020). The version incorporates the following main changes:

- Updates background information relative to treatments approved and recommended for treatment of coronavirus disease 2019 (COVID-19).
- Clarifies that all patients, regardless of study treatment assignment (zilucoplan or placebo) will receive antibiotic prophylaxis. This clarification affects the following sections:
  - Section 1.2, Schedule of Activities (footnote d).
  - Section 2.3, Benefit/Risk Assessment.
  - Section 3.2, Eligibility Criteria.
  - Section 4.1.1.1, Adverse Events from Zilucoplan.
  - Section 5.6, Concomitant Medications.
- Clarifies criteria for discontinuation of study treatment and discontinuation/withdrawal from the study.

Protocol Version 1.1

Protocol Version 1.1 (dated 26 October 2020) replaced the final Version 1.0 protocol (dated 12 October 2020). The version incorporated the following main changes:

- In the Schedule of Activities:
  - Clarified procedures for obtaining/recording patient height and weight.
  - Removed the optional clinical safety laboratory assessments (hematology, clinical chemistry, and liver function tests) on Days 5, 11, and 18.

1.0 SUB-PROTOCOL SUMMARY

1.1 Overview of Sub-protocol

COVID-19 Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY) is an adaptive, randomized, placebo-controlled platform study, designed to rapidly evaluate candidate agents for the treatment of coronavirus disease 2019 (COVID-19). This sub-protocol will treat hospitalized adult patients (≥ 18 years) who have an active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, as confirmed by laboratory tests and/or point of care tests.

Zilucoplan is a 15-amino acid macrocyclic peptide complement inhibitor designed for the treatment of conditions in which inappropriate activation of complement component 5 (C5) has been demonstrated to play a role.

Zilucoplan will be administered subcutaneously to patients infected with SARS-CoV-2 every day for 14 days (if the patient is discharged before 14 days of treatment, zilucoplan should be stopped at time of discharge or 24 hours before discharge). This sub-protocol outlines the scientific rationale, additional eligibility criteria, treatment schema, and other specifics where different from the Master Protocol.

1.2 Schedule of Activities

	Screening	**Baseline**				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (± 2 days)**	**Day 29[a] (± 3 days)**	**Day 60[a] (± 4 days) (End of Study)**
ELIGIBILITY						
Informed consent	X					
Demographics	X					
Relevant medical history[b]	X					
Review of SARS-CoV-2 diagnostic tests (obtained during the previous 72 hours, if available)	X					
SARS-CoV-2 diagnostic test[c]	X					
Inclusion and exclusion criteria	X	X				
12-lead ECG	X					
STUDY INTERVENTION						
Randomization		X				
Administration of study treatment		***Daily from Day 1 to Day 14 or until hospital discharge, whichever occurs first***				
Treatment with SoC		SoC will be based on the practices of the study center				
Antibiotic prophylaxis		***X***	***X[d]***	***X[d]***	***X[d]***	
STUDY PROCEDURES						
Physical examination (including height and weight)[e]	X					

	Screening	**Baseline**				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (± 2 days)**	**Day 29[a] (± 3 days)**	**Day 60[a] (± 4 days) (End of Study)**
Vital signs, including body temperature, pulse rate, blood pressure, respiratory rate, SpO_2, FiO_2[f]		X[g]	X	X[h]	X[h]	
CCI						
Ordinal scale		X[g]	X	X	X	X
Clinical assessments[i]		X[g]	X	X	X	X[j]
Assessment of floor status (ICU yes/no)		X	X[h]	X[h]	X[h]	
Assessment of rehospitalization for discharged patients[k]				X	X	X
Concomitant medication review (including use of vasopressors)	X	X[g]	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X
SAFETY LABORATORY						
Clinical safety laboratory assessments	X[l,m]	X[g,n,o]	Days 3[p], 8[n], 22[n], and at discharge[n,q] All other days while hospitalized[r]	X[n,s]	X[n]	
Pregnancy test for females of childbearing potential	X[l]					
RESEARCH LABORATORY						
CCI						
Blood (EDTA and SST) for zilucoplan concentration analysis (PK), pharmacodynamic, and exploratory biomarkers[t]		***X***	***Days 3 and 8 (± 1 day) while hospitalized, and day of discharge***	***X[u]***	***X[u]***	

	Screening	Baseline				
Day (± Window)	**Day -1 or Day 1**	**Day 1**	**Daily Until Hospital Discharge (or Daily Until Day 29 While in Hospital)**	**Day 15[a] (± 2 days)**	**Day 29[a] (± 3 days)**	**Day 60[a] (± 4 days) (End of Study)**
Blood (SST) ADA		***X***	***Day of discharge***	***X[u]***	***X[u]***	
CCI						

ADA = anti-drug antibody; ARDS = acute respiratory distress syndrome; C = component; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; eCRF = electronic case report form; EDTA = ethylenediaminetetra-acetic acid; FiO_2 = fraction of inspired oxygen; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICU = intensive care unit; IFNγ = interferon gamma; IL = interleukin; IL-1RA = interleukin-1 receptor antagonist; IP-10 = interferon gamma-induced protein 10; MASP = mannose-associated serine protease; MCP-1 = monocyte chemoattractant protein 1; MIP-1a = macrophage inflammatory protein 1a; CCI ; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoC = standard of care; SpO_2 = oxygen saturation; SST = serum-separating tubes; TNFα = tumor necrosis factor alpha.

Note: Additional assessments for this sub-protocol are highlighted in bold and italics.

[a] These visits will be performed even if a patient has already been discharged. If discharged prior to scheduled visit, these visits will be conducted via telemedicine. For visits conducted by telephone, it may not be possible to perform some scheduled assessments (eg, vital signs). The Day 29 assessments will also be performed, where possible, for patients who discontinue the study prematurely.

[b] Medical history includes estimated date and time of first COVID-19 related symptoms and co-morbidities (eg, respiratory [including date of diagnosis of ARDS, if present], cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, renal).

[c] Oropharyngeal/nasal swab for polymerase chain reaction determination of SARS-CoV-2 or for SARS-CoV-2 antigen testing. Only to be performed if no diagnostic test results are available that have been obtained during the previous 72 hours.

[d] ***Antibiotic prophylaxis decided by the Investigator for a maximum of 28 days starting with the first dose of zilucoplan or placebo (ie, during zilucoplan or placebo treatment and an additional 14 days after cessation of zilucoplan or placebo). Consultation with a local microbiologist and/or infectious disease specialist is recommended to select the antibiotic prophylaxis. Guidelines about treatment and prevention of Neisseria meningitidis-caused meningitis should also be considered. If the patient is discharged prior to finishing antibiotic prophylaxis, it can be confirmed by telephone at Day 29 if prophylaxis was completed at home.***

[e] If height and/or weight cannot be obtained at the Screening Visit (Day -1 or Day 1), these parameters can be recorded as a combination of patient-reported data and data obtained from recent medical records (ie, at hospital admission).

[f] For patients requiring high-flow oxygen, mechanical ventilation (invasive/noninvasive), or extracorporeal membrane oxygenation only, provide FiO_2 requirement.

[g] Baseline assessments should be performed prior to study drug administration.

[h] To be assessed only while hospitalized.

[i] Includes oxygen requirement (ie, mode of delivery/liters of oxygen flow, FiO_2 requirement), stop date of oxygen for patients who were discharged on home oxygen, extracorporeal membrane oxygenation support, noninvasive or invasive ventilator requirement, including start and stop of low- or high-flow oxygen supply or of any form of ventilation, and need for renal replacement therapy. Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.

[j] Only stop date of oxygen for patients who were discharged on home oxygen.
[k] Information recorded is yes/no, hospitalization date, discharge date.
[l] Laboratory tests performed within the 48 hours prior to enrollment will be accepted for determination of eligibility.
[m] Hematology and clinical chemistry.
[n] Hematology, clinical chemistry, liver function tests, cardiac panel, and coagulation.
[o] Any laboratory tests performed as part of routine clinical care can be used for safety laboratory testing.
[p] Hematology, clinical chemistry, and liver function tests.
[q] If not done or entered into the eCRF form within previous day.
[r] Hematology, clinical chemistry, and liver function tests will be collected on the eCRF, if available, while the patient is in hospital.
[s] This assessment will be performed on Day 15 or date of discharge, if earlier.
[t] CCI [redacted]
[u] ***This assessment will be performed if the patient is in the hospital.***

1.3 End of Study Definition for Sub-protocol

The Master Protocol defines the end of study for the overall platform study.

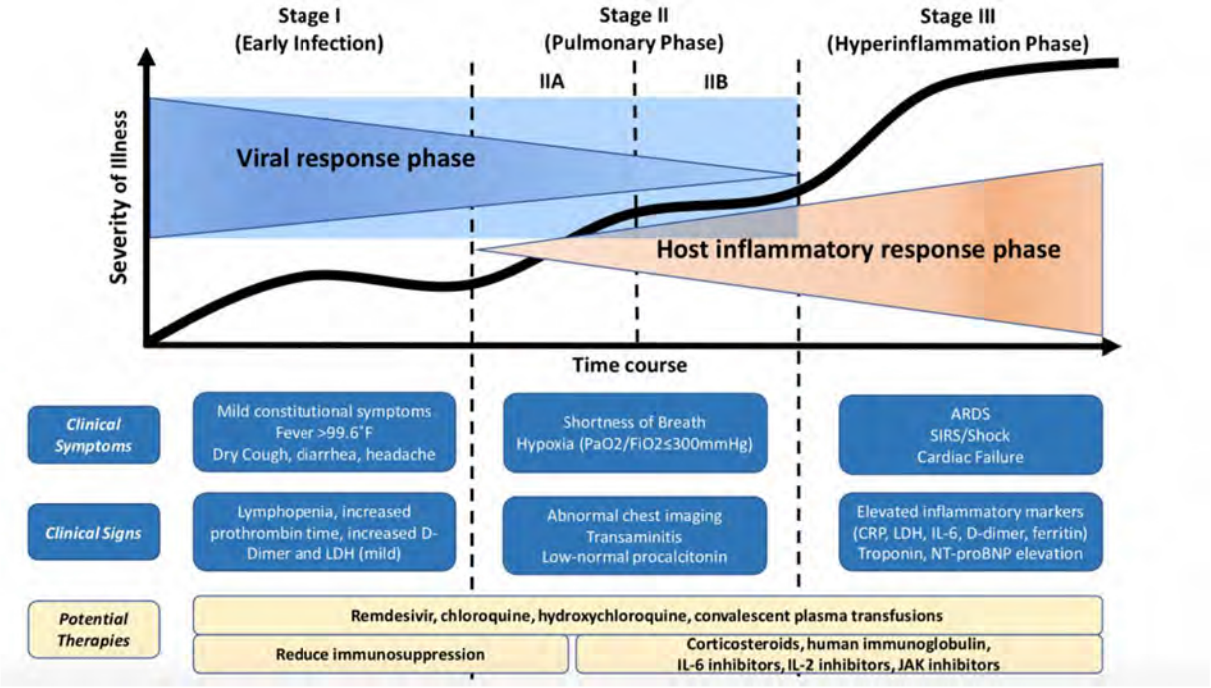
For this specific sub-protocol, the end of the study will be defined as the date on which the last patient randomized to this sub-protocol completes the last scheduled procedure as shown in the Schedule of Activities (SoA; Section 1.2).

2.0 BACKGROUND/RATIONALE IN SUPPORT OF ZILUCOPLAN IN COVID-19

2.1 Background - Inflammation in COVID-19 Infection

Pharmacotherapy targeted against SARS-CoV-2 holds the greatest promise when applied early in the course of COVID-19, but its usefulness in advanced stages may be doubtful. Similarly, use of anti-inflammatory therapy applied too early may not be necessary and could even provoke viral replication such as in the case of corticosteroids. It appears that there are 2 distinct but overlapping pathological subsets, the first triggered by the virus itself and the second by the host response (Figure 1).

Figure 1 Escalating Phases of Disease Progression with COVID-19, with Associated Signs, Symptoms, and Potential Phase-specific Therapies



ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; IL = interleukin; FiO_2 = fraction of inspired oxygen; JAK = janus kinase; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro b-type natriuretic peptide; PaO_2 = partial pressure of oxygen; SIRS = systemic inflammatory response syndrome.
Source: Siddiqi and Mehra, 2020 [12]

Acute respiratory distress syndrome (ARDS) is characterized by severe, acute inflammatory responses in the lung, resulting in diffuse damage to the alveolar-capillary barrier, flooding the airspaces with protein-rich edema fluid, with severe gas-exchange abnormalities as a result. Among well-known causes of ARDS are viral pneumonia caused by influenza and corona viruses such as SARS-CoV (including SARS-CoV2, the strain of coronavirus that causes

COVID-19) and Middle East respiratory syndrome coronavirus (MERS-CoV). Acute respiratory distress syndrome is a cause of death and the main reason for the current need of intensive care unit beds and ventilators to treat patients with COVID-19.

Remdesivir is the only approved treatment in the United States (US) for COVID-19. It is approved for use in adult and pediatric patients 12 years of age and older, who weigh at least 40 kg, for the treatment of COVID-19 requiring hospitalization. In addition, the COVID-19 Treatment Guidelines Panel recommends using dexamethasone for the treatment of COVID-19 in patients who are mechanically ventilated, and in patients who require supplemental oxygen but who are not mechanically ventilated, on the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial. Alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone may also be used. The Food and Drug Administration has also issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product COVID-19 convalescent plasma to treat hospitalized patients with COVID-19.

Currently, limited information is available on the host innate immune status of SARS-CoV-2-infected patients. The descriptions of increased total neutrophils, reduced total lymphocytes, increased serum levels of interleukin (IL)-6, and increased serum levels of C-reactive protein suggest a strong inflammatory response [2]. This is supported further by reports detecting abnormally high plasma levels of innate cytokines such as interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein-1a (MIP-1a); or of high levels of pro-inflammatory cytokines (including IL-2, IL-7, IL-10, granulocyte colony-stimulating factor [G-CSF], IP-10, MCP-1, MIP-1a, and tumor necrosis factor alpha [TNFα]). The overall picture is like other high consequence coronavirus epidemics (SARS-CoV and MERS-CoV) and underlines the fact that leukocyte alterations, dysregulated interferon signaling, and cytokine release syndrome (CRS) could be important in the pathogenesis of COVID-19.

The symptoms of COVID-19 vary from mild to ARDS, the latter of which is generally associated with dysregulated immune cytokine production. Currently, little is known about the interplay between the compositions of the immune responses and the extent of clinical symptoms. Some patient populations (eg, ages > 70 years, patients with co-morbidities) are prone to develop more severe symptoms and require medical interventions. In some severe cases, infection can cause pneumonia, ARDS, kidney failure, and even death [7]. Death results from respiratory failure and is associated in a substantial percentage of patients with an inflammatory syndrome and a cytokine storm with ARDS and features of macrophage activation syndrome/hemophagocytic lymphohistiocytosis that should be better defined [10].

2.2 Evidence for C5 Inhibition in COVID-19

Early defense against coronavirus infections includes a role for the "early" components of the complement pathway, in particular mannose-binding lectin (MBL). In SARS-CoV, the surface S protein contains highly glycosylated, high-mannose structures. Case control studies of 569 patients with SARS and 1188 control subjects identified that MBL of the lectin pathway played a key role in the initiation of the innate immune response and that the distribution of MBL gene polymorphisms was significantly different between patients with SARS and control subjects, with a higher frequency of haplotypes associated with low or deficient serum levels of MBL in patients with SARS than in control subjects [8].

In vitro studies demonstrated that MBL could bind SARS-CoV in a dose- and calcium-dependent fashion, suggesting that binding is through the carbohydrate recognition domains of MBL. These results suggest that MBL contributes to the first-line host defense against SARS-CoV and that MBL deficiency is a susceptibility factor for the acquisition of SARS. It is therefore likely that MBL might play a role in the first-line host defense against SARS-CoV-2.

Currently, there is no evidence that "late" components (ie, component 3 [C3] and C5) of the complement pathway are involved in the defense against SARS-CoV-2; however, aberrant activation of these components by virus-induced cellular damage is thought to promote broad tissue injury in coronavirus infections. Complement activation has long been known to be associated with ARDS and sepsis. Component 5a (C5a), a potent anaphylatoxin, recruits neutrophils to the site of initial damage or infection and drives tissue damage by the release of reactive oxygen species and tissue-degrading enzymes. Component 5a also induces inflammatory cytokines such as IL-8, IL-6, IL-17, and TNFα from a variety of cell types and contributes to the cytokine storm associated with ARDS and sepsis [1, 11, 15].

A report assessing C5a levels, polymorphonuclear granulocyte aggregation, and development of ARDS demonstrated a highly significant relationship between C5a positivity and ARDS; and this was significant even when excluding patients with sepsis from the analysis [5]. Historical studies document the formation of soluble C5b-9 complex in plasma preceding the development of ARDS [9].

A broad role for complement in mediating ARDS-like tissue injury in mouse models has been demonstrated. In a mouse model of SARS-CoV infection, inhibition by knock-out of the late complement pathway (C3-/-) results in protection from disease [4]. Component 3 deficiency eliminates the key component required for C5 activation and, as a result, animals are unable to generate C5a or C5b. In C3-deficient mice, weight loss and respiratory function were significantly improved relative to that of control mice (wild-type C3 background). Neither depletion of component 4 (C4) nor factor B (upstream in the complement cascade to C3) resulted in similar protection. Lung pathology scores were reduced in the C3-/- mice relative to controls. Analysis of the cellular inflammatory response to mouse-adapted SARS-CoV (SARS-CoV

MA15) infection reveals significant reductions in pathogenic inflammatory monocyte and neutrophil populations, both of which are implicated in human SARS-CoV pathology [16], indicating that complement signaling contributes to pulmonary disease and inflammatory cell recruitment. Finally, several pro-inflammatory cytokines, including IL-6, TNFα, IL-1a, and G-CSF were reduced in lungs of C3-/- mice relative to controls. Importantly, no change in viral loads were observed in C3-/- mice, underscoring that inhibiting the late/distal part of the complement cascade does not affect virus neutralization [4].

In another mouse model, MERS-CoV infection-induced inflammation and pyroptosis was found to be mediated by C5a release and nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. Blocking the C5a-Complement C5a Receptor 1 (C5aR1) axis with an anti-C5aR1 antibody, when administered immediately prior to virus inoculation, ameliorated lung inflammation (pyroptosis and macrophage infiltration) together with markers of systemic inflammation [4].

Further support for a role of complement in COVID-19 infection can be found in animal studies of avian influenza viruses. In humans, avian influenza H5N1 virus is associated with ARDS and is histopathologically similar to patients infected with SARS-CoV. In mice, acute lung injury in avian influenza H5N1-infected mice appears to be complement-mediated. C3, C5b-9, and MBL were deposited in lung tissue; and complement receptors C3aR and C5aR were up-regulated. Treatment of H5N1 infected mice with a C3aR antagonist, an anti-C5a monoclonal antibody, or cobra venom factor to deplete complement C3 and C5 significantly alleviated lung inflammation and disease [14]. Likewise, avian influenza H7N9 virus causes lung injury and ARDS resembling the disease in H5N1 and SARS-CoV infected patients.

Infection of African green monkeys with H7N9 virus resulted in intense acute lung injury and systemic inflammatory response syndrome (SIRS) associated with complement activation. Treatment of H7N9-infected monkeys with an intravenously administered monoclonal antibody against C5a substantially attenuated disease, reducing lung histopathological injury and lung infiltration of macrophages and neutrophils. The treatment decreased the intensity of SIRS with minimal changes in body temperature and markedly reduced plasma levels of inflammatory cytokines [14]. These data indicate that excessive complement activation plays an important role in viral-induced lung damage, and that complement inhibition at the level of C3 or C5 may be effective in the treatment of ARDS.

Recent preliminary data assessing an anti-C5a monoclonal antibody in COVID-19 further support the use of C5 inhibition in this illness. A strong deposition of complement components MBL, mannose-associated serine protease (MASP)-2, C4, C3, and C5-9 in the lung tissue of deceased COVID-19 patients was reported, as well as a significant increase in serum C5a levels in patients with severe disease [3]. As expected, activation was via the lectin pathway of complement [8]. Two hospitalized patients were treated with repeated injections of an anti-C5a monoclonal antibody over approximately 13 days. Fever was reduced almost immediately; and

rapid improvements in oxygen saturation, C-reactive protein, lymphocyte numbers, and clinical condition were observed.

Zilucoplan binds complement C5 and blocks generation of the 2 active fragments: C5a, a potent anaphylatoxin and neutrophil chemoattractant; and C5b, a component of the membrane attack complex (MAC), and the subsequent binding of C5b to C6 to assemble MAC. This will block the activation of C5b-9; and the formation of MAC causes endothelial cell and platelet activation, and loss of membrane integrity and lysis/damage in other cell types.

Overall, these data support the conclusion that the use of zilucoplan to inhibit C5, and to prevent the production of C5a and C5b, may be effective in reducing inflammatory cytokine production, neutrophil activation, and ultimately progression to ARDS in patients who have been infected with the SARS-CoV-2 virus.

2.3 Benefit/Risk Assessment

The current world-wide pandemic of COVID-19 is putting unforeseen stress on the entire primary, secondary, and tertiary medical systems, leading to unseen triage of patients that potentially benefit or not from admission to intensive care units when they develop respiratory failure.

Across the program, 196 participants have been exposed to zilucoplan with > 100 patient-years (> 40,000 injections) in healthy study participants, patients with generalized myasthenia gravis (gMG), paroxysmal nocturnal hemoglobinuria (PNH), immune mediated necrotizing myopathy, and renal impairment.

To date, zilucoplan has shown a favorable safety and good tolerability profile across all studies. Completed clinical studies are summarized in Table 1.

Table 1 Exposure to Zilucoplan in Completed Clinical Studies

Dosing	Study Population	Total N Exposed
Single and multiple sc doses up to CCI [redacted]	Healthy study participants	83
Multiple sc doses up to CCI [redacted]	Adult study participants with gMG	78
Multiple sc doses up to CCI [redacted]	Adult study participants with PNH	29
Multiple sc doses up to CCI [redacted]	Adult study participants with IMNM	6

IMNM = immune mediated necrotizing myopathy; gMG = generalized myasthenia gravis; PNH = paroxysmal nocturnal hemoglobinuria; sc = subcutaneous.

CCI [redacted]

No major safety risks have been identified. A difference in the overall adverse event (AE) profiles was seen among the clinical trials in different populations: few AEs occurred in healthy controls and stable renally impaired patients; the AE profile in PNH reflected the hemolytic anemia characteristic of the underlying disease; in the gMG population, many AEs were reflective of multiple comorbidities, longstanding use of corticosteroid and immunosuppressive therapies, and the more advanced age of this population.

Treatment with the approved C5 inhibitors eculizumab and ravulizumab, as well as rare genetic deficiencies in C5, are associated with an increased risk for infection with encapsulated bacteria, most notably *Neisseria meningitidis* (*N. meningitidis*), but not for viral infections generally, or for coronavirus infections in particular. Immune protection against coronavirus infection is understood to rely primarily upon neutralizing humoral immunity and cluster of differentiation 8 cytotoxic adaptive T cell cellular immunity, rather than innate immunity and the complement system. Therefore, C5 inhibition is not expected mechanistically to impair the immune response to coronavirus (or to a vaccine once one is available).

Given the increased risk for *N. meningitidis* infection with complement C5 inhibition or deficit, patients who had received zilucoplan in ambulatory clinical trials were required to have documentation of *N. meningitidis* vaccination (and booster if appropriate) prior to treatment initiation. In addition, while on zilucoplan, patients were monitored closely for signs and symptoms of *N. meningitidis* infection, including self-monitoring based on detailed instructions about the signs and symptoms of possible meningococcal infections.

To prevent the risk of meningococcal disease and prevent other infections with encapsulated bacteria, patients need to receive prophylactic antibiotics (eg, intravenous third generation cephalosporin while in the hospital, followed by oral ciprofloxacin upon discharge until 14 days after the last zilucoplan or placebo administration).

The potential benefits of C5 inhibition by the administration of zilucoplan treatment in COVID-19 patients are considered to outweigh the potential risks associated with this treatment.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of zilucoplan may be found in the Investigator's Brochure.

2.4 Dose Justification for Zilucoplan

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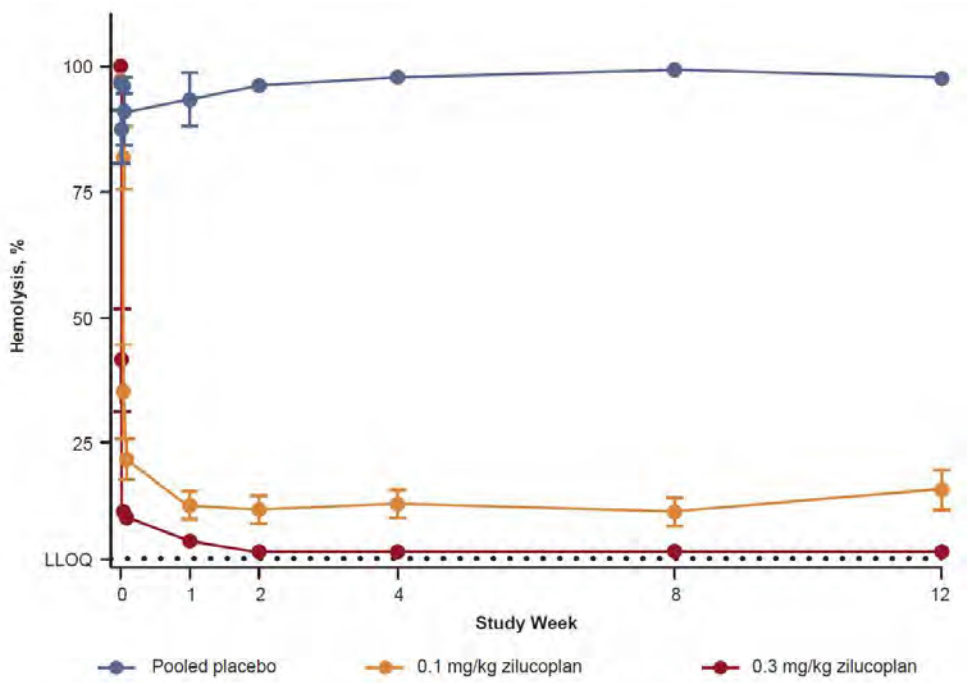
[redacted]

Figure 2 Mean Complement Activity as Measured by Sheep Red Blood Cell Assay (% Hemolysis)



LLOQ = lower limit of quantification.
Source: Howard et al., 2020 [6]

3.0 STUDY POPULATION

3.1 Enrollment and Screening

Refer to the Master Protocol for enrollment and screening procedures.

3.2 Eligibility Criteria

Overall inclusion and exclusion criteria are presented in Sections 5.1 and 5.2 of the Master Protocol, respectively. Patients must meet all inclusion criteria and no exclusion criteria for the Master Protocol to be considered for inclusion in this COV-01-005 sub-protocol.

The following sections detail the variations to those criteria that are specific to this sub-protocol.

3.2.1 Inclusion Criteria

An additional inclusion criterion that is specific to the sub-protocol is as follows:

X1. Antibiotic prophylaxis: PLEASE NOTE that all patients must be willing to take antibiotic prophylaxis concomitantly, starting with the first dose of zilucoplan or placebo.

3.2.2 Exclusion Criteria

An additional exclusion criterion that is specific to the sub-protocol is as follows:

X1. Participants with unresolved or suspected infection with *N. meningitidis* or a past history of *N. meningitidis* (eg, in a complement-deficient patient) should not receive treatment with zilucoplan or placebo.

3.3 Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

The reason for and the date of discontinuation from study treatment and/or from study participation will be collected for all randomized patients who prematurely discontinue study treatment or participation.

3.3.1 Discontinuation of Study Treatment

A patient in this study may discontinue the study treatment per the criteria listed in Section 7 of the Master Protocol. In addition, a patient may discontinue study treatment if UCB or its designee stops the patient's participation in this sub-protocol for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

Regardless of study treatment discontinuation, all patients who maintain consent to be followed for additional outcome information will remain in the study for all important safety and efficacy assessments, as specified in the Master Protocol.

3.3.2 Patient Discontinuation/Withdrawal from the Study

In line with the Master Protocol, a patient in this study may:

- Withdraw himself or herself from the study via withdrawal of consent.
- Be withdrawn from the study due to loss to follow-up.

4.0 STUDY ASSESSMENTS AND PROCEDURES

In addition to the study assessments and procedures described in Section 8.0 of the Master Protocol, assessments specific to this COV-01-005 sub-protocol will be performed as described in the following sections. The SoA for this sub-protocol is presented in Section 1.2.

4.1 Safety Assessments

Safety assessments include treatment-emergent AEs, including serious AEs (SAEs).

4.1.1 Adverse Events

4.1.1.1 Adverse Events from Zilucoplan

To date, zilucoplan has shown a favorable safety and good tolerability profile across all studies in healthy participants and patients with gMG, PNH, immune mediated necrotizing myopathy (IMNM), and renal impairment. No major safety risks have been identified to date, with > 100 patient years of exposure and > 40,000 injections administered in clinical trials. A difference in the overall AE profiles was seen among the clinical trials in different populations: few AEs occurred in healthy controls and stable renally impaired patients; the AE profile in PNH reflected the hemolytic anemia characteristic of the underlying disease; and in the gMG population, many AEs were reflective of multiple comorbidities, longstanding use of corticosteroid and immunosuppressive therapies, and the more advanced age of this population.

Although no meningococcal infections have been identified with zilucoplan treatment to date, it is well established that inhibition of complement C5 and the terminal complement pathway increases the susceptibility to infection with encapsulated bacteria, in particular *N. meningitidis*. This risk is also described in the prescribing information for the approved complement C5 inhibitor eculizumab (Soliris® US Package Insert 2017) [13].

Given the increased risk for *N. meningitidis* infection with complement C5 inhibition or deficit, patients who have received zilucoplan in ambulatory clinical trials were required to have documentation of *N. meningitidis* vaccination (and booster if appropriate) prior to treatment initiation. In addition, while on zilucoplan, patients were monitored closely for signs and symptoms of *N. meningitidis* infection, including self-monitoring based on detailed instruction about the signs and symptoms of possible meningococcal infections.

Considering the acuity of the indication and short duration of treatment (maximum of 14 days), vaccination and induction of humoral immunity prior to initiation of zilucoplan therapy is not feasible in the context of COVID-19. Therefore, the risk of Neisseria infection must be mitigated by the concomitant administration of antibiotic prophylaxis as decided by the Investigator for a maximum of 28 days starting with the first dose of zilucoplan or placebo (ie, during study drug treatment and an additional 14-day period after the cessation of zilucoplan or placebo). Antibiotics can be, eg, intravenous third generation cephalosporin while in the hospital followed

by oral ciprofloxacin upon discharge until 14 days after the last zilucoplan or placebo administration. Consultation with a local microbiologist and/or infectious disease specialist is recommended to select the antibiotic prophylaxis. Guidelines about the treatment and prevention of *N. meningitidis*-caused meningitis should also be considered.

4.1.1.2 Adverse Events of Special Interest

No adverse events of special interest have been defined for zilucoplan in this sub-protocol.

4.1.1.3 Safety Reporting

All SAEs and overdoses will be recorded and reported to CCI Safety within 24 hours after becoming aware of its occurrence. The initial and follow-up reports should be made using the Electronic Data Capture tool. If necessary, as a backup, reports can be made by e-mail or facsimile (fax). The contact details are:

CCI

The CCI Medical Safety Advisor (or designee) must also be notified within 24 hours if any patient experiences an SAE. Contact information for the CCI SAE Coordinator will be provided on the SAE form/completion instructions.

Notification by the Investigator to the Sponsor of an SAE as per the timelines detailed in the safety management plan is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Candidate Agent Owner has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

4.1.2 Clinical Safety Laboratory Assessments

Blood samples will be collected for safety assessments during hospitalization, in accordance with the SoA (Section 1.2) and Appendix 2. The safety parameters will be the same as those included in the Master Protocol.

4.1.2.1 Reviewing and Recording Test Results

The Investigator and/or appropriate designee must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the electronic case report form (eCRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

4.1.2.2 Repeating Testing After Clinically Significant Abnormal Findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Medical Monitor during study participation. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Candidate Agent Owner notified.

4.2 Pharmacokinetic Assessments

Plasma samples (from whole blood collection) will be collected from all patients (placebo and active treatment arms) for the measurement of plasma concentrations of zilucoplan, as specified in the SoA (Section 1.2). Sample analysis may be limited to a select set of samples collected throughout the study. Plasma concentrations of zilucoplan will be summarized descriptively at each scheduled assessment. Plasma concentrations of zilucoplan may be used for population PK modeling and may be combined with data from other studies where plasma concentrations of zilucoplan were collected. The actual date and time (24-hour clock time) of each sample will be recorded in the electronic case report form (eCRF). Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.

CCI [redacted]

4.3 Pharmacodynamic and Biomarker Assessments

Blood samples (plasma and serum) for pharmacodynamic and biomarker analysis will be collected as specified in the SoA (Section 1.2) from all patients (placebo and active treatment arms). Sample analysis may be limited to a select set of samples collected throughout the study.

CCI [redacted]

CCI [redacted]

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the Laboratory Manual for this study. CCI [redacted]

4.4 Anti-drug Antibody Testing

Serum samples (from whole blood collection) will be collected for the evaluation of the presence or absence of ADA response as specified in the SoA (Section 1.2) from all patients (placebo and active treatment arms). Sample analysis may be limited to a select set of samples collected throughout the study.

Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. CCI [redacted]

4.5 CCI [redacted]

CCI [redacted]

5.0 STUDY TREATMENT

5.1 Treatment Plan

Patients eligible for treatment will receive treatment once daily as a sc injection for the planned treatment duration.

5.2 Study Drug Administration

The investigational drug product will be provided in prefilled syringes containing 32.4 mg of zilucoplan (0.81 mL) or placebo for sc injection in the abdomen (preferred site), thigh, or upper arm.

The investigational drug product is placed into a Becton Dickinson UltraSafe Plus device assembled with a finger flange and plunger rod. The prefilled syringes are designed for self-administration.

The prefilled syringes containing 32.4 mg of zilucoplan or placebo will be provided in kits containing 7 prefilled syringes each.

This dose is equivalent to that administered to the highest weight bracket in prior weight-based dosing regimens and is expected to achieve rapid, profound, and sustained complement inhibition with acceptable safety and tolerability.

5.3 Preparation/Handling/Storage/Accountability

Zilucoplan should be stored at 2°C to 8°C (36°F to 46°F) at the study site. Once dispensed, zilucoplan may be stored at room temperature (20°C to 25°C [68°F to 77°F]) for up to 45 days protected from sources of heat, light, and damage. Storage of zilucoplan outside of room temperatures should be avoided. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment, and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

5.4 Dose Modifications and Toxicity Management

To date, zilucoplan has shown good tolerability and a favorable safety profile across studies in healthy participants and patients with renal impairment, PNH, and gMG. No major safety risks have been identified to date.

No dose modifications are anticipated; stopping zilucoplan will be left to the decision of the Investigator in consultation with the CCI Medical Monitor based on the clinical evaluation of the patient.

5.5 Treatment of Overdose

For this study, any dose of zilucoplan or placebo greater than 32.4 mg within a 24-hour time period will be considered an overdose.

It is not anticipated that overdose of zilucoplan or placebo will lead to acute or specific systemic AEs. In the case of overdose, clinically appropriate supportive measures should be instituted as determined by the clinical scenario and in consultation with the CCI Medical Monitor.

In the event of an overdose, the Investigator should:

1. Contact the CCI Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the CCI Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the CCI Medical Monitor based on the clinical evaluation of the patient.

5.6 Concomitant Medications

To mitigate the risk of Neisseria infection, concomitant administration of antibiotic prophylaxis decided by the Investigator is required for a maximum of 28 days starting with the first dose of zilucoplan or placebo (ie, during study drug treatment and an additional 14 days after cessation of zilucoplan or placebo). Consultation with a local microbiologist and/or infectious disease specialist is recommended to select the appropriate antibiotic prophylaxis. Guidelines about treatment and prevention of *N. meningitidis*-caused meningitis should also be considered.

If the patient is discharged prior to finishing antibiotic prophylaxis, it can be confirmed by telephone at Day 29 if prophylaxis is completed at home.

Additional antibiotics can be administered as per the Investigator's judgment.

5.6.1 Dosing with Remdesivir or Dexamethasone

No change in dose is recommended for patients taking both zilucoplan and remdesivir or dexamethasone. Safety monitoring under Early Access to Medicines scheme guidance must be followed as outlined in the Master Protocol.

5.6.2 Rescue Medicine

Rescue medicines are not applicable to this sub-protocol.

5.7 Study Drug Information

Zilucoplan (RA101495) is a 15-amino acid macrocyclic peptide complement inhibitor designed for the treatment of conditions in which inappropriate activation of complement C5 has been demonstrated to play a role. Zilucoplan binds to C5 with high affinity and prevents its cleavage by C5 convertases into the cleavage products C5a and C5b. Inhibition of C5 cleavage prevents the downstream assembly and cytolytic activity of the Mac.

Zilucoplan binds to the domain of C5 that corresponds to C5b. If any C5b is generated, it will be blocked from binding to C6 by zilucoplan, thereby preventing the subsequent assembly of the Mac (C5b-9).

CCI [redacted]

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7.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
C3	Component 3
C4	Component 4
C5	Component 5
C5aR1	Complement C5a Receptor 1
COMMUNITY	COVID-19 Multiple Agents and Modulators Unified Industry Members Trial
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EUA	Emergency use authorization
Fax	Facsimile
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
gMG	Generalized myasthenia gravis
ICU	Intensive care unit
IEC	Independent Ethics Committee
IL	Interleukin
IMNM	Immune mediated necrotizing myopathy
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
JAK	Janus kinase
LDH	Lactate dehydrogenase

Abbreviation	Definition
MAC	Membrane attack complex
MASP	Mannose-associated serine protease
MBL	Mannose-binding lectin
MCP-1	Monocyte chemoattractant protein 1
MERS-CoV	Middle East respiratory syndrome coronavirus
MIP-1a	Macrophage inflammatory protein 1a
NLRP3	NOD-like receptor family pyrin domain containing 3
N. meningitidis	*Neisseria meningitidis*
NOD	Nucleotide-binding oligomerization domain
NT-proBNP	N-terminal pro b type natriuretic peptide
PaO_2	Partial pressure of oxygen
PNH	Paroxysmal nocturnal hemoglobinuria
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIRS	Systemic inflammatory response syndrome
SoA	Schedule of Activities
TNFα	Tumor necrosis factor alpha
US	United States

Appendix 2 Clinical Laboratory Tests

The minimum tests to be performed are detailed in Table 2. Clinical laboratory tests will be performed at a local laboratory.

Protocol-specific requirements for the inclusion or exclusion of patients are detailed in the Master Protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Changes to some laboratory parameters are anticipated for any patients moving on to extracorporeal membrane oxygenation therapy.

Investigators must document their review of each laboratory safety report.

Table 2 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Hemoglobin White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	D-dimer test Fibrinogen Activated partial thromboplastin time Prothrombin time International Normalized Ratio C-reactive protein Ferritin Lactate dehydrogenase Procalcitonin
Clinical Chemistry	Potassium Sodium Calcium Magnesium Phosphate Bicarbonate Creatinine Glucose
Liver Function Tests	Alkaline phosphatase Total bilirubin Aspartate aminotransferase Alanine aminotransferase Gamma-glutamyl transferase
Cardiac Panel	Creatine kinase (myocardial band fraction) Triglycerides Troponin

Appendix 3 Signature of Investigator

PROTOCOL TITLE: Industry Alliance Platform Trial to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalized Patients

SUB-PROTOCOL NO: COV-01-005

SUB-PROTOCOL FOR CANDIDATE AGENT: Zilucoplan

VERSION: 1.2

This sub-protocol is a confidential communication of the Sponsor (Amgen) and Candidate Agent Owner (UCB Biopharma SPRL). I confirm that I have read this sub-protocol; I understand it; and I will work according to this sub-protocol, in conjunction with the Master Protocol for the overall platform study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the contract research organization (CRO)/Candidate Agent Owner (UCB Biopharma SRL).

I have read this sub-protocol in its entirety and agree to conduct this part of the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____