Protocol Title: Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients

Protocol Number: CPI-006-003

NCT Number: NCT04734873

Protocol Version 003 – 23 March 2021

Protocol Version 002 – 11 January 2021

Protocol Version 001 – 06 November 2020

Protocol

Protocol Title:	**Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients**
Protocol Number:	**CPI-006-003**
Regulatory Agency Identifier Number(s):	[redacted] **EudraCT: 2020-005305-54**
Compound Number:	**CPI-006**
Study Phase:	**3**
Sponsor Name:	**Corvus Pharmaceuticals**
Sponsor Address:	**863 Mitten Rd, Suite 102 Burlingame, CA 94010, USA**
Version Number:	**003**
Date Final:	**23 March 2021**

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	003

This clinical trial protocol was subject to critical review and has been approved by Corvus Pharmaceuticals.

[redacted]

Sponsor Signatory **Date**

[redacted]

Medical Monitor Name and Contact Information:

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Cell Phone:	

INVESTIGATOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	003

I have read and understood the current version of the protocol (as listed above). I agree to conduct this trial in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), all applicable regulatory requirements, and the general ethical principles outlined in the Declaration of Helsinki.

I agree to ensure that no deviation from, or changes to the protocol will take place without prior agreement from Corvus Pharmaceuticals and documented approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I will ensure that all staff members under my supervision involved in the conduct of this study are informed about the protocol and protocol amendments, the investigational products, and their study-related duties and functions.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational products and processes or methods of Corvus.

Investigator Signatory Name: **Title:**	**Date**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin converting enzyme 2
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the serum or plasma concentration-time curve
$AUC_{(0\text{-}169)}$	AUC from the start of infusion to 169 hours after the start of infusion
AUC_{last}	AUC from time zero to the time of the last quantifiable concentration
BCR	B cell receptor
$C_{(0)}$	the initial CPI-006 concentration measured 30 minutes after completion of the infusion
CBC	complete blood count
CCP	Covid-19 Convalescent Plasma
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum drug concentration in serum or plasma
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
DLT	dose-limiting toxicity
ELISA	enzyme-linked immunosorbent assay
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	United States Health Insurance Portability and Accountability Act

Abbreviation	Definition
HLA-DR	human leukocyte antigen – DR isotype
IC_{50}	concentration required for 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2, -6, -10	interleukin 2, 6, 10
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MERS	Middle East respiratory syndrome
NEWS2	National Early Warning Score 2
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed adverse effect level
O_2	oxygen
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PD1	programmed cell death 1 receptor
PE	polyethylene

Abbreviation	Definition
PES	polyethersulfone
PK	pharmacokinetic(s)
PO	by mouth (orally)
PO/PE	polyolefin/polyethylene
PT	prothrombin time
PVC	polyvinylchloride
RBC	red blood cell
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sickle cell disease
SoA	schedule of activities
SOB	shortness of breath
SOC	standard of care
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US/USA	United States of America
USP	United States Pharmacopeia
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Name of Sponsor: Corvus Pharmaceuticals, Inc.

Investigational Product: CPI-006

Title of Study: Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients

Phase of Development: 3

Number of Participants: Approximately 1000 evaluable participants for an estimated total of 330 evaluable participants per treatment group

Study Centers: Multicenter

Study Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the proportion of participants alive and respiratory failure free during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who are alive and free from respiratory deterioration during the 28 days after dosing defined as follows per the 8-point ordinal scale (Appendix 6): o Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 o Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Key Secondary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) during the 28 days after dosing

Objectives	Endpoints
• To compare the mortality rate due to any cause during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who died during the 28 days after dosing
Supportive Secondary	
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28
• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of all Covid-19 attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline to score of none or mild during the 28 days after dosing
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, 14, 21, and 28
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21, and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity during the 28 days after dosing • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 (Appendix 7) consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)

Objectives	Endpoints
• To compare the medical interventions/procedures during the 28 days after dosing of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate and duration of mechanical ventilation (days receiving invasive or non-invasive mechanical ventilation during the 28 days after dosing) • Rate and duration of any supplemental oxygen (if applicable) in days during the 28 days after dosing • Rate and duration of invasive mechanical ventilation (if applicable) in days during the 28 days after dosing • Rate and duration (if applicable) in days of non-invasive ventilation/ high flow oxygen devices during the 28 days after dosing • Oxygenation free days during the 28 days after dosing • Rate of rehospitalization during the 28 days after dosing
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment -emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0

Objectives	Endpoints
Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• To characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO_2 = oxygen saturation.

Study Design:

This is a Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) or antigen testing for SARS-CoV-2.

Approximately 1000 participants will be randomized at a 1:1:1 ratio to the 3 treatment arms and stratified by the following factors:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg (Treatment A - maximum dose of 200 mg) or 1 mg/kg (Treatment B - maximum dose of 100 mg) intravenously (IV) on Day 1. A placebo will be given at the same schedule as the active drug for participants who receive the control (Treatment C). Participants, investigators, and Corvus will be blinded to the treatment allocation. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies, or any other approved treatment) per those guidelines at the discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an interactive response technology (IRT) system to obtain the participant number. Every

participant that signs the informed consent form (ICF) must be assigned with a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the National Early Warning Score 2 (NEWS2), Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if a participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be asked to attend post-hospitalization assessments on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 60 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when approximately 120, 250, 400, 600, and 800 participants have completed the Day 28 assessments. The analysis with 250 and 600 participants will be a futility evaluation. Safety and efficacy data will be analyzed for the iDMC review at both interim analyses.

Study enrollment will be paused after the first 60 participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, when 120 participants are enrolled, the study enrollment will not be paused. For the review of the futility analysis (~250 participants), study enrollment will also be paused at that time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for enrollment for the subsequent reviews after the futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data.

The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

Eligibility: Hospitalized mild to moderately symptomatic Covid-19 patients. Participants may have controlled pre-existing conditions such as cancer and diabetes. All participants will receive standard care for Covid-19.

Test Product, Dose and Administration: CPI-006 single dose at either 1 mg/kg or 2 mg/kg given by IV infusion over 10-15 minutes.

Rationale:

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary redistribution in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients. The high anti-SARS-CoV-2 titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 27 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This Phase 3 study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in participants who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

Overall Design:

This is a randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized participants with Covid-19. An iDMC will monitor safety, efficacy, and conduct of the study.

All participants will be followed for 28 days for production of anti-SARS-CoV-2 antibodies followed by an optional period of 5 months. While in the hospital, participants will receive standard of care monitoring including vital signs every 4-6 hours, or per institutional guidelines and safety assessments. Safety and other disease assessments will be conducted at Days 3, 7, 14, 21, and 28. Discharged participants will be asked to attend post-hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed.

Treatment Groups and Duration:

Participants meeting study entry criteria will be randomized in a 1:1:1 ratio to receive either Treatment A (CPI-006 2 mg/kg plus SOC) or Treatment B (CPI-006 1mg/kg plus SOC) or Treatment C (placebo plus SOC). Participants randomized to Treatment A will receive a single dose of CPI-006 at 2 mg/kg given by IV infusion plus SOC (maximum dose of 200 mg). Participants randomized to Treatment B will receive a single dose of CPI-006 at 1 mg/kg given by IV infusion plus SOC (maximum dose of 100 mg). A placebo will be given at the same schedule as the active drug for participants randomized to Treatment C. All participants will be managed per physician using best SOC for Covid-19 patients. No dose modifications will be allowed.

Statistical Methods:

Statistical Hypothesis for the Primary and Key Secondary Endpoints

Five hypotheses will be tested for the comparison of Treatment A to Treatment C (Treatment A Hypotheses Family). The first 3 hypotheses are to test the superiority of Treatment A over Treatment C in terms of the primary endpoint and the first and second secondary endpoints in the priority as they are listed in the Objectives and Endpoints module above. The fourth hypothesis is to test non-inferiority of Treatment A relative to Treatment C in terms of the ratio of Treatment A mortality over Treatment C mortality. If non-inferiority is established, then the fifth hypothesis will be tested for the superiority of Treatment A over Treatment C in terms of the mortality ratio.

The same 5 hypotheses will be tested for the comparison of Treatment B to Treatment C (Treatment B Hypotheses Family).

The overall one-sided Type-I error rate α=0.025 is initially equally split for the Treatment A Family and Treatment B Family for testing the 5 hypotheses within a treatment family. A parallel gatekeeping strategy with multiplicity adjustment is designed to control the overall Type I error rate α at the one-sided 0.025 level for testing the hypotheses in the 2 families. The 5 hypotheses are arranged in the hierarchical order described above for statistical testing within each treatment family. The details of the gatekeeping strategy and stepwise testing procedures are presented in Appendix 11.

Sample Size

Approximately 1000 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1:1 ratio between Treatment A, Treatment B, and Treatment C within each of the strata defined by:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - CKD
    - SCD
    - Organ transplantation
    - Cancer

With approximately 330 participants per treatment arm, there would be an approximately 80% power to show a statistically significant superiority of Treatment A over Treatment C in the proportion of participants alive and free from respiratory deterioration during the 28 days after dosing at a 1-sided α level of 0.0125 when the true proportion of Treatment A is 92% and that of Treatment C is 84%. The same sample size and power statement also holds for the comparison between Treatment B and C.

Populations for Analyses

For purposes of analyses, the following populations are defined in Table 1.

Table 1 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study and analyzed according to treatment assigned at randomization.
Efficacy	All participants who receive any amount of study drug (CPI-006 or placebo) and have post-baseline efficacy assessment based on the 8-point ordinal scale. The participants will be analyzed according to the treatment actually received.
Safety	All participants who receive any amount of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

Statistical Design

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis and will be performed when approximately 250 of participants have been enrolled into the study with 28 days of follow-up time. Safety and efficacy will be analyzed for futility evaluation.

The second interim analysis is also a non-binding futility and efficacy analysis and will be performed when approximately 600 of participants have been enrolled and with 28 days of follow-up time. Comparison between Treatment A and C, and between Treatment B and C, with respect to the primary and key secondary efficacy endpoints will be performed.

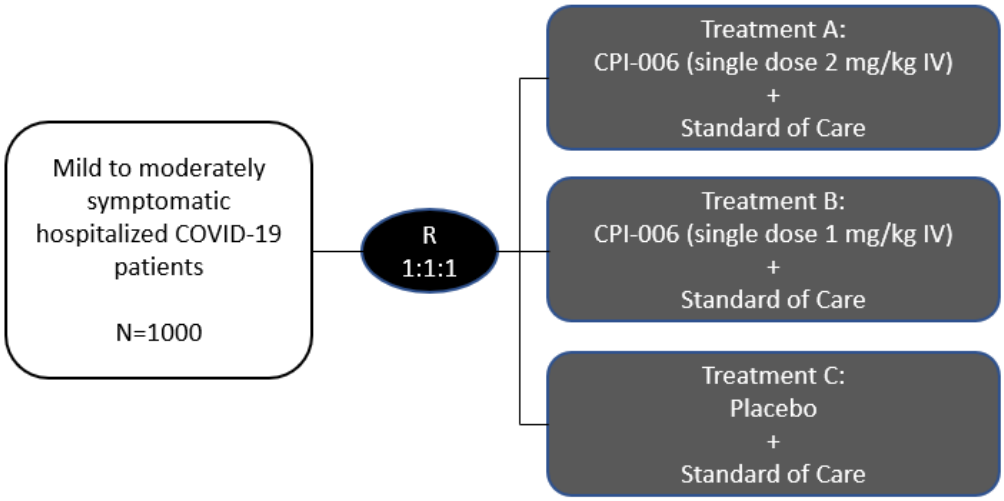
At both interim analyses, unblinded analyses will be provided by a separate unblinded statistician to the iDMC for making futility assessment.

As part of the second interim analysis, Corvus may request the iDMC to assess the primary efficacy endpoint and its conditional power of establishing a significant treatment effect at the final analysis based on the interim data. The total sample size of the study may be increased with the recommendation by iDMC. The sample size adaptation plan and increase rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the first interim analysis.

The primary analysis of the study is the final analysis. Safety and efficacy analyses will be performed when all the participants of the study have completed the Day 28 assessments.

1.2. SCHEMA

Figure 1 Study Schematic



IV = intravenous; R = randomization

1.3. SCHEDULE OF ACTIVITIES (SOA)

For the schedule of activities, please see Appendix 1, Table 6.

2. INTRODUCTION

2.1. STUDY RATIONALE

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary redistribution in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients. The high anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are

supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 27 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This Phase 3 study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in participants who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

The Covid-19 pandemic is not yet under control and there is fear that infections could spread and/or recur in a seasonal manner, even if controlled now or with vaccination efforts. There is also the possibility of viral mutation or emergence of other virulent coronaviruses. Based on encouraging preliminary data, CPI-006 may improve the magnitude, duration, and diversity of antibody responses to SARS-CoV-2 and improve clinical outcome. It also may result in prolonged immunity to SARS-CoV-2, its variants, and related coronaviruses. It is also possible that experience gained with treating Covid-19 with CPI-006 could be applied to treatment of other infectious diseases including future viral pandemics, and potential use in conjunction with vaccination of healthy participants.

2.2. BACKGROUND

Since its emergence in Hubei province, China in December of 2019, the novel coronavirus (2019-nCoV, Covid-19) has become a global health crisis (Wu et al, 2020; Chan et al, 2020). There is an urgent need for therapies that can improve survival, clinical outcomes, and reduce the requirements for intensive supportive care and prolonged hospitalization (Huang et al, 2020). There are efforts underway to re-purpose direct acting antivirals targeting the ribonucleic acid (RNA)-dependent RNA polymerase including remdesivir and favipiravir both of which are being actively studied in multiple clinical trials. Similarly, inhibitors of the virally encoded proteases are being evaluated. To compliment therapeutic approaches there is an intense effort underway to develop vaccines. A number of approaches to vaccine development have begun clinical trials or are planned. To support vaccine strategies, there is a growing understanding of the key viral/host interaction required for viral entry and replication (Du et al, 2009). Indeed, it is increasingly clear that the virally encoded spike protein binds to angiotensin converting enzyme 2 (ACE2) on target cells to facilitate entry and replication. The spike protein is a multidomain viral envelop glycoprotein which

contains a receptor binding domain (RBD) in subunit 1 of the spike protein (Wrapp et al, 2020). This RBD directly interacts with N-terminal domain of ACE2. This interaction is absolutely required and initiates a sequence of steps leading to efficient viral infection. Thus, antibodies that disrupt this key interaction may be effective in viral neutralization and clearance. A recent publication from Zhang and colleagues have identified neutralizing antibodies from 8 Covid-19 infected patients that bind to the RBD of the spike protein and are neutralizing (Yuan et al, 2020). This provides evidence that neutralizing antibody responses to SARS-CoV-2 are possible and may provide clinical benefit in patients with Covid-19 and protection from disease in healthy subjects. Indeed, the U.S. Food and Drug Administration (FDA) has given emergency use authorization for the use of Covid-19 Convalescent Plasma (CCP) and monoclonal antibodies for the treatment of Covid-19. Clinical studies with CCP suggest that higher titers of neutralizing antibody provide superior clinical benefit to recipients (Joyner et al, 2020; Rasheed et al 2020). These findings support the value of anti-viral antibodies in eradicating viral infection in patients, lessening disease severity, improving clinical course and potentially reducing transmission.

CD73 is an adhesion molecule that was initially found to be important for lymphocyte trafficking and T cell activation (Resta & Thompson, 1997). It also functions as an ectoenzyme that converts adenosine monophosphate (AMP) to immunosuppressive adenosine. Several companies are developing anti-CD73 antibodies to inhibit production of adenosine and thereby augment immune response in patients with cancer. These antibodies have been designed primarily to block enzymatic activity. Corvus has designed a novel anti-CD73 antibody with agonistic, immunomodulatory properties that binds CD73 resulting in activation of immune cells such as B cells, and results in antibody production in vitro (Luke et al, 2019a). This antibody, CPI-006, is under investigation in a Phase 1b trial (NCT03454451) in advanced cancer as monotherapy and in combination with other immunotherapies such as anti- programmed cell death 1 receptor (PD1). Over 90 participants have received doses of this antibody ranging from 1 mg/kg to 24 mg/kg given IV every 21 days. Treatment has been safe and tolerable, with chills and rigor seen during antibody infusion, that are managed by premedication with acetaminophen and diphenhydramine.

CPI-006 is a humanized FcγR binding-deficient monoclonal antibody. In vitro studies have revealed binding to CD73 and direct effects on B cells, morphologic transformation to plasmablasts and induction of IgM and IgG secretion (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary drop in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in HLA-DR expression. Molecular studies of the BCR in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients.

CPI-006 is under investigation in a Phase 1 trial (NCT04464395) in mild to moderately symptomatic hospitalized Covid-19 patients. The results from the study (CPI-006-002) shows IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained overtime. Similar results were observed in anti-SARS-CoV-2 IgA titers. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days for the 1.0 mg/kg and 3.0 mg/kg cohorts, and 28 days for the 5.0 mg/kg cohort in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase for all isotypes toward each antigen from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. An increase of IgG titer toward spike protein was observed from 1.0 mg/kg to 3.0 mg/kg at Day 28. High and durable neutralizing titers were observed in subjects where ID_{50} values up to 23,000 were measured using a functional pseudovirus neutralizing antibody assay. Neutralizing titers were observed to persist at least 84 days following onset of symptoms in the ongoing trial. Immunophenotyping of peripheral blood mononuclear cells (PBMCs) at baseline and at 14, 28, or 56 days after treatment provided preliminary evidence that CPI-006 increased the frequency of memory B cells in 7 evaluated participants. An increased frequency of memory/effector $CD4^{POS}$ and $CD8^{POS}$ T cells was also observed in 5 ($CD4^{POS}$) and 6 ($CD8^{POS}$) evaluable participants. CPI-006 has been well tolerated in participants with Covid-19 in this study. No DLTs or treatment-related AEs have been reported in the study. The AEs reported in the study were due to the underlying Covid-19 or comorbidities.

In this Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized participants with Covid-19. Approximately 1000 participants will be randomized in a 1:1:1 fashion to receive Treatment A (CPI-006 at 2 mg/kg plus SOC) or Treatment B (CPI-006 at 1 mg/kg plus SOC) or Treatment C (matching placebo plus SOC). Standard of care will be per institutional guidelines. Corvus will assess if administering CPI-006 to participants with Covid-19 along with SOC can lead to clinical benefit and enhance humoral immune response to the SARS-CoV-2. The production of neutralizing antibodies would be expected to shorten disease interval and improve clinical outcome, and treatment is expected to be safe. Therefore, CPI-006 treatment is expected to have a positive benefit/risk profile (see Section 2.4.1).

2.3. CPI-006 NONCLINICAL EVALUATION

CPI-006 recognizes and binds human CD73 with high affinity (KD values of 0.64–7.1 nM), inhibits CD73 catalytic activity (mean concentration required for 50% inhibition [IC_{50}]

values of 2.1 nM and 4.0 nM for human and cynomolgus monkey CD73), and has downstream biological effects on T cells as evidenced by restoration of CD3+ T cell proliferation in the presence of AMP. CPI-006 also binds to and inhibits cynomolgus monkey CD73, but not mouse or rat CD73, supporting the use of cynomolgus monkeys for studies of the pharmacokinetics (PK) and toxicology of CPI-006.

Complete CD73 occupancy on CD8+ T cells in peripheral blood samples from cynomolgus monkeys by CPI-006 was observed at all doses of CPI-006. Complete CD73 occupancy was also observed in the axillary lymph nodes, indicating successful solid tissue penetration by CPI-006 with full coverage at least 24 hours after the final dose.

An in vitro cytokine release assay was conducted with CPI-006 to evaluate the potential for CPI-006 to induce an immune response resulting in production of multiple cytokines (cytokine storm). The results demonstrated that CPI-006 did not directly induce cytokine (interferon gamma [IFN-γ], interleukin 2 [IL-2], interleukin 6 [IL-6], interleukin 10 [IL-10], and tumor necrosis factor alpha [TNF-α]) release from fresh human PBMCs at 0.1-10 µg/mL of CPI-006.

Safety of CPI-006 was evaluated in male and female cynomolgus monkeys in two toxicity studies. In the first, a dose range finding study, CPI-006 was administered over 15-minutes by IV infusion at doses up to 120 mg/kg CPI-006, weekly (5 doses) for 31 days. The second, was a Good Laboratory Practice (GLP)-compliant toxicity study in which doses up to 100 mg/kg CPI-006 were administered by IV infusion over 60 minutes, weekly (5 doses) for 28 days. Toxicokinetics, safety pharmacology, and local tolerance assessments were built into the GLP compliant toxicity study. CPI-006 administered by IV infusion was well tolerated in both studies up to, and including, the highest doses administered. No definitive CPI-006-related changes were observed in the animals. No-observed adverse effect levels (NOAEL) were the highest doses administered, 120 mg/kg and 100 mg/kg CPI-006. Additional nonclinical information is provided in the Investigational Brochure for CPI-006.

2.4. SUMMARY OF CLINICAL EXPERIENCE WITH CPI-006

In CPI-006-001 oncology study, CPI-006 has been administered as a single agent and in combination with ciforadenant (an A2a receptor antagonist), and /or pembrolizumab (a blocking anti-PD-1 antibody). CPI-006 has been well tolerated when administered every 3 weeks as monotherapy and in combination with ciforadenant and/or pembrolizumab.

As of 20 Oct 2020, 35 participants have been treated with CPI-006 (every 3 weeks) monotherapy at doses up to 24 mg/kg, and no maximum tolerated dose was established. The most common adverse reactions were infusion related reactions (IRRs), primarily chills and rigors. These IRRs were non-serious, mild to moderate in severity (Grade 1-2), transient and did not lead to discontinuation. The IRRs have been observed during (or immediately after) Cycle 1, Day 1 and are uncommon at subsequent infusions of CPI-006. To mitigate the risk of IRRs, premedication with diphenhydramine (50 mg orally [PO]) and acetaminophen 500–

1000 mg PO (or equivalents) was required prior to infusion of CPI-006 at Cycle 1, Day 1 and has shown a decreased rate and intensity of IRRs.

As of 29 Dec 2020, in the ongoing Phase 1 CPI-006-002 study, 27 hospitalized participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg with follow-up data. CPI-006 was well tolerated. IRRs have not been observed with CPI-006 infusion. No DLTs or treatment related AEs have been reported. The safety data in this Phase 1 study is reviewed on an ongoing basis by an Independent Data Monitoring Committee (iDMC).

2.4.1. Benefit/Risk Assessment

This study proposes to administer single doses of CPI-006 to hospitalized mild or moderately symptomatic participants with Covid-19.

Study treatment will be administered in the hospital and participants will be monitored closely. CD73 is expressed on endothelial cells and it is possible that negative effects or exacerbation of disease could be seen in participants with Covid-19. However, data from the GLP general toxicity study did not show any CPI-006 related changes in coagulation parameters (Section 4.3). Data from 27 participants with Covid-19 in the CPI-006-002 study did not indicate any effect of CPI-006 on systemic inflammatory response or coagulopathy. In addition, data from over 90 participants in study CPI-006-001 in participants with cancer did not show any CPI-006 related systemic inflammatory response or coagulopathy. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. The benefit of therapy to participants who receive Treatment A or Treatment B is the development of neutralizing antibodies which could lead to more rapid clinical improvement, avoidance of complications of Covid-19 disease, and the potential for longer lasting immunity.

Participants enrolled in Treatment C will receive standard of care (SOC) per institutional guidelines. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. Overall data will be used to assess any difference between the participants who receive Treatment A, Treatment B, and Treatment C in terms of clinical outcome and anti-SARS-CoV-2 levels.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the proportion of participants alive and respiratory failure free during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who are alive and free from respiratory deterioration during the 28 days after dosing defined as follows per the 8-point ordinal scale (Appendix 6): o Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 o Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Key Secondary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) during the 28 days after dosing
• To compare the mortality rate due to any cause during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who died during the 28 days after dosing
Supportive Secondary	
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28
• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of all Covid-19 attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline to score of none or mild during the 28 days after dosing
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, 14, 21, and 28

Objectives	Endpoints
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21, and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity during the 28 days after dosing • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 (Appendix 7) consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)
• To compare the medical interventions/procedures during the 28 days after dosing of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate and duration of mechanical ventilation (days receiving invasive or non-invasive mechanical ventilation during the 28 days after dosing) • Rate and duration of any supplemental oxygen (if applicable) in days during the 28 days after dosing • Rate and duration of invasive mechanical ventilation (if applicable) in days during the 28 days after dosing • Rate and duration (if applicable) in days of non-invasive ventilation/ high flow oxygen devices during the 28 days after dosing • Oxygenation free days during the 28 days after dosing • Rate of rehospitalization during the 28 days after dosing
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment -emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0

Objectives	Endpoints
Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• To characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO_2 = oxygen saturation.

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) or antigen testing for SARS-CoV-2.

Approximately 1000 participants will be randomized at a 1:1:1 ratio to the 3 treatment arms and stratified by the following factors:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa)
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg (Treatment A – maximum dose of 200 mg) or 1 mg/kg (Treatment B – maximum dose of 100 mg) intravenously (IV) on Day 1. A placebo will be given at the same schedule as the active drug for participants who receive the control (Treatment C). Participants, investigators, and Corvus will be blinded to the treatment allocation. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies, or any other approved treatment) per those guidelines at the discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an

interactive response technology (IRT) system to obtain the participant number. Every participant that signs the informed consent form (ICF) must be assigned with a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. SARS-CoV-2 PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if the participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be asked to attend post-hospitalization assessments on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first approximately 60 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when approximately 120, 250, 400, 600, and 800 participants have completed the Day 28 assessments. The analysis with 250 and 600 participants are the interim analyses for futility evaluation. Safety and efficacy data will be analyzed for the iDMC review at both interim analyses. Study enrollment will be paused after the first 60 participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, when 120 participants are enrolled, the study enrollment will not be paused. For the review of the futility analysis (~250 participants), study enrollment will also be paused at that time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for enrollment for the subsequent reviews after the futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data.

The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting. Further details on the iDMC are provided in Section 9.2.8.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

CPI-006 activates B cells in vitro leading to B cell differentiation and secretion of immunoglobulins. Studies in patients with cancer have demonstrated differentiation of B cells into plasmablasts, trafficking from blood and return of memory B cells to blood. The in vitro and in vivo effects indicate that CPI-006 stimulates B cell differentiation, antigen driven clonal selection and differentiation into antibody producing cells. Novel anti-tumor antibodies have been produced in some treated patients with cancer. B cell receptor molecular studies have demonstrated the emergence of novel B cell clones in the blood of CPI-006 treated patients with cancer. No changes in total serum immunoglobulins have been seen to date (Willingham et al., 2020). It is believed that the activation of B cells and enhancement of antibody production will lead to a more robust humoral immune response to SARS-CoV-2 and provide clinical benefits such as shorter disease duration, less disease severity, fewer complications, and greater long-term immunity.

In Study CPI-006-002 (in mild to moderate hospitalized participants with Covid-19), IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels has been observed in participants. Fourteen of 22 evaluable participants had low pre-treatment antibody titers despite relatively long durations of symptoms in some participants. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days for the 1.0 mg/kg and 3.0 mg/kg cohorts, and 28 days for the 5.0 mg/kg cohort in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase for all isotypes toward each antigen from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. An increase of IgG titer toward spike protein was observed from 1.0 mg/kg to 3.0 mg/kg at Day 28. High and durable neutralizing titers were observed in subjects where ID_{50} values up to 23,000 were measured using a functional pseudovirus neutralizing antibody assay. Neutralizing titers were observed to persist at least 84 days following onset of symptoms in the ongoing trial. No changes in total serum immunoglobulins have been seen to date.

4.3. JUSTIFICATION FOR DOSE

Two active doses of CPI-006, 1.0 mg/kg up to a maximum dose of 100 mg or 2.0 mg/kg up to a maximum dose of 200 mg, were selected based on safety, PD, and PK parameters. Safety is summarized in the CPI-006 Investigational Brochure and in Section 2.3 and Section 2.4.

In the GLP general toxicity study in cynomolgus monkeys, CPI-006 was administered by 60-minute IV infusion once weekly for 5 consecutive weeks at dose levels of 10, 30, or 100 mg/kg, followed by a 28-day recovery period. CPI-006 doses of up to 100 mg/kg/week (5 total doses) were well tolerated. CD73 is expressed weakly on endothelial cells. No CPI-006-related changes in hematologic coagulation parameters, which included prothrombin time (PT) activated partial thromboplastin time (aPTT), or fibrinogen, occurred during the study. The NOAEL was the highest dose administered, 100 mg/kg/week, corresponding to maximum drug concentration in serum or plasma (C_{max}) of 3,560 and 3,280 µg/mL and AUC from the start of infusion to 169 hours after the start of infusion ($AUC_{(0-169)}$) of 167,000 and 186,000 hr•µg/mL, for males and females, respectively. The C_{max} and AUC from time zero to the time of the last quantifiable concentration (AUC_{last}) for the GLP repeat dose cynomolgus monkey toxicity study are 60 and 66 times higher, respectively, than the C_{max} and AUC_{last} after a single administration of 3 mg/kg to humans in the CPI-006-001 study. Safety margins are anticipated to be even greater for the 1 mg/kg and 2 mg/kg doses selected for the subject protocol.

In clinical study CPI-006-001, 93 participants with advanced cancers received repeated IV infusions ranging from 1 mg/kg to 24 mg/kg CPI-006 once every 3 weeks until disease progression. CPI-006 was administered as a single agent or in combination with other oncology therapies. No DLTs were observed for CPI-006 at doses below 24 mg/kg in the dose escalation portion of the study. A DLT was observed in a single participant who received 24 mg/kg CPI-006 (Grade 3 hyponatremia in a participant with NSCLC who had a history of hyponatremia). The 24 mg/kg cohort was expanded, and no more DLTs were reported. Thus, a maximum tolerated dose was not established, and the 24 mg/kg cohort was defined as maximum administered dose per protocol.

A covariate analysis was performed using serum CPI-006 levels, participant demographics, vital signs, laboratory values, and concomitant medications data from 93 participants who received 1-24 mg/kg CPI-006 in the CPI-006-001 study. Clearance was strongly associated with participant body weight, indicating a body weight-adjusted dose is preferred over a fixed dose. CPI-006 showed non-linear PK and modeling with clearance being a linear function of dose. The fit of the model to the data was excellent. Area under the curve (AUC) after a dose of 24 mg/kg is 453-fold higher than the AUC after a dose of 1 mg/kg and it is estimated to be 31-fold higher than the area under the serum concentration-time curve (AUC) after a dose of 2 mg/kg. The serum CPI-006 concentration 30 minutes after infusion was not modeled for a dose of 2 mg/kg, but the geometric mean 30-minute serum CPI-006 concentration after administration of 24 mg/kg was 11.6 times higher than after administration of 3 mg/kg, and 40.2 times higher than after administration of 1 mg/kg, indicating a more than dose proportional increase in C_{max} over the range of doses.

In clinical study CPI-006-002, a single dose, dose escalation study, 27 participants hospitalized for mild to moderate Covid-19 symptoms were treated with a single IV infusion of CPI-006 ranging from 0.3 mg/kg to 5.0 mg/kg in combination with SOC. CPI-006 was

well tolerated in all participants with no DLTs or treatment-related AEs reported in the study. Safety was monitored in the study by an iDMC.

The preliminary geometric mean 30-minute serum CPI-006 concentrations in study CPI-006-002 (n = 3 per cohort) for the 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg cohorts are 1.9 μg/mL, 9.3 μg/mL, and 56.4 μg/mL, respectively. The 30-minute serum CPI-006 concentrations are similar to those for samples collected from the corresponding 1 mg/kg and 3 mg/kg cohorts at the same time in the CPI-006-001 oncology study. CPI-006 is rapidly cleared from serum and is undetectable (serum concentration < 50 ng/mL) 1-7 days after a 1 mg/kg IV infusion or 14-21 days after a 3 mg/kg infusion. In CPI-006-002, the relationship between clearance and weight was less well defined; however, there was a small statistical preference for a model in which clearance was weight-proportional, presumably because of fewer subject for whom PK data are available and the larger variability in this group of participants.

Serum IgG and IgM antibody titers against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable participants in CPI-006-002 within 7 days of a single infusion of CPI-006. Similar results were observed in serum anti-SARS-CoV-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels was observed in these participants. Thirteen of 17 evaluable participants had low pre-CPI-006 infusion antibody titers despite relatively long durations of symptoms in some participants. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were observed in antibody responses to the RBD. At doses higher than 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved for at least 84 days, 56 days, and 28 days for the 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg cohorts, respectively. Peak serum anti-SARS-CoV-2 titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase from 1.0 mg/kg to 5.0 mg/kg at the evaluable time points suggesting that the peak pharmacodynamic effect occurred in the range of 1.0-3.0 mg/kg CPI-006. In addition, the duration of sustained high antibody titers appeared optimum in the 1.0 mg/kg-3.0 mg/kg cohorts and was not improved at 5.0 mg/kg.

Immunophenotyping of peripheral blood from participants enrolled in clinical study CPI-006-001 demonstrated that doses greater than 1 mg/kg are sufficient to activate B cells, resulting in a temporary redistribution to lymphoid tissues and corresponding increase in the frequency of memory B cells returning to circulation. A similar increase in the frequency of memory B cells was observed in Covid-19 patients tested in the CPI-006-002 trial, including participants receiving 0.3 mg/kg CPI-006. In vitro, CPI-006 induced B cell activation is dose-dependent with concentrations of 1 μg/mL achieving near maximal induction of CD69. This initial activation leads to a morphologic transformation of B cells into plasmablasts and secretion of IgM and IgG in vitro. These levels of CPI-006 also result in increased expression of various markers involved in antigen presentation e.g. HLA-DR, CD86. A dose of 1 mg/kg is sufficient to sustain CPI-006 serum concentrations above 1 μg/ml for up to 48 hours and a dose of 2 mg/kg to sustain CPI-006 serum concentrations up to 1 week.

In summary, a dose of 1 mg/kg appeared to be sufficient to achieve the maximum level of IgG and IgM anti-SARS-CoV-2 titers in serum. Immunophenotyping of peripheral blood in participants from CPI-006-001 suggested that a higher dose may be required to activate B cells, resulting in a temporary redistribution to lymphoid tissues and corresponding increase in the frequency of memory B cells returning to circulation. Thus, a dose of 2 mg/kg was selected for investigation.

4.4. END OF STUDY DEFINITION

A participant in this study is considered to have completed the study if he/she has completed all study visits including Day 28 study assessments. The study visits beyond Day 28 will be optional for exploratory endpoint of antibody levels at Days 56, 84, and 168.

The end of the study is defined as the date that the last expected study visit is completed for all participants.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Participants must be ≥ 18 years of age at the time of signing the informed consent.
2. Confirmed positive by PCR or antigen test for SARS-CoV-2 with sample collection ≤ 10 days prior to the day of randomization. PCR is the preferred method; however other tests for SARS-CoV-2 are allowed if authorized for use in the country.
3. Covid-19 illness of any duration of symptoms.
4. Participant capable of understanding the study and giving informed consent. Participant capable of signing and dating the written ICF. Participant must understand and agree to comply with planned study procedures for the duration of the study. The study visits beyond Day 28 will be optional and require a separate consent.
5. Hospitalized for Covid-19 illness for ≤ 5 days with mild to moderate Covid-19 symptoms, including:
    - Mild: Symptoms of Covid-19 including fever, rhinorrhea, mild cough, sore throat, headache, muscle pain, malaise but not requiring supplemental oxygen
    - Moderate: Lower respiratory symptoms: shortness of breath (SOB) or signs of pneumonia or lung infiltrates based on X-ray or computed tomography (CT) scan < 50% present

    And

    Meets the criteria for:

    - Category 4 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (Covid-19 related or otherwise) OR
    - Category 5 - Hospitalized, requiring supplemental oxygen, OR
    - Category 6 - Hospitalized, on non-invasive ventilation or high flow oxygen devices per 8-point ordinal scale (see Appendix 6).

6. Adequate organ function, as defined by:
   - CBC: ANC >1000/mm^3, platelets>75,000mm^3, Hgb >9 gm/100 cc
   - Calculated creatinine clearance based on ideal body weight per Cockcroft-Gault formula or 24-hour urine ≥ 30 mL/min
   - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN)
   - D-dimer < 10,000 ng/mL
7. Eligible participants of child-bearing age (male or female) must agree to use adequate contraception for a total of 6 weeks after study treatment administration (Appendix 5). Female participants or the female partners of male participants who become pregnant during the study or within the protocol-specified period after their last CPI-006 administration should immediately inform their treating physicians.

5.2. EXCLUSION CRITERIA

1. Signs of acute respiratory distress syndrome (ARDS) or respiratory failure necessitating mechanical ventilation at the time of screening (and randomization) or anticipated impending need for mechanical ventilation.
2. History of severe chronic respiratory disease and requirement for long-term oxygen therapy.
3. Any uncontrolled active systemic infection or hemodynamic instability requiring admission to an intensive care unit (ICU).
4. Participants with malignant tumor receiving treatment, or other serious systemic diseases affecting life expectancy within 29 days of Screening.
5. Receipt of cancer chemotherapy or immunomodulatory drugs including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6, anti-IL6 receptor; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use equivalent to prednisone >10 mg/day, during preceding 2 months.

   Note: Steroids for treatment of Covid-19 are acceptable.
6. Convalescent plasma (CCP) or anti-SARS-CoV-2 monoclonal antibodies administered less than 24 hours prior to randomization. Participants must have recovered from any adverse events related to CCP treatment. Received chloroquine or hydroxychloroquine within last 7 days or during the study.
7. Patients who are participating in other clinical trials including participants in an extended access program.
8. Active deep vein thrombosis or pulmonary embolism as confirmed by the investigator within last 6 months.
9. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 48 hours of admission as confirmed by the investigator.

10. Any active uncontrolled co-morbid disease that might interfere with study conduct or interpretation of findings.
11. Known to be positive for HIV or positive test for chronic HBV infection (defined as positive hepatitis B surface antigen [HbsAg]) or positive test for hepatitis C antibody.
12. Pregnancy or breast feeding.
13. Persons under legal protection or currently incarcerated.

5.3. LIFESTYLE CONSIDERATIONS

Blood, sperm, and ova donations are restricted for at least 6 weeks after CPI-006 administration.

5.3.1. Meals and Dietary Restrictions

No dietary restrictions.

5.3.2. Activity

No required restrictions.

5.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Reasons for screen failure will be recorded.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. STUDY TREATMENT ADMINISTERED

A summary of study treatment information is provided in Table 2.

Table 2 Study Treatment

Study Treatment Name:	**CPI-006 Injection, 200 mg/20 mL**	**CPI-006 Placebo**
Dosage formulation:	10 mg/mL with 20 mM histidine, 9 % sucrose, 0.01 % (w/v) polysorbate 80, pH 5.5.	(5% Dextrose Injection, USP [5% dextrose (glucose)[a]])
Unit dose strength (s)	200 mg / 20 mL (10 mg/mL)	5% Dextrose
Route of administration	IV	IV

Dose[b]	Treatment Group A: 2 mg/kg up to a maximum of 200 mg -or- Treatment Group B: 1 mg/kg up to a maximum of 100 mg	Treatment Group C: Placebo (no CPI-006)
Dosing instructions:	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP (5% dextrose [glucose]). CPI-006 Injection is diluted with 5% Dextrose Injection, USP (5% dextrose [glucose]).	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP (5% dextrose [glucose]).
Packaging and labeling	Study Treatment will be provided in a sterile, single-use vial with a rubber stopper and a blue cap. One vial is packaged inside a carton. Each vial will be labeled as required per country requirement.	Not Applicable
Manufacturer	Manufactured for Corvus Pharmaceuticals, Inc. by Vetter Development Services USA, Inc.	Placebo will be purchased by the clinical institution from commercial vendors approved by that institution

Abbreviations: IV = intravenous; US/USA = United States of America; USP= United States Pharmacopeia
[a] 5% Dextrose Injection, USP will be used at clinical sites within the United States; similar sterile, low-endotoxin grades of 5% dextrose (glucose) that are commercially available and meet local or compendial laws and regulations may be substituted outside of the US.
[b] The CPI-006 dose for participants who weigh more than 100 kg will be limited to a fixed dose of 200 mg in the 2 mg/kg dose group (Treatment A), or a fixed dose of 100 mg for the 1 mg/kg dose group (Treatment B).

6.2. STUDY TREATMENT: PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. 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.
2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment 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 site staff.
3. The unblinded site staff preparing the study treatment is responsible for study treatment accountability, log of receipt, inventory, reconciliation, dispensing, return of study treatment, destruction of study treatment and record maintenance (i.e., receipt, reconciliation, and final disposition records). The study treatment logs and records must be kept current and blinded from others (e.g. investigators, site staff,

participants, Sponsor and contract research organization (CRO) staff with oversight of study conduct). Study treatment logs must be kept in a secure location with access limited only to the unblinded staff members.

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

6.2.1. Handling and Storage

6.2.1.1. CPI-006 Injection

CPI-006 Injection is provided as a sterile solution in a single use vial that delivers up to 200 mg of active ingredient in 20 mL (10 mg/mL). CPI-006 vials will be stored at 2°C to 8°C and protected from direct light. Excursions up to 25°C are allowed up to 3 days. Refer to the product labeling for product storage.

The prepared CPI-006 can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared CPI-006.

Do not freeze CPI-006 vials or diluted CPI-006 infusion solution.

6.2.1.2. Placebo

The placebo, 5% Dextrose Injection, USP will be purchased by each clinical site within the United States. Either 5% Dextrose Injection, USP or a similar sterile, low-endotoxin grade of 5% dextrose (glucose) that is commercially available and meets local or compendial laws and regulations may be substituted outside of the US. The placebo should be handled and stored according to manufacturer's specifications.

The prepared placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

Do not freeze the placebo.

6.2.2. Preparation and Dispensing

Refer to the Pharmacy Manual for detailed instructions on how to prepare study treatment for administration. Study treatment will be prepared using aseptic techniques and dispensed by an appropriately qualified and experienced member of the study staff (e.g., pharmacist, pharmacy assistant, or pharmacy technician) who is unblinded to study treatment (see blinding plan in the pharmacy manual). The identity of the study treatment should not be revealed by markings on labels or the infusion bag or infusion set except for a blinded randomization code.

CPI-006 infusion will be prepared using aseptic techniques by withdrawing the appropriate amount of CPI-006 Injection, 10 mg/mL from a vial into a sterile syringe. The contents of the syringe will be emptied into a sterile polyolefin/polyethylene (PO/PE) or polyvinyl chloride (PVC) infusion bag and diluted with 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose). Apply gentle mixing by inverting the IV bag; avoid shaking the IV bag.

Placebo will be prepared using aseptic techniques. The placebo infusion is 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) in a sterile polyolefin/ polyethylene (PE) or polyvinyl chloride (PVC) infusion bag. After it is prepared, the placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

6.2.3. Administration

Administration of study treatment will be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and infusion-experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Site staff administering the study treatment will be blinded to the treatment (active or placebo) being administered. Participants will receive a single dose of study treatment by IV infusion on Day 1 of the study. Study treatment must be infused through an in-line filter. Infusion lines should be made of PO/PE or PVC, equipped with a 0.2 μm or 0.22 μm in-line polyethersulfone (PES) filter.

The infusion should be administered via a port as close to the participant's vein as possible to ensure that the full dose is administered in the allotted time. The total infusion time from start of infusion to completion of infusion will be 10-15 minutes. As soon as the infusion is complete, the infusion line used for the study treatment will be flushed with the greater of the priming volume of the infusion set or 30 mL of 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) solution. The same infusion rate used for the study treatment infusion will be used for the flush.

Infusion reactions are possible, thus appropriate drugs and medical equipment to treat acute infusion reactions must be immediately available and study personnel must be trained to recognize and treat infusion reactions. Premedication with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo is recommended for participants who are not receiving steroids for treatment of Covid-19. Oral premedication should be administered 30-60 minutes prior to the start of the CPI-006/placebo infusion. IV diphenhydramine should be administered 15-30 minutes prior to the start of the CPI-006/placebo infusion.

Study treatment administration details will be recorded on the CRF and will include at a minimum: participant number, infusion start time and stop time, interruption stop and restart times, flush start and stop times.

6.2.4. Management of Infusion Reactions

Any CPI-006-associated infusion reactions should also be managed as shown in Table 3.

Table 3 CPI-006 Infusion-Related Reaction Management Guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; treatment not indicated	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Provide supportive care. Increase monitoring of vital signs as medically indicated. If symptoms do not improve within 1 hour, provide medical treatment until the participant is deemed medically stable in the opinion of the investigator. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g., from 10 mL/min to 5 mL/min).

NCI CTCAE Grade	Treatment
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Additional appropriate medical therapy may include but is not limited to: – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Narcotics – Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms have not subsided or worsen with reduced infusion rate, stop infusion. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g. from 10 mL/min to 5 mL/min). Otherwise, if symptoms do not resolve, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity with premedication and do not have symptom resolution within 2 hours of medical treatment should be permanently discontinued from further study drug treatment.

NCI CTCAE Grade	Treatment
Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: – Epinephrine[a] – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Corticosteroids – Narcotics – Oxygen – Vasopressors
Grade 4 Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - Epinephrine[a] - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Vasopressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Participant is permanently discontinued from further study drug treatment.

Abbreviations: : IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

[a] In cases of anaphylaxis, epinephrine should be used immediately.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be randomized to Treatment A, Treatment B, or Treatment C in a 1:1:1 ratio using an Interactive Response Technology (IRT). Before the study is initiated, the log-in information & directions for the IRT will be provided to each site.

Participants will receive a single IV administration of study treatment on Day 1 of the study.

Returned study treatment should not be redispensed to any participants.

6.3.2. Blinding

This is an observer blinded design, so investigators, site staff (except the unblinded pharmacy personnel preparing the study treatment), participants, Sponsor, and CRO staff with oversight of study conduct will remain blinded to treatment allocation throughout the course of the study. The IRT will provide the unblinded pharmacist(s) the randomized treatment arm assignment to be allocated to the participant at the administration visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

CPI-006 Injection is a clear colorless solution and will remain clear and colorless when diluted in 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) solution. At full concentration, CPI-006 is slightly more viscous than water and may create minimal foam if vigorously shaken. Once diluted, CPI-006 is not visually distinguishable from the 5% Dextrose Injection, USP placebo.

To maintain the blind, an otherwise uninvolved staff member (e.g. pharmacist, pharmacy assistant, or pharmacy technician) will prepare and dispense the study treatment for administration such that the identity (active or placebo) of the treatment is blinded to all other site staff responsible for administration and study conduct throughout the study. The unblinded personnel are responsible for study treatment preparation and accountability only and will not participate in any other aspect of the study. The unblinded personnel will endeavor to ensure that there are no differences in time taken to dispense following randomization or preparation that might reveal the identity of the study treatment to investigators, site staff, participants, Sponsor, and CRO staff.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.3. Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant'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 case report form, as applicable.

6.4. Study Treatment Compliance

Investigational Product will be administered on a single occasion by the investigator or qualified designee to participants who are hospitalized. Randomization code, treatment

volume, start and stop times for the study treatment infusion, flush volume, and start and stop times for the flush will be accurately recorded in the CRF.

The study site is responsible for ensuring that participants comply with the specified study windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Appendix 1 Schedule of Activities). If a participant does not complete a visit within the specified time, the visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (e.g. clinical laboratory testing, and immunologic testing, as applicable).

6.5. CONCOMITANT THERAPY

Investigators may prescribe any concomitant medications, procedures, or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.3.

Any medication or vaccine (including influenza vaccine and Covid-19 vaccine, which are both allowed concomitant medications), over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

6.5.1. Rescue Medicine

The study site will supply infusion reaction rescue medication that will be obtained locally by the clinical site. The following rescue medications may be used:

- Antihistamine such as diphenhydramine administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Analgesics such as acetaminophen administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Corticosteroids administered according to standard practices at the site/hospital for treating infusion related reactions
- The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the CRF

6.5.2. Permitted Concomitant Therapy

The following concomitant medications and vaccinations are allowed and will be recorded in the CRF:

- Therapies that are either approved or accepted as standard of care therapies for Covid-19 per site/institutional guidelines (e.g., remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies)
- Prophylactic or therapeutic anticoagulation
- Supportive care for management of Covid-19 symptoms and complications
- It is recommended that participants who are not being treated with steroids for Covid-19 be premedicated with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo (see Section 6.2.3).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.3. Prohibited Concomitant Therapy

The following medications are prohibited and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications, however, will not definitively require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol analysis set.

If a participant receives a prohibited concomitant medication, the investigator in consultation with the medical monitor will evaluate any potential impact on receipt of the study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data.

The following concomitant medications are prohibited:

- Chloroquine or hydroxychloroquine
- Cancer chemotherapy or immunomodulatory drugs for management of medical conditions or comorbidities other than Covid-19, including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6, anti-IL6 receptor; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use equivalent to prednisone >10 mg/day, during preceding 2 months.
- Investigational medication or device (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment and throughout the study unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

The medical monitor should be contacted if there are any questions regarding concomitant therapies.

6.6. Dose Modification

No dose modifications for CPI-006 are allowed.

6.7. Study Treatment After the End of the Study

No study treatment will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

- Participant or participant's physician may elect to discontinue their participation in the study at any time. Reasons for withdrawal will be recorded on the CRF.
- All randomized participants will be followed for 28 days.
- Participants who consent to optional follow-up visits will be followed for 168 days.

7.1. DISCONTINUATION OF STUDY TREATMENT

A single dose of CPI-006/placebo is administered only on Day 1 for participants, thus there is no discontinuation from study treatment unless the participant does not receive full dose due to toxicity during the infusion. Standard of care will be administered to all participants at the discretion of the investigator per institutional guidelines.

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. LOST TO FOLLOW-UP

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of

maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Appendix 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) 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 time frame defined in the SoA (Appendix 1).

Hospitalized participants will receive daily monitoring and testing while in the hospital including routine vital sign monitoring and labs per institutional standards. Once discharged, participants will be asked to attend post- hospitalization study visits as described in Section 4.1.

Follow-up visits after discharge could include, but are not limited to, clinic visits, outpatient hospital visits, home health visits or telehealth, depending on local or institutional standards. If no other method of follow-up is feasible, home visits may be used.

Study assessments will utilize local labs and procedures at the clinical sites except for the key secondary endpoint, anti-SARS-CoV-2 antibody levels and various exploratory endpoints such as neutralizing antibody levels and peripheral blood immunophenotyping which will be assessed by the central lab. Other exploratory endpoints such as BCR repertoire analysis and systemic cytokine/chemokine analysis will be performed by external vendors outside of the central lab. Results of tests conducted at central lab, are not considered as critical to the management of Covid-19 in participants and will not be reported to the investigator or participant.

The anti-RBD IgG level will be measured using an electrochemiluminescent immunoassay on serum specimens stored at -20°C. The method is based on reactivity to immunogenic viral protein where a recombinant form of viral RBD antigen is absorbed to the surface of a 96-well microtiter plate. Participant serum will be dispensed to the wells where antibodies recognizing the antigen are allowed to react before removal of unbound immunoglobulin from the wells. Anti-RBD IgG bound to the viral protein will be detected using standard enzyme-linked immunosorbent assay (ELISA) techniques.

Immediate safety concerns should be discussed with the Sponsor directly upon occurrence or awareness to determine if the participant should continue or discontinue study treatment regardless of SoA assessments. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. SCREENING

Screening assessments and procedures are detailed in Appendix 1, Table 6.

8.2. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are detailed in Appendix 1, Table 6.

8.3. EFFICACY ASSESSMENTS

The following assessments will also be performed for all participants at the time points described in the SoA (Appendix 1, Table 6):

- Covid-19 Symptoms Assessment – Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath (Appendix 8)
- 8-point Ordinal Scale Assessment (Appendix 6)
- SARS-CoV-2 viral load
- PCR negativity
- NEWS2 Assessment (Appendix 7)
- Anti-RBD antibody titers will be measured in sera collected at the time points described in the SoA (Appendix 1, Table 6). Collection of the predose timepoint is critical for subsequent analysis. The assays will measure IgM, IgG and IgA levels targeting the RBD for key and additional secondary endpoints using the electrochemiluminescent immunoassay. The assays will be conducted at a centralized testing facility using validated methods.
- A viral PCR test by nasal swab will be obtained to demonstrate a negative test and viral load. Participants with positive PCR or antigen tests will have repeat PCR tests

on subsequent visits until a negative test. This test will be conducted by the clinical lab at the investigator sites.

- Exploratory measurements will be conducted at Sponsor's research laboratories or through use of outside vendors including immunophenotyping analysis, immune cell functional assays, BCR repertoire analysis, systemic cytokine/chemokine analysis, and, anti-SARS-CoV-2 antibody characterization, and anti-viral neutralization assays.

- Clinical assessments will include time to clinical improvement, time to resolution of the Covid-19 attributable symptoms, change in clinical status, rate of participants with clinical improvement, time to discharge, requirement for ICU, requirement for mechanical ventilation, duration of mechanical ventilation, oxygenation free days during the 28 days after dosing, and incidence and duration of new O_2 use during the study.

8.4. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Serum samples will be collected from each participant enrolled in the study for measurement of serum concentrations of CPI-006 as specified in the SoA (Appendix 1, Table 6). A maximum of 4 additional samples may be collected at time points during the study if warranted and agreed upon between the investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor.

The actual collection date and time (24-hour clock time) for each sample will be recorded.

Samples will be used to evaluate the PK of CPI-006. Each serum sample will be divided into 3 aliquots (1 each for PK, backup, and for potential analysis of anti-drug antibodies [ADA], and/or neutralizing antibodies [refer to Section 8.7.1 Immunogenicity Assessments]). Samples collected for analyses of serum CPI-006 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

At visits during which serum samples for the determination of PK, backup, ADA, and/or neutralizing antibodies of CPI-006 will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points, up to 4 time points, for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5. SAFETY ASSESSMENTS

The following assessments will also be performed for all participants at the time points described in the SoA (Appendix 1, Table 6):

- Incidence, type, and severity of AEs and SAEs assessed by NCI CTCAE v 5.0 to compare safety of CPI-006 plus SOC to placebo plus SOC.
- Safety assessments will be made using local lab testing (Appendix 3) for hematology, chemistry, coagulation, inflammatory markers and serum quantitative immunoglobulins.
- Routine physical exams.
- Vital signs (pulse rate, blood pressure, respiratory rate, temperature and blood oxygen saturation) including at start, at conclusion and at approximately 2 hours after completion of the CPI-006/placebo infusion.

8.6. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, or surrogate).

The investigator and any qualified 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 participant to discontinue the administration of CPI-006/ placebo, or the study (see Section 7).

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by protocol-mandated procedures (e.g., study related procedures, discontinuation of medications) should be reported (see Appendix 4).

After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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

For participants with worsening of Covid-19, the clinical event(s) that mark the worsening should be reported as AE or an SAE (see definitions in Appendix 4). Investigators are not obligated to actively seek AEs or SAEs outside clinical practice after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant 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 the Sponsor.

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.

8.6.2. Method of Detecting AEs and SAEs

The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event CRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 4.

For each AE recorded on the Adverse Event CRF, the investigator assesses seriousness, severity, and causality as per Appendix 4.

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

Reporting requirements for SAEs can be found in Appendix 4.

8.6.3. Follow-up of AEs and SAEs

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

8.6.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants 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, IRB/IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigational Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.7. BIOMARKERS

Serum at baseline and at specified times will be stored at -20°C for use in various serology studies which include:

Supportive Secondary Endpoints

- Measurement of anti-RBD IgG, IgM, and IgA levels.

Exploratory Endpoints

- Measurement of neutralizing antibody levels that block association of viral RBD and human ACE2 assessed in a biochemical ELISA.
- Measurement of neutralizing antibody levels that block infection assessed in a pseudovirus assay, and in a live virus assay
- Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins.
- Additional exploratory serum assays may be conducted with extra serum not required for primary analysis.

Peripheral blood collected at baseline and at specified times will be analyzed while fresh or processed into PBMCs and cryopreserved for use in various studies including:

- Immunophenotyping using flow cytometry to evaluate the frequency of memory B cells and memory/effector T cells
- Functional B and T cell assays to evaluate ex vivo immune responses to SARS-CoV-2 antigens compared to controls.
- BCR repertoire analysis to evaluate effects of CPI-006 on B cell clonality and antibody isotype switching

8.7.1. Immunogenicity Assessments

Antibodies to CPI-006 may be evaluated in serum samples collected from participants according to the SoA. These samples may be tested by the Sponsor or Sponsor's designee.

Serum samples may be screened for antibodies binding to CPI-006 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to CPI-006 and/or further characterize the immunogenicity of CPI-006

The detection and characterization of antibodies to CPI-006 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment may also be evaluated for CPI-006 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to CPI-006.

9. STATISTICAL CONSIDERATIONS

9.1. SAMPLE SIZE DETERMINATION

Approximately 1000 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1:1 ratio between Treatment A, Treatment B and Treatment C (approximately 330 per arm) within each of the strata defined by:

- Region of the world (North America [(US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - CKD
    - SCD
    - Organ transplantation
    - Cancer

With approximately 330 participants per treatment arm, there would be an approximately 80% power to show a statistically significant superiority of Treatment A over Treatment C in

the proportion of participants alive and free from respiratory deterioration during the 28 days after dosing at a 1-sided α level of 0.0125 when the true proportion of Treatment A is 92% and that of Treatment C is 84%. The same sample size and power statement also holds for the comparison between Treatment B and C.

9.2. STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be developed and finalized before the first interim analysis (the futility analysis, see Section 9.2.7) and will describe the study populations to be included in the analyses. This section is a summary of the planned statistical analyses of the primary and key secondary endpoints.

9.2.1. POPULATION FOR ANALYSES

For purposes of analyses, the following populations are defined in Table 4.

Table 4 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study and analyzed according to treatment assigned at randomization.
Efficacy	All participants who receive any amount of study drug (CPI-006 or placebo) and have post-baseline efficacy assessment based on the 8-point ordinal scale. The participants will be analyzed according to the treatment actually received.
Safety	All participants who receive any amount of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

Abbreviations: ITT = intent-to-treat; SOC = standard of care

9.2.2. General Approach

Unless otherwise specified, the following general analysis will be performed. Continuous variables will be summarized using the following descriptive statistics: number of observed values, mean, standard deviation, median, and minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Time-to-event variables, when appropriate, will be summarized by the median with 95% confidence intervals (CI) and the 25% and 75% quartiles. Kaplan-Meier curves will be provided. The baseline value for analysis variable is the last measurement before administration of study treatments.

In addition to the analyses specified below for the key estimands, the primary and key secondary endpoints will be summarized with univariate analyses including point estimates and associated confidence intervals by treatment group.

9.2.3. Demographic and Participant Characteristics

Demographic information such as age, gender, race, body weight, and participant characteristics such as baseline disease severity, symptoms, and comorbidities will be listed and summarized.

9.2.4. Efficacy Analyses

Table 5 Efficacy Endpoints

	Endpoints
Primary	The primary efficacy endpoint is the proportion of participants who are alive and free from respiratory deterioration during the 28 days after dosing defined as follows per the 8-point ordinal scale (Appendix 6): • Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 • Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Secondary	**Key Secondary Endpoints**: • Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): o Not hospitalized, no limitations on activities. o Not hospitalized, limitation on activities and/or requiring home oxygen; o Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care. • Time clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) during the 28 days after dosing. • Proportion of participants who died during the 28 days after dosing. **Supportive Secondary Endpoints:** • Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28. • Time to resolution of all Covid-19 attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline to score of none or mild during the 28 days after dosing • Change in in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, 14, 21, and 28. • Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28. • Change from baseline level of IgM targeting the RBD at Days 7, 14, 21, and 28. • Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28. • Time to PCR negativity during the 28 days after dosing • Percentage of participants with PCR negative at Days 7, 14, 21, and 28 • Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 (Appendix 7) consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C). • Rate and duration of mechanical ventilation (days receiving invasive or non-invasive mechanical ventilation during the 28 days after dosing)

	• Rate and duration of any supplemental oxygen (if applicable) in days during the 28 days after dosing • Rate and duration of invasive mechanical ventilation (if applicable) in days during the 28 days after dosing • Rate and duration (if applicable) in days of non-invasive ventilation/ high flow oxygen devices during the 28 days after dosing • Oxygenation free days during the 28 days after dosing • Rate of rehospitalization during the 28 days after dosing
Exploratory	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168

All efficacy analyses will be performed based on the ITT population, with appropriate estimands that include strategies to address potential intercurrent events (ICE). Three possible ICEs have been identified for this trial within the 28-day study duration after randomization. They are: all-cause death (ICE-1), receiving life-saving procedures including ICU admission (ICE-2), and all other intercurrent events (ICE-3) (receiving investigational or non-approved treatments intended for treatment of Covid-19 at the time of randomization, incomplete study dosing/infusion, usage of prohibited medications, early study discontinuation, etc.). See the description and details of possible types of intercurrent event in Appendix 9 (Table 11).

9.2.4.1. Analysis of Primary and Key Secondary Efficacy Endpoints

Estimands for the primary and key secondary endpoints are defined and presented in detail in Appendix 9 (Table 12).

9.2.4.1.1. Analysis of Primary Endpoint: Estimand 1

For the primary endpoint, **Estimand 1a** (main estimand) will be defined as a hybrid estimand, which combines two strategies for handling intercurrent events. The intercurrent event of death (ICE-1) is part of the composite endpoint, and all other intercurrent events will be addressed with the treatment policy strategy (ICH E9 [R1] Addendum 2017). The primary analysis will be based on a logistic regression model adjusted for the stratification factors (region of the world, age, and presence of comorbidities) (Ge et al. 2011). The potential-

outcome framework will be applied to compute population-level estimates of the proportions of participants alive and free from respiratory deterioration during the 28 days after dosing in the 2 treatment groups. The treatment effect will be assessed by the difference between Treatment A (or B) and Treatment C at the population level. Confidence interval with appropriate confidence level for the difference between treatments will also be provided. Further details of the potential outcome framework are provided in Appendix 10.

Estimand 1b is a sensitivity analysis for the primary endpoint. The intercurrent event of death (ICE-1) and receiving life-saving procedures including ICU admission (ICE-2) will be a part of the composite endpoint. All other intercurrent events (ICE-3) will be addressed with the treatment policy strategy. In this analysis, ICE-1 and ICE-2 will be considered equivalent in analysis. In other words, a participant will be considered as a treatment failure equivalent to death if the participant receives life-saving procedures. Ge's method will be used for this sensitivity analysis. Details regarding receiving life-saving procedures will be provided in the SAP.

Other Sensitivity analyses which are based on control-based imputation and delta-adjusted imputation (tipping point), will be conducted as part of the proposed estimand framework. The missing 8-point ordinal scale assessments after baseline for participants with ICE-2 or ICE-3 will be imputed. For the control-based imputation, imputation for all treatment groups will be informed by participants in the control group with the ICE's who have outcomes collected after the ICE. For the delta-adjusted imputation, imputation will be informed by the participants in the respective treatment group with ICE's who have outcomes collected after the ICE. For each imputation method, the estimated treatment effects and associated standard errors from the individual completed data sets will be combined using Rubin's rules to produce a single inferential statement (treatment effect, standard error and p-value). A detailed description of the sensitivity analyses will be provided in the SAP.

9.2.4.1.2. Analysis of Secondary Endpoints: Estimand 2, 3, and 4

For the key secondary endpoints time to recovery (**Estimand 2**) and time to clinical improvement (**Estimand 3**), Kaplan-Meier estimates will be presented by treatment group. Overall homogeneity of the distribution functions of time to recovery as well as time to clinical improvement between Treatment A (or B) and Treatment C will be tested using log-rank method with adjustment for stratification (region of the world, age, and presence of comorbidities). Participants hospitalized beyond Day 28 or experiencing death due to all causes prior to or on Day 28 will be censored at Day 28. Participants withdrawing consent and not achieving the endpoint will be censored at their last day in the study up to Day 28.

Sensitivity analysis for time to recovery (Estimand 2) and time to clinical improvement (Estimand 3) will be carried out using Restricted Mean Survival Time (RMST) method. The RMST of time to the event (with cutoff at Day 28) will be estimated by treatment group using the Kaplan-Meier method. Participants hospitalized beyond Day 28 or experiencing death prior to or on Day 28 will be censored at Day 28. Participants withdrawing consent and not achieving the endpoint will be censored at their last day in the study up to Day 28. The

difference in RMST between two compared groups will be tested using a two-sample t-test. Further details of the sensitivity analyses including descriptive statistics by RMST will be provided in the SAP.

The cumulative mortality rate over the 28 day period from dosing (**Estimand 4**) will be estimated with time to death of participants in each treatment group using Kaplan-Meier methods. The absolute difference in the log-transformed estimated mortality rate will be calculated between Treatment A (or B) and Treatment C. A multiplicity adjusted 2-sided CI (97.5% or 95%, depending on the multiplicity adjustment) will be obtained for this difference in log-transformed mortality rates, using a variance for this difference being the sum of the variances of the two compared treatment groups obtained using Greenwood's formula. Results will be anti-logged to give the estimated ratio of the cumulative mortality rates through day 28 (Treatment A [or B] relative to Treatment C) and its associated multiplicity adjusted CI. The CI will be used to assess the non-inferiority of Treatment A (or B) in comparison to Treatment C against the non-inferiority margin of 1.3. If the upper limit of the anti-logged CI of the mortality ratio of Treatment A (or B) relative to Treatment C is below 1.3, then that treatment would be established as non-inferior to Treatment C. Appendix 13 contains a summary of a simulation study overviewing the operating characteristics of the test for non-inferiority relative to the 1.3 testing boundary.

If Treatment A (or B) is established as non-inferior to Treatment C, then that treatment will be tested for superiority against Treatment C. The test of superiority will compare the upper limit of the anti-logged CI of the mortality ratio of Treatment A (or B) relative to Treatment C to 1.0. If it is less than 1.0 then Treatment A (or B) would be established as superior to Treatment C. Further details of the tests for non-inferiority and superiority in mortality will be provided in the SAP.

9.2.4.1.3. Statistical Hypotheses for the Primary and Key Secondary Endpoints

The following hypotheses are defined for the comparisons between Treatment A and Treatment C - Treatment A Hypotheses Family:

Null Hypothesis H_{Ai}: Treatment A is not superior to Treatment C with respect to endpoint i

versus

H'_{Ai}: Treatment A is superior to Treatment C with respect to endpoint i,

where i = 1 for the primary endpoint "proportion of participants alive and free from respiratory deterioration during the 28 days after dosing";

i = 2 for the secondary endpoint "time to recovery during the 28 days after dosing";

i = 3 for the secondary endpoint "time to clinical improvement by at least 2 points during the 28 days after dosing";

Null Hypothesis $H_{A4:}$ Treatment A is inferior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

versus

H'_{A4}: Treatment A is non-inferior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

Null Hypothesis $H_{A5:}$ Treatment A is not superior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

versus

H'_{A5}: Treatment A is superior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

The same hypotheses H_{Bi} versus H'_{Bi}, for the endpoints indicated by i = 1, 2, 3, 4, and 5 will be tested for the comparison between Treatment B and C - Treatment B Hypotheses Family.

9.2.4.1.4. Parallel Gatekeeping Procedure for Testing Hypotheses

The overall one-sided Type-I error rate α=0.025 is initially equally split for the Treatment A Family and Treatment B Family for testing the 5 hypotheses within a treatment family. A parallel gatekeeping strategy with multiplicity adjustment is designed to control the overall Type I error rate α at the one-sided 0.025 level for testing the hypotheses in the 2 families. The 5 hypotheses are arranged in the hierarchical order described above for statistical testing within each treatment family. The details of the gatekeeping strategy and stepwise testing procedures are presented in Appendix 11.

9.2.5. Supportive Secondary and Exploratory Endpoints

Analysis methodologies for the supportive secondary endpoints and exploratory endpoints will be described in the SAP, including the analyses for PK, pharmacodynamic (PD), and biomarkers, before database lock.

9.2.6. Safety Analyses

The safety analyses will include all participants in the Safety Population.

Safety will be assessed through summaries of AEs (including SAEs), changes in laboratory test results, physical examination findings, and vital signs.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0) to categorize each AE by System Organ Class and Preferred Term. The number of participants who experienced at least 1 AE; treatment-related AE; severe (Grade 3 or higher) AE, SAE; and the number of participants withdrawn from treatment due to AEs will be summarized. The incidence of AEs will be presented overall, by System

Organ Class and Preferred Term, by intensity (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5), by severity, by relationship to study treatment or if treatment-emergent, and by treatment. Individual listings of AEs will be provided. Study treatment related AEs will be listed individually.

Laboratory tests will be listed and summarized for each test. Lab values will be graded according to the NCI-CTCAE criteria and summarized.

Deaths and related information will be listed.

9.2.7. Interim and Final Analyses

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis and will be performed when approximately 250 of participants have been enrolled into the study with 28 days of follow-up time. Safety and efficacy will be analyzed for futility evaluation.

The second interim analysis is a non-binding futility and efficacy analysis and will be performed when approximately 600 of participants have been enrolled with 28 days of follow-up time. Comparison between Treatment A and C, and between Treatment B and C, with respect to the primary and key secondary efficacy endpoints will be performed at this interim analysis.

At both interim analyses, unblinded analyses will be provided by a separate unblinded statistician to the iDMC for making futility assessment.

As part of the second interim analysis, Corvus may request the iDMC to assess the primary efficacy endpoint and its conditional power of establishing a significant treatment effect at the final analysis based on the interim data. The total sample size of the study may be increased with the recommendation by iDMC. The sample size adaptation plan and increase rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the first interim analysis.

The primary analysis of the study is the final analysis. Safety and efficacy analyses will be performed when all the participants of the study have completed the Day 28 assessments.

9.2.7.1. Efficacy Stopping Criteria

The following non-binding efficacy stopping criteria will be applied for the two interim analyses after approximately 250 and 600 participants are enrolled:

- At the first interim analysis, stop enrollment if the z-score is $\leq$ -0.4.
- At the second interim analysis, stop enrollment if the z-score is $\leq$ 1.2.

The efficacy stopping criteria applies independently to either or both Treatment A and/or B when compared to Treatment C. The z-score is the standardized difference of Treatment A

(or B) minus Treatment C with respect to the primary efficacy endpoint. Further details regarding the efficacy stopping criteria are provided in Appendix 12.

9.2.8. Independent Data Monitoring Committee (iDMC)

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 60 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when approximately 120, 250, 400, 600, and 800 participants have completed the Day 28 assessments. The analysis with 250 and 600 participants are the interim analyses for futility evaluation., Safety and efficacy data will be analyzed for the iDMC review for futility evaluation.

Study enrollment will be paused after the first 60 participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, when 120 participants are enrolled, the study enrollment will not be paused. For the review of the first futility analysis (~250 participants), study enrollment will also be paused at that time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for enrollment for the subsequent reviews after the first futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data. In addition, the iDMC is available for ad hoc reviews for safety concerns. The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

iDMC membership includes:

- Three clinicians experienced in care/management of Covid-19 and an unblinded independent statistician (all voting members)

9.2.8.1. Safety Stopping Criteria

The following safety stopping criteria will be applied for the two safety assessments (after 60 and 120 participants are enrolled) and at the time of the futility analysis after 250 participants are enrolled:

- Grade 5 AEs in the active arms ≥20% compared to placebo.
- Grade 3-4 AEs in the active arms ≥20% compared to placebo.

The iDMC may recommend stopping at any time for safety concerns. The IDMC will make the determination based on review of unblinded safety and efficacy data.

10. REFERENCES

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Statistics in medicine. 2009;28(4):586-604.

Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-523.

Dmitrienko A, D'Agostino Sr R. Traditional multiplicity adjustment methods in clinical trials. Statistics in Medicine. 2013;32(29):5172-218.

Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV –- a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226-36.

European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials – Addendum – Step 5. 2017 Jul.

Ge M, Durham LK, Meyer RD, et al. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug information journal: DIJ/Drug Information Association. 2011 Jul;45(4):481-93.

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with Covid-19: initial three-month experience. MedRxiv. 2020.

Luke JJ, Merchan J; Harshman L, et al. Immunobiology and clinical activity of CPI-006, an anti-CD73 antibody with immunomodulating properties in a Phase 1/1b trial in advanced cancers. J. Immunother. Cancer 2019b Nov;7(suppl.1) 282.

Luke JJ, Powderly JD, Merchan JR, et al. Immunobiology, preliminary safety, and efficacy of CPI-006, an anti-CD73 antibody with immune modulating activity, in a phase 1 trial in advanced cancers. J. Clin. Oncol. 2019a 37(15 suppl.).

Rasheed AM, Ftak DF, Hashim HA, et al. The therapeutic effectiveness of Convalescent plasma therapy on treating Covid-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. medRxiv. 2020.

Resta R, Thompson LF. T cell signaling through CD73. Cell Signal. 1997 Feb;9(2):131-9.

Royal College of Physicians. National early warning score (NEWS) 2. Standardising the assessment of acute-illness severity in the NHS. 2017.

Willingham SB, Criner G, Hill C, et al. Characterization and Phase 1 Trial of a B Cell Activating Anti-CD73 Antibody for the Immunotherapy of Covid-19. medRxiv. 2020.

World Health Organization. Coronavirus disease 2019 (Covid-19): situation report, 72.

Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367(6483):1260-1263.

Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Apr; 580(7803):E7.

Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. Science. 2020 Apr 3. pii: eabb7269

APPENDIX 1
SCHEDULE OF ACTIVITIES

Table 6 Schedule of Activities

Procedure	Screening (up to 3 days before Day 1) [a]	Day 1	Day 2 to X (during hospital stay) [b]	Day 7 (if participant remains in the hospital) [c]	Day of Hospital Discharge [c]	Day 7 (if participant is discharged from hospital) [d]	Day 14 [c, d, e]	Day 21 [c, d, e]	Early Termination D28 [d]	Optional Assessment		
										Day 56 [d]	Day 84 [d]	Day 168 [d]
Informed Consent	X											
Inclusion and Exclusion Criteria	X											
Demography	X											
Physical Examination	X											
Limited Physical Exam		X	X	X	X				X			
Medical History	X											
Covid-19 Symptoms Assessment [f]	X	X	X	X	X	X	X	X	X			
National Early Warning Score 2 Assessment	X	X	X	X	X				X			
8-point Ordinal Scale Assessment	X	X	X	X	X		X [g]	X [g]	X			
Vital Signs [h]	X	X	X	X	X				X			
Hematology Panel [i]	X	X	X	X	X				X			
Chemistry Panel [j]	X	X	X	X	X				X			
Serum Quantitative Immunoglobulins [j]	X	X			X				X			
Serum Ferritin	X	X	X	X	X				X			
Coagulation Test (PT, aPTT, INR)	X	X	X	X	X				X			
D-dimer	X	X	X	X	X				X			

Procedure	Screening (up to 3 days before Day 1)[a]	Day 1	Day 2 to X (during hospital stay)[b]	Day 7 (if participant remains in the hospital)[c]	Day of Hospital Discharge[c]	Day 7 (if participant is discharged from hospital)[d]	Day 14[c, d, e]	Day 21[c, d, e]	Early Termination D28[d]	Optional Assessment		
										Day 56[d]	Day 84[d]	Day 168[d]
Fibrinogen	X	X	X	X	X				X			
Pregnancy Test[k]	X								X			
SARS-CoV-2 PCR Test[l]	X	X		X	X							
Viral load sample (for Central Lab)		X	X[m]	X	X		X	X	X			
Influenza and RSV PCR Test	X											
C-Reactive Protein	X	X	X	X	X				X			
Anti-SARS-CoV-2 Serum Antibody Test Blood Sample (Central Lab)[n]		X[n] (pre-dose)		X	X		X	X	X	(X)	(X)	(X)
Exploratory Biomarker Blood Samples		X[o]			X		X		X			
PK[n] and Immunogenicity Serum Samples	See Table 7 for details											
Treatment Administration		X										
Adverse Event Review[p]		<==========							==========>			
Serious Adverse Event Review[p]	<==========								==========>			
Concomitant Medication Review	<==========								==========>			
Covid-19 Medical Intervention Review[q]	<==========								==========>			

NOTE: Procedures indicated with parentheses "(X)" are conditional. Refer to the appropriate footnote for details.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; NEWS2 = National Early Warning Score 2 Assessment; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RSV = Respiratory Syncytial Virus; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Screening and Day 1 testing can be combined, providing they are separated by less than 24 hours from the time of dosing and there are no signs of changes in the participant's status. Clinical lab tests as defined in Appendix 3 performed within 24 hours prior to consent will be acceptable for screening.

[b] Participants will be monitored daily while in the hospital for a minimum of 48 hours after study treatment administration. Participants will be monitored with vital signs including blood oxygen saturation every 4-6 hours or per institutional standards. Laboratory assessment will be taken daily or per institutional standards and should include but are not limited to hematology panel, chemistries, ferritin, CRP, LDH, D-dimer, fibrinogen, PT, aPTT and INR. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital.

[c] All participants will have samples collected for viral load, anti-SARS-CoV-2 serum antibody test, and exploratory biomarkers on day of discharge. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Participants who are discharged before Day 7, do not need a Day 7 sample collection but will be assessed for Covid-19 symptoms.

[d] Day 7 can be ± 1 day, Day 14, and Day 21 can be ± 2 days, Day 28 can be + 7 days. Day 56, Day 84, and Day 168 can be ± 5 days.

[e] All efforts should be made to have the blood draws and exams done and assessments completed. When needed a telemedicine or home health visit can replace a clinical visit for the post-hospitalization visits.

[f] Assessment of Covid-19 symptoms (per Appendix 8) should happen daily during the hospital stay. In the post- hospitalization setting, assessment of symptoms should happen on Day 7 (for those discharged before Day 7), Day 14, Day 21 and Day 28. Day 7, Day 14, and Day 21 assessments can be a telemedicine or phone call visit.

[g] If the participant is hospitalized, the assessment should be conducted in the hospital. If discharged and participant is at home, assessment may be conducted over the phone.

[h] Vital signs includes pulse, blood pressure, temperature, respiratory rate, and oxygen saturation by pulse oximeter. Height and weight collected at screening only. On Day 1 vital signs will be collected pre-dose, at completion of treatment administration (at the end of the flush) (+ 15 minute window), and 2 hours post-dose (± 15 minutes window).

[i] Hematology panel should include the parameters detailed in protocol Appendix 3.

[j] Chemistry panel should include the parameters detailed in protocol Appendix 3 and serum quantitative immunoglobulins (Screening, Day 1, day of discharge and Day 28).

[k] Pregnancy test (serum or urine) for women of child-bearing potential only (Appendix 5).

[l] Participants must have a confirmed positive PCR or antigen test for SARS-CoV-2 within 10 days of randomization (screening sample). PCR test will also be obtained on Days 1 and 7, while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally.

[m] Viral load sample to be collected on Day 3 while hospitalized as well as Day 1 (pre-dose), Day of discharge, Day 7 (if hospitalized), 14, 21 and 28.

[n] Anti-SARS-CoV-2 serum antibody test blood sample to be collected pre-dose administration. Anti-SARS-CoV-2 serum antibody samples will be collected to be assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be asked to attend post-hospitalization assessments on Days 56, 84, and 168.

[o] Exploratory biomarker samples on Day 1 will be collected pre-dose.

[p] After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by protocol-mandated procedures will be reported. After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

[q] Review of medical interventions/ procedures for management of Covid-19 such as intubation, ventilation, and supplemental oxygen and rehospitalization.

Table 7 PK, ADA, and Neutralizing Antibody Sampling Schedule

Sample[a]	Collection Timepoint	PK Variance	ADA and Neutralizing Antibody Only
1	pre-dose	-1 hour-0 hours	X (collected as part of PK)
2	0.5 hours	± 5 min	
3	2 hours	± 30 min	
4	4 hours	± 30 min	
5	8 hours	± 2 hours	
6	24 hours	± 6 hours	
7	48 hours	± 8 hours	
8	Day 28		X

Abbreviation: ADA = anti-drug antibodies; min = minutes; PK = pharmacokinetics
[a] Time post CPI-006 infusion and line flush except for pre-dose sample

APPENDIX 2
REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- In accordance with applicable laws and regulations, protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- 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 site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor 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 study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants 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 participant.

The ICF will address the use of remaining mandatory samples. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

Sites will be allowed to use all processes approved by their IRB to ensure safety of staff and patients from Covid-19, while maintaining appropriate consent procedures for the duration of this study.

DATA PROTECTION

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant 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.

COMMITTEES STRUCTURE

The objectives of the iDMC are to evaluate interim clinical and safety data to protect participant welfare and to provide recommendations regarding study conduct. Details of iDMC responsibilities and procedures are specified in the iDMC charter.

DISSEMINATION OF CLINICAL STUDY DATA

Clinical Study Reports, periodic safety reports, and clinical study summary reports will be disclosed after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.

Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

Publication planning and other activities related to non-promotional, peer-reviewed publications will be conducted to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies should be through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

DATA QUALITY ASSURANCE

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing CRF verification to confirm that data entered into the CRF by authorized site personnel are accurate and complete; that the safety

and rights of participants 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.

- U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. No records may be transferred to another location or party without written notification to the Sponsor.

SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the CRF 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 study monitoring plan.

STUDY TERMINATION

Potential reasons for closing the study include:

- Unsatisfactory subject enrollment
- Potentially unacceptable risk to study subjects
- Decision to modify clinical development plan
- Decision by the regulatory authority

In the event of a decision to close the study, the Sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed explanation of the reason for closure. The Sponsor and investigator will ensure that the safety of the subjects is protected and that IRB/IEC reporting continues per the requirements of the IRB/IEC and applicable local laws or requirements.

SITE CLOSURE

The Sponsor or designee reserves the right to close a study site at any time for any reason at the sole discretion of the Sponsor. Potential reasons for closing a site include:

- Investigator noncompliance

- Unsatisfactory subject recruitment and enrollment
- Lack of adherence to protocol procedures, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision by the regulatory authority

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or confirmed as destroyed and a study-site closure visit has been performed.

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

PUBLICATION POLICY

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 3
CLINICAL LABORATORY TESTS

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.

Table 8 Protocol-Required Safety Laboratory Assessments

Chemistry	Hematology	Serum Quantitative Immunoglobulins	Inflammatory Biomarkers	Coagulation Testing
BUN (Blood Urea Nitrogen)	Platelet Count	IgA	C-reactive protein	PT
Potassium	RBC Count	IgG	Ferritin	aPTT
Creatinine	Hemoglobin	IgM		INR
Sodium	Hematocrit			D-dimer
Glucose	RBC (Red Blood Cell) indices: MCV MCH % Reticulocytes			Fibrinogen
Calcium				
Bilirubin (total & direct)				
Protein (total)				
LDH (Lactate Dehydrogenase)	WBC count (White Blood Cell) with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils			
AST				
ALT				

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell.

APPENDIX 4
ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, 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 or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, is accompanied by clinical symptoms, results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), results in a medical treatment (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
  - 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.
- For worsening of Covid-19 symptoms, the clinical event(s) that mark the worsening should be reported as AE or an SAE.
- If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event CRF.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Deaths that occur within 28 days after study treatment (CPI-006) should be reported as an SAE.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- "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
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., 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 (e.g., hospitalization for signs/symptoms of the progression of disease under study). Hospitalization or ICU admissions due to Covid-19, worsening of Covid-19 in the 28 days during this study, or pulmonary conditions attributable to Covid-19 infection are considered efficacy-related endpoints. Therefore, Covid-19-related hospitalization or ICU admission is excluded from this definition.

A 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 participant 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 **Any adverse event that causes prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event).** • For this study, the subjects will be hospitalized for Covid-19 treatment so initial hospitalization will not be considered as an SAE. Complications that occur during hospitalization are AEs/SAEs. If a complication prolongs hospitalization (or requires admission to ICU) or fulfills any other serious criteria, the event is serious. **An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:** • Hospitalization for respite care • Planned hospitalization required by the protocol (e.g., for the Covid-19 treatment).

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 (e.g., 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 participant or may require medical or surgical treatment to prevent 1 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 (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- 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. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF
- If vomiting results in severe dehydration, both events should be reported separately on the CRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the CRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF

All AEs should be recorded separately on the Adverse Event CRF if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient or participant evaluation timepoints. Such events should be recorded with each severity change on the Adverse Event CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported, with each subsequent change in severity recorded on the same AE CRF with the exception of a non-serious event becoming serious. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious.). A new AE should be recorded as serious in the CRF with the date the event became serious recorded as the start date and completing all data fields related to SAEs.

- A recurrent AE is one that resolves between patient or participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event CRF.

Assessment of Intensity

The guidelines outlined below will be used for assessing the severity of AEs. The severity/intensity of AEs and SAEs will be graded based upon the participant's symptoms according to the NCI CTCAE v5.

AEs that are not defined in the NCI CTCAE v5 should be evaluated for severity/intensity according to the following scale:

Table 9 Assessment of Severity of Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or treatment not indicated
2	Moderate; minimal, local, or non-invasive treatment indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living.[b,c] An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
4	Life-threatening consequences or urgent treatment indicated [d]
5	Death related to AE [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE per the definition of SAE in (see section above).

[d] Grade 4 and 5 events must be reported as SAEs per the definition of SAE (see section above).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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 Investigational Brochure (IB) 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 Sponsor. 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 Sponsor.
- 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

- Treatment related AEs and SAEs should be followed up until resolution or until the AE is stable.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor 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 participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE Reporting to Corvus via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Corvus will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone or email.

SAE Reporting via Paper Report Forms

The primary mechanism for reporting an SAE to Sponsor will be through EDC. If EDC is down or not available, then the paper SAE report form can be used for SAE reporting.

Events That Occur Prior to the Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment (non-treatment emergent), **only SAEs caused by protocol-mandated procedures** should be reported in EDC using the EDC SAE form. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event CRF and submit the report via the paper report form. All other non-treatment emergent AEs should be reported in the Medical History CRF.

Events That Occur after Study Treatment Initiation

- After initiation of study treatment, all AEs and SAEs will be reported for 28 days following stopping of study treatment and until participants complete the study. The site will enter the SAE data into the EDC SAE report form.

Adverse Events That Occur after the Adverse Event Reporting Period are described in the following section.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, then the site can report this information in EDC (see next section) or to the Sponsor's designee by telephone on the number listed in a section below.

If EDC is unavailable, then the paper Clinical Trial Serious Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators below. Please note that email is preferred over fax and phone.

Note: For Ex-US country-specific safety fax and phone numbers, refer to the study manual.

- 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 CRF pages within the designated reporting time frames.

APPENDIX 5
CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

WOMAN OF CHILDBEARING POTENTIAL (WOCBP) AND OF FERTILE MEN

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

1. Women in the following categories are not considered WOCBP
2. Premenarchal
    a. Premenopausal female with 1 of the following:
        i. Documented hysterectomy
        ii. Documented bilateral salpingectomy
        iii. Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the participant'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 hormonal 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.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

CONTRACEPTION GUIDANCE:

MALE PARTICIPANTS

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following for 6 weeks after study treatment.

- 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 Table 10 of this appendix when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 6 weeks after study treatment.

FEMALE PARTICIPANTS

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10. In addition, female participants must refrain from donating ova for the duration of the study and for 6 weeks after study treatment.

Table 10 Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent[b]
Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[c]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[c] • IUD • IUS • Bilateral tubal occlusion

Vasectomized partner

A vasectomized partner is a highly effective contraception 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 defined as 6 weeks after receiving 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 participant.

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system; WOCBP = woman of childbearing potential

[a] Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhea method (LAM) are not considered acceptable methods of contraception. A male and female condom should not be used together as friction between the two can result in either product failing.

[b] 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 participants participating in clinical studies.

[c] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 6 weeks corresponding to time needed to eliminate study treatment after the last dose of study treatment. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.

PREGNANCY TESTING:

- WOCBP should only be included after a negative (urine or serum) pregnancy test at screening.
- Additional pregnancy testing is required at end of study or at early termination (see Appendix 1 – Schedule of Activities).

COLLECTION OF PREGNANCY INFORMATION:

MALE PARTICIPANTS WITH PARTNERS WHO BECOME PREGNANT

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

FEMALE PARTICIPANTS WHO BECOME PREGNANT

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. 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 post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

APPENDIX 6
8-POINT ORDINAL SCALE FOR CLINICAL IMPROVEMENT

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

APPENDIX 7
NEWS2 SCORING SYSTEM

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

National Early Warning Score (NEWS) 2

APPENDIX 8
EXAMPLE OF AN ASSESSMENT OF 14 COMMON COVID-19-RELATED SYMPTOMS: ITEMS AND RESPONSE OPTIONS

Example items *For items 1–10, sample item wording could be: "What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you **vomit (throw up)** in the last **24 hours**?**	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?**	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

APPENDIX 9
INTERCURRENT EVENT (ICE) AND ESTIMAND STRATEGY

Table 11 Intercurrent Event Types

Label	Intercurrent Event Type
ICE-1 (Death)	Death from any cause during the 28 days after dose initiation
ICE-2 (Life-saving procedures including ICU admission)	Any life-saving procedures including ICU admission for any reason during the 28-day period after dosing.
ICE-2 (All other events)	All other events including receiving investigational or non-approved treatments intended for treatment of Covid-19 at the time of randomization, incomplete study dosing/infusion, usage of prohibited medications, early study discontinuation, etc.

Table 12 Primary and Key Secondary Objectives and Estimands with Rationale for Strategies to Address Intercurrent Events

Primary Objective	
Primary Objective	To compare the proportion of participants alive and free from respiratory deterioration during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection
Estimand Label	**Estimand 1a (Main Estimand)**
Estimand Description	Risk difference in the *proportions of participants who alive and free from respiratory deterioration defined per the 8-point ordinal scale* during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic and virologic-confirmed COVID-19 infection.
Target Population	Mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19 who meet all inclusion and exclusion criteria
Endpoint	Participants who alive and free from respiratory deterioration defined per the 8-point ordinal scale: o Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5, or o Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Treatment Condition(s)	One infusion on Day 1 of CPI-006 at dose of 1 mg/kg or 2 mg/kg, or placebo in 15 minutes plus SOC per the guideline of the investigation site.
Population-Level Summary	Risk difference in the proportions of participants of alive and free from respiratory deterioration between a CPI-006 dose plus SOC versus placebo plus SOC.
Intercurrent Event Strategy:	(ICEs are described in Table 11.)
ICE-1 (Death)	Composite strategy (see ICH E9 (R1) Addendum 2017)
ICE-2 (Life-saving procedures including ICU admission)	Treatment policy strategy (see ICH E9 (R1) Addendum 2017)
ICE-3 (All other events)	Treatment policy strategy

Rationale for Strategies	The primary estimand is defined as a hybrid estimand, which combines the two strategies (composite and treatment policy) for handling the three types of intercurrent events. ICE-1: Death is a part of primary endpoint and is considered treatment failure regardless of the outcome from the most recent assessment of the 8-point ordinal scale prior to the event. ICE-2 and 3: Treatment policy strategy will be used for all these intercurrent events, meaning that, for the participants who experience the intercurrent events, all outcomes collected from the participants after the intercurrent event will be used in the analysis.
Estimand Label	**Estimand 1b (Sensitivity Analyses)**
Intercurrent Event Strategy:	(ICEs are described in Table 11.)
ICE-1 (Death)	Composite strategy
ICE-2 (Life-saving procedures including ICU admission)	Composite strategy
ICE-3 (All other events)	Treatment policy strategy
	The estimand is defined as a hybrid estimand, which combines the two strategies (composite and treatment policy) for handling the three types of intercurrent events. ICE-1: Death is a part of primary endpoint and is considered treatment failure regardless of the outcome from the most recent assessment in the 8-point ordinal scale prior to the death event. ICE-2: A participant who receives life-saving procedures including ICU admission at any time during the 28 day period after dosing will be considered as a treatment failure regardless of the outcome of the assessment based on the 8-point ordinal scale, as the need of life-saving procedures is likely due to clinical deterioration. ICE-3: Treatment policy strategy will be used for all other intercurrent events, meaning that all outcomes collected from the participants experiencing this intercurrent event after the intercurrent event will be used in the analysis.
Estimand Label	**Estimand 1c (Sensitivity Analyses)**

Intercurrent Event Strategy:	(ICEs are described in Table 11.)
ICE-1 (Death)	Composite strategy
ICE-2 (Life-saving procedures including ICU admission)	Treatment policy strategy
ICE-3 (All other events)	Treatment policy strategy
Rationale for Strategies	The sensitivity analysis for the primary estimand will be conducted using a control-based imputation and a delta-adjusted imputation (tipping point). ICE-1: For both control-based and delta-adjusted imputation, the worst outcome will be imputed, i.e., treatment failure. ICE-2 and 3: For the control-based imputation, missing outcomes are imputed based on an imputation model informed by participants with ICE-2 or 3 who had outcomes collected after the ICE. The imputation model is informed only by the participants in the placebo group when imputing for all treatment groups. For the delta-adjusted based imputation, missing outcomes will be imputed based on an imputation model informed by participants with ICE-2 or 3 who had outcomes collected after the ICE. The probability of an imputed outcome is adjusted by adding a pre-defined delta (on the logit scale). Imputation will be informed by respective treatment groups. Separate values of the delta parameter will be used in the treatment and control groups, giving rise to a two-dimensional tipping point analysis.

First Key Secondary Objective	
First Key secondary objective	To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection.
Estimand Label	**Estimand 2**
Estimand Description	Compare distribution of *time to recovery during the 28 days after dosing* between each of CPI-006 plus SOC groups versus placebo plus SOC group in hospitalized participants with mild to moderately symptomatic and virologic-confirmed COVID-19 infection.
Target Population	Mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19 who meet all inclusion and exclusion criteria
Endpoint	Time to recovery during the 28 days after dosing where day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
Treatment Condition(s)	One infusion on Day 1 of CPI-006 at dose of 1 mg/kg or 2 mg/kg, or placebo in 15 minutes, plus SOC per the guideline of the investigation site.
Population-Level Summary	Compare the distribution of time to recovery between a CPI-006 dose plus SOC versus placebo plus SOC within 28 days after dosing.
ICE-1 (Death)	Composite strategy
ICE-2 (Life-saving procedures including ICU admission)	Treatment policy strategy
ICE-3 (All other events)	Treatment policy strategy
Rationale for Strategies	A Treatment policy strategy is used to assess the treatment effect during 28-days after dosing irrespective of the ICE's except death as this reflects the intended usage in this population. Needing of life-saving procedures would impact on and therefore be reflected by the time-to-recovery endpoint. Every attempt will be taken to measure the endpoint through 28-day period. All-cause death will be considered as non-recovery and censored at Day 28 in the Kaplan-Meier estimate and log-rank test.

Second Key Secondary Objective	
Second Key secondary objective	To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection
Estimand Label	**Estimand 3**
Estimand Description	Compare distribution of *time to clinical improvement during the 28 days after dosing* between each of CPI-006 plus SOC groups versus placebo plus SOC group in hospitalized participants with mild to moderately symptomatic and virologic-confirmed COVID-19 infection.
Target Population	Mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19 who meet all inclusion and exclusion criteria
Endpoint	Time (in days) to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) where clinical improvement is determined by ≥ 2 points improvement in the 8-point ordinal scale with no relapsing during the 28 days after dosing.
Treatment Condition(s)	One infusion on Day 1 of CPI-006 at dose of 1 mg/kg or 2 mg/kg, or placebo in 15 minutes, plus SOC per the guideline of the investigation site.
Population-Level Summary	Compare the distribution of time to clinical improvement during 28 days study after dosing between each CPI-006 dose plus SOC versus placebo plus SOC.
Intercurrent Event Strategy:	
ICE-1 (Death)	Composite strategy
ICE-2 (Life-saving procedures including ICU admission)	Treatment policy strategy
ICE-3 (All other events)	Treatment policy strategy
Rationale for Strategies	A Treatment policy strategy is used to assess the treatment effect during 28-days after dosing irrespective of the ICE's except death as this reflects the intended usage in this population. Needing of life-saving procedures would impact on and therefore be reflected by the time-to-improvement endpoint. Every attempt will be taken to measure the endpoint through 28-day period. All-cause death will be considered as non-improvement and censored at Day 28 in the Kaplan-Meier estimate and log-rank test.

Third Key Secondary Objective	
Third Key secondary objective	Mortality rate over the 28 days after dosing between CPI-006 plus SOC and placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection
Estimand Label	**Estimand 4**
Estimand Description	Ratio in cumulative *mortality* rates up to 28 days after dosing between each of CPI-006 plus SOC groups versus placebo plus SOC group in hospitalized participants with mild to moderately symptomatic and virologic-confirmed COVID-19 infection.
Target Population	Mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19 who meet all inclusion and exclusion criteria
Endpoint	The event is all-cause death up to 28 days after dosing. Time (in days) to death will be defined as from the study dose infusion day to date of death through Day 28.
Treatment Condition(s)	One infusion on Day 1 of CPI-006 at dose of 1 mg/kg or 2 mg/kg, or placebo in 15 minutes, plus SOC per the guideline of the investigation site.
Population-Level Summary	Ratio in cumulative mortality rates during the 28 days after dosing between each CPI-006 dose plus SOC group versus placebo plus SOC group.
Intercurrent Event Strategy	
ICE-1 (Death)	Composite strategy
ICE-2 (Life-saving procedures including ICU admission)	Treatment policy strategy
ICE-3 (All other events)	Treatment policy strategy
Rationale for Strategies	The cumulative mortality rate is the endpoint. Treatment policy strategy will be used to estimate the treatment effect regardless of the other ICEs (ICE-2 and 3). This strategy aligns with the Intent-To-Treatment principle.

APPENDIX 10
EFFICACY ANALYSIS FOR THE PRIMARY ENDPOINT

The primary endpoint is the proportion of participants alive and free from respiratory deterioration during the 28 days after dosing. The endpoint will be analyzed using the method described in (Ge et al. 2011). This method computes a population-level estimate for the treatment difference (i.e., difference in the proportions of patients alive and free of respiratory failure during the 28 days after dosing) and incorporates adjustment for the stratification factors.

The method is based on a logistic regression model. To define this model, consider the ith participant, $i = 1, \ldots, n$, where n is the total number of participants in the trial, and let y_i denote the binary outcome for the primary endpoint, i.e., alive and free of respiratory deterioration during the 28 days with 1 to denote alive and free of respiratory deterioration, and 0 for otherwise. The treatment indicator for the ith patient will be denoted by t_i, where $t_i = 0$ corresponds to the control arm, Treatment C, and $t_i = 1$ corresponds to the treatment arm, Treatment A (or B). Finally, the vector of stratification factors for the ith patient (age, presence of comorbidities, and region of the world) will be denoted by $\boldsymbol{x}_i$. The logistic regression model is given by

$$\text{logit}\, p_i = \beta_1 + \beta_2 t_i + \boldsymbol{\beta}_3' \boldsymbol{x}_i,$$

where $p_i = P(y_i = 1)$ is the probability of being alive and free of respiratory deterioration of participant i, β_1 is the control effect, β_2 is the treatment effect, $\boldsymbol{\beta}_3$ is the vector of model parameters corresponding to the stratification factors and the prime denotes transposition of $\boldsymbol{\beta}_3$.

After the model has been fitted to the data, the model parameters will be estimated. The estimates are denoted by $\hat{\beta}_1$, $\hat{\beta}_2$ and $\widehat{\boldsymbol{\beta}}_3$, respectively. The two potential outcomes will be computed from the model for each patient. These outcomes represent the outcome probabilities for the ith patient if this patient had been assigned to the control or CPI-006 arm:

$$p_{i0} = P(y_i = 1 | t_i = 0) = (1 + \exp(-\hat{\beta}_1 - \widehat{\boldsymbol{\beta}}_3' \boldsymbol{x}_i))^{-1},$$

$$p_{i1} = P(y_i = 1 | t_i = 1) = (1 + \exp(-\hat{\beta}_1 - \hat{\beta}_2 - \widehat{\boldsymbol{\beta}}_3' \boldsymbol{x}_i))^{-1}.$$

The population-level estimate for the treatment difference is defined as

$$d = n^{-1} \sum_{i=1}^{n} p_{i1} - n^{-1} \sum_{i=1}^{n} p_{i0}.$$

The standard error of d, SE(d), will be estimated using the delta method (Ge et al. 2011, Appendix A).

The test statistics $d/\,\text{SE}(d)$ is asymptotically distributed as the standard normal distribution. The hypothesis H_{A1} (Protocol 9.2.4.1.3.) will be rejected if the value of $d/\,\text{SE}(d)$ is above $z_{(1-\alpha)}$ where $\alpha = 0.025$ or 0.0125 depending on the multiplicity adjustment of the gatekeeping procedure. Here $z_{(1-\alpha)}$ denotes the quantile of the standard normal distribution above which

the probability (area under the curve) equals to α. Same testing criteria will be applied for H_{B1}. The confidence interval of d will be provided by $d \pm Z_{(1-\alpha)}\, SE(d)$.

APPENDIX 11
GATEKEEPING STRATEGY FOR TESTING HYPOTHESES

1. STATISTICAL HYPOTHESES

The following hypotheses are defined for the comparisons between Treatment A (CPI-006 at a dose of 2 mg/kg plus SOC) and Treatment C (placebo plus SOC) - Treatment A Family:

Null Hypothesis H_{Ai}: Treatment A is not superior to Treatment C with respect to endpoint i

versus

H'_{Ai}: Treatment A is superior to Treatment C with respect to endpoint i,

where i = 1 for the primary endpoint "proportion of participants alive and free from respiratory deterioration during the 28 days after dosing";

i = 2 for the secondary endpoint "time to recovery during the 28 days after dosing";

i = 3 for the secondary endpoint "time to clinical improvement by at least 2 points during the 28 days after dosing";

Null Hypothesis H_{A4}: Treatment A is inferior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

versus

H'_{A4}: Treatment A is non-inferior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

Null Hypothesis H_{A5}: Treatment A is not superior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

versus

H'_{A5}: Treatment A is superior to Treatment C with respect to the secondary endpoint "mortality rate over the 28 days after dosing".

The same hypotheses will be tested for the comparison between Treatment B and C - Treatment B Family: H_{Bi} versus H'_{Bi}, where i = 1, 2, 3, 4, and 5.

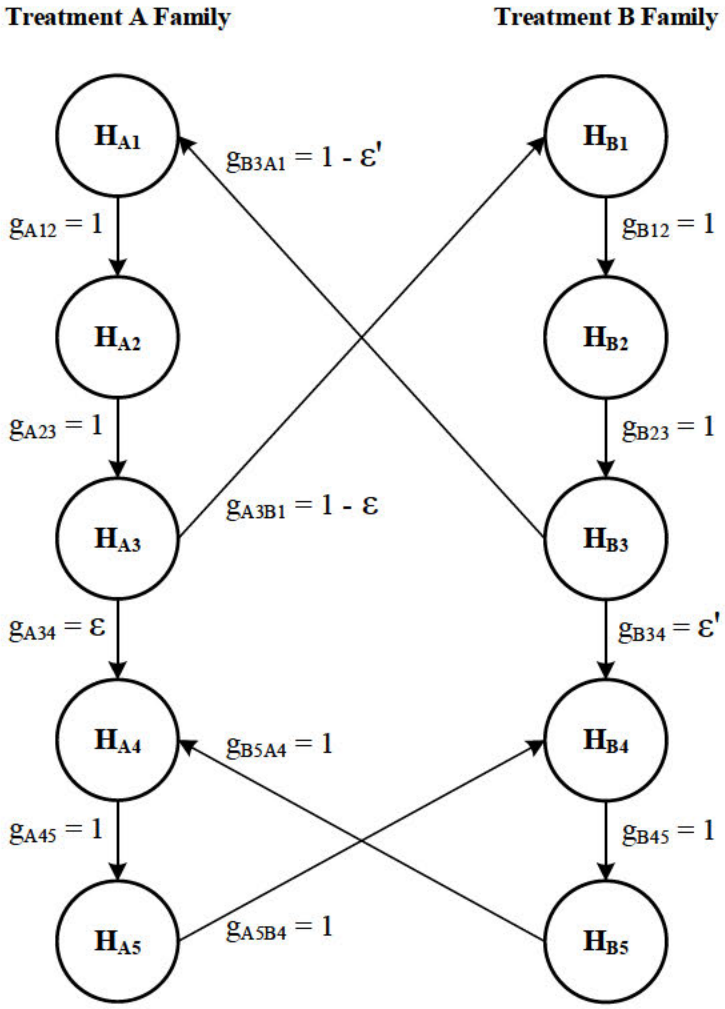
2. PARALLEL GATEKEEPING PROCEDURE FOR TESTING HYPOTHESES

A multiplicity adjustment strategy is designed to control the study level overall Type I error rate α at a one-sided 0.025 for the hypotheses in Treatment A and B families defined above and illustrated using Bretz's graphical method (Bretz et al., 2009). Note that the five null hypotheses are arranged in a hierarchical order within the hypothesis family of each treatment. This multiplicity adjustment is aligned with the logical restrictions among the ten null hypotheses, i.e., a hypothesis in a given treatment family can be tested only if all

preceding null hypotheses in the same treatment family are rejected. For example, H_{A3} can be tested only if H_{A1} and H_{A2} are rejected.

The testing strategy for the ten hypotheses is depicted graphically in Figure 2.

Figure 2 Testing Strategy Based on the Gatekeeping Procedure



The testing strategy is designed using the following gatekeeping parameters to control the overall Type I error rate α at a one-sided 0.025 level:

- The overall α=0.025 is initially equally split for Treatment A Family and Treatment B Family for testing the null hypotheses within a family.
- The transition parameters are:
  - $g_{A12} = 1$;
  - $g_{A23} = 1$;
  - $g_{A34} = \varepsilon$;
  - $g_{A45} = 1$;
  - $g_{B12} = 1$;
  - $g_{B23} = 1$;

- $g_{B34} = \varepsilon'$;
- $g_{B45} = 1$;
- $g_{A3B1} = 1 - \varepsilon$;
- $g_{B3A1} = 1 - \varepsilon'$;
- $g_{A5B4} = 1$;
- $g_{B5A4} = 1$;

The transition parameters determine the fraction of the local α level that is to be allocated to a designated hypothesis in case the prior hypothesis in the same family is rejected.

- The values of ε and ε' are dependent on the Step (see below) at which the hypotheses are rejected. Note that as indicated in Figure 2, the choice of transition parameters ensures that the hypotheses H_{A4} and H_{B4} will be tested only if H_{A3} and H_{B3} are both rejected, or, in other words, only if the hypotheses H_{Ai} and H_{Bi}, i=1, 2, and 3 are all rejected.

In details, the multiplicity adjustment strategy will be implemented using the following serial testing algorithm (Dmitrienko and D'Agostino, 2013). The algorithm follows the hierarchical order and is defined as follows:

- Step 1: Test the hypotheses H_{A1} and H_{B1} each at the $\alpha = 0.0125$ level.
  - Proceed to Step 2 if at least one hypothesis is rejected at this step.
  - Otherwise, stop the test procedure.
- Step 2: Test the hypotheses H_{A2} and/or H_{B2} each at the $\alpha = 0.0125$ level if H_{A1} and/or H_{B1}, respectively, is/are rejected at Step 1.
  - Proceed to Step 3 if at least one hypothesis is rejected at this step.
  - Otherwise, stop the test procedure.
- Step 3: Test the hypotheses H_{A3} and/or H_{B3} each at the $\alpha = 0.0125$ level if H_{A2} and/or H_{B2}, respectively, is/are rejected at Step 2.
  - Proceed to Step 4 if only one hypothesis is rejected.
  - Proceed to Step 5 if both hypotheses are rejected at this step. In this case, set $\varepsilon = \varepsilon' = 1$, i.e., $g_{A34} = g_{B34} = 1$ and $g_{A3B1} = g_{B3A1} = 0$.
  - Otherwise, stop the test procedure.
- Step 4:
  - If the hypothesis H_{A3} is rejected at Step 3 and if any of the hypotheses in the Treatment B Family up to Step 3 is not rejected, then return to Step 1 and re-test all the hypotheses in the Treatment B Family at the full $\alpha = 0.025$ level following the hierarchical order defined in Figure 2. In this case, $\varepsilon = 0$, and $g_{A3B1} = 1$. If H_{B3} is rejected as the outcome of re-testing, proceed to Step 5. If H_{B3} is not rejected, stop the testing procedure.
  - Similarly, if the hypothesis H_{B3} is rejected at Step 3 and if any of the hypotheses in the Treatment A Family up to Step 3 is not rejected, then return to Step 1 and re-test all the hypotheses in the Treatment A Family at the full α

= 0.025 level following the hierarchical order defined in Figure 2. In this case, $\varepsilon' = 0$, and $g_{B3A1} = 1$. If H_{A3} is rejected as the outcome of re-testing, proceed to Step 5. If H_{A3} is not rejected, stop the testing procedure.

- Step 5: Test the hypotheses H_{A4} and H_{B4} each at the $\alpha = 0.0125$ level.
  - Proceed to Step 6 if at least one hypothesis is rejected at this step.
  - Otherwise, stop the test procedure.
- Step 6: Test the hypotheses H_{A5} and/or H_{B5} each at the $\alpha = 0.0125$ level if H_{A4} and/or H_{B4}, respectively, is/are rejected at Step 5.
  - Proceed to Step 7 if only one hypothesis is rejected.
  - If both hypotheses are rejected or neither hypothesis is rejected at this step, stop the test procedure.
- Step 7:
  - If the hypothesis H_{A5} is rejected and if H_{B5} is not rejected at Step 6, then return to Step 5 and re-test the hypotheses H_{B4} and H_{B5} at the full $\alpha = 0.025$ level following the hierarchical order defined in Figure 2.
  - Similarly, if the hypothesis H_{B5} is rejected and if H_{A5} is not rejected at Step 6, then return to Step 5 and re-test the hypotheses H_{A4} and H_{A5} at the full $\alpha = 0.025$ level following the hierarchical order defined in Figure 2.
  - This is the end of the testing procedure.

APPENDIX 12
FUTILITY CRITERIA AND ITS OPERATING CHARACTERISTICS FOR GO OR NO-GO DECISIONS BASED ON EFFICACY DATA AT INTERIM ANALYSES 1 AND 2

1. INTRODUCTION

This document provides a description of the futility criteria and its operating characteristics that will guide the Go or No-Go decisions for the study based on the primary efficacy endpoint at the interim analyses 1 and 2. The efficacy endpoint is the proportion of participants who are alive and free from respiratory deterioration during the 28 days after dosing (the Response Rate) (Protocol Section 3. OBJECTIVES AND ENDPOINTS). At each interim analysis, the difference between Treatment A (CPI-006 2 mg/kg plus SOC) and Treatment C (placebo plus SOC) with respect to the primary efficacy endpoint will be evaluated. A Go or No-Go decision will be made by comparing the difference between the treatments according to the futility criteria. A similar evaluation will be made to assess the difference between Treatment B (CPI-006 1 mg/kg plus SOC) and C. A Go or No-Go decision will be made for Treatment B independent of the decision for Treatment A.

2. SIMULATION STUDY FOR THE FUTILITY CRITERIA BASED ON THE PRIMARY EFFICACY ENDPOINT

The purpose of the simulation study was to determine a set of futility criteria for the study and to investigate the operating characteristics of the futility criteria including the estimation of the probability of No-Go outcome according to the futility criteria at the interim analyses.

Extensive simulations were performed based on the primary efficacy endpoint in response rate. Since there was no difference in response rates assumed for Treatment A and B in the simulation study, the selected futility criteria and the described operating characteristics apply to both Treatment A and B (the Treatment) in comparison to Treatment C (the Control). In the simulation study, the response rate for Control was assumed to be 78%, 80%, 82% and 84%. The 84% for Control was used for the sample size and power assessment for the study (Protocol, Section 9.1. SAMPLE SIZE DETERMINATION).

The response rates of Treatment that were considered as an “inferior treatment”, “ineffective treatment”, or “highly effective treatment” in comparison to Control were investigated for the performance of the futility criteria. The response rates of Treatment that were investigated for the Control rates of 78% and 84% are given in Table 13. The Control rates of 78% and 84% represent the range of investigation for the operating characteristics of the futility criteria. The simulations for the Control rates of 80% and 82%, being in between 78% and 84%, yielded comparable outcomes to these for 78% and 84%, and hence are not provided in this document.

Table 13 Simulation Scenarios

Simulation Scenarios	Response Rate for Treatment (Difference) vs Control	
	Control = 84%	**Control = 78%**
Inferior Treatment vs Control	76% (-8%)	70% (-8%)
	80% (-4%)	74% (-4%)
Ineffective Treatment vs Control	86% (+2%)	80% (+2%)
Highly Effective Treatment vs Control	92% (+8%)	86% (+8%)
	94% (+10%)	88% (+10%)

3. SIMULATION PROCEDURES

For each of the above simulation scenarios, 100,000 studies were simulated. Each study was simulated in either 1 step (for the study that met the No-Go criteria at Step 1) or 2 steps:

Step 1: For each study, 75 "participants" being either a "Responder" or "Non-responder" were simulated for Treatment and Control arms from a Bernoulli distribution with the single parameter being the Response Rate specified for Treatment or Control as in the above table. The difference between Treatment and Control was calculated based on the response rate of the treatment arms. The difference was then standardized to a value on the Normal(0,1) scale using the formula for the 2-sample binomial test with standard normal approximation:

$$z = \frac{(\hat{p}_T - \hat{p}_C)}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_T} + \frac{\hat{p}_C(1-\hat{p}_C)}{n_C}}} *$$

* Sample estimates are denoted by the ^ symbol; $\hat{p}_T, \hat{p}_C$ are the response rate of Treatment and Control, n_T and n_C are the number of subjects in Treatment and Control.

Then the standardized treatment difference was compared to a value pre-determined as the "futility threshold" on the Normal(0,1) scale. On the Normal(0,1) scale, negative numbers correspond to comparisons that the Treatment response was lower than Control. The larger the magnitude of the negative numbers on the Normal(0,1) scale, the worse the corresponding Treatment responses are compared to Control. Conversely, positive numbers on the Normal(0,1) scale correspond to comparisons that Treatment response was higher than Control. The larger the positive numbers on the Normal(0,1) scale, the better the corresponding Treatment are compared to Control. The value 0 corresponds to no difference between Treatment and Control.

A simulated study was stopped at Step 1 if the standardized treatment difference is equal to or less than the futility threshold indicating that Treatment failed to achieve the level of efficacy in response rate compared to Control as defined by the futility threshold at interim analysis 1, and therefore the study was discontinued. The probability of No-Go per the futility criteria at interim analysis 1 is estimated by the percentage of the simulated studies that were stopped out of the 100,000 simulated studies.

Step 2: For a simulated study that was not stopped at interim analysis 1 (i.e., that the standardized difference between treatment response rates was greater than the futility threshold), an additional 125 participants were simulated for each treatment arm from the respective Bernoulli distributions, making the total number of participants to be 200 per arm for interim analysis 2. Similarly, the standardized treatment difference in response rates was calculated and compared to the futility threshold pre-determined for interim analysis 2. The study was stopped at interim analysis 2 if the standardized treatment difference is equal to or less than the futility threshold. The probability of No-Go at either interim analysis 1 or 2 was estimated by the percentage of the simulated studies that were stopped at either interim analysis out of the 100,000 simulated studies.

4. FUTILITY CRITERIA AND OPERATING CHARACTERISTICS BASED ON SIMULATION RESULTS

The futility criteria for interim analyses 1 and 2 were determined based on the simulation study, and summarized with the operating characteristics for 2 Control response rates of 84% and 78% in Table 14 and Table 15, respectively. Additionally, the Conditional Power (CP) assuming that the futility thresholds at interim analyses 1 and 2 are the observed Treatment vs Control differences, and assuming the future data would be consistent with the pre-defined alternative hypothesis of beneficial effect (Column 2, Table 14 and Table 15) is provided in Column 4 in the tables. For example, if at the interim analysis 2 (Table 15), the observed response rates are 88.2% vs 84% (z-score 1.2) for Treatment vs Control, then the CP for reaching a significance at $\alpha = 0.0125$ at the end of the study would be 38.6% assuming that the actual response rates for Treatment and Control are still 92% vs 84%, respectively. With the response rates of 92% vs 84%, based on simulation, there would be approximately 13% chance that the study could be stopped for futility at either the interim analysis 1 or 2.

Table 14 Operating Characteristics of the Futility Stopping Criteria at Interim Analysis 1 with 25% Information

Simulation Scenarios	Response Rate for Treatment vs Control	Futility Threshold on N(0,1) Scale for No-Go at Interim Analysis 1 (N=75 per Arm)	Conditional Power (%) at Interim Analysis 1 under the Hypotheses in Column 2	Probability (%) of No-Go at Interim Analysis 1 based on Simulation
Inferior Treatment vs Control	76% vs 84%	**-0.4** (Corresponding to 81.5% vs 84%)	2.3E-07	80.4
	80% vs 84%		3.5E-05	61.4
Ineffective Treatment vs Control	86% vs 84%		1.4	24.4
Highly Effective Treatment vs Control	92% vs 84%		46.5	2.9
	94% vs 84%		76.7	0.8
Inferior Treatment vs Control	70% vs 78%	**-0.4** (Corresponding to 75.2% vs 78%)	6.2E-07	74.7
	74% vs 78%		5.6E-05	55.0
Ineffective Treatment vs Control	80% vs 78%		1.1	24.2
Highly Effective Treatment vs Control	86% vs 78%		30.6	5.1
	88% vs 78%		55.4	2.3

Table 15 Operating Characteristics of the Futility Stopping Criteria at Interim Analysis 2 with 60% Information

Simulation Scenarios	Response Rate for Treatment vs Control	Futility Threshold on N(0,1) Scale for No-Go at Interim Analysis 2 (N=200 per Arm)	Conditional Power (%) at Interim Analysis 2 under the Hypotheses in Column 2	Probability (%) of No-Go at Interim Analyses 1 or 2
Inferior Treatment vs Control	76% vs 84%	**1.2** (Corresponding to 88.2% vs 84%)	1.2E-04	99.9
	80% vs 84%		1.6E-03	98.6
Ineffective Treatment vs Control	86% vs 84%		4.20	75.8
Highly Effective Treatment vs Control	92% vs 84%		38.6	13.0
	94% vs 84%		60.5	3.1
Inferior Treatment vs Control	70% vs 78%	**1.2** (Corresponding to 82.8% vs 78%)	1.9E-04	99.8
	74% vs 78%		2.3E-03	98.2
Ineffective Treatment vs Control	80% vs 78%		4.7	77.4
Highly Effective Treatment vs Control	86% vs 78%		35.1	22.7
	88% vs 78%		53.5	9.8

5. SUMMARY OF RESULTS

A reasonably broad range of the Response Rate of Control, and the selected Response Rates of Treatment that were considered as inferior, ineffective, or highly effective in comparison to Control were studied to determine a set of futility stopping criteria by simulations. The simulation study supported using -0.4 and 1.2 on the Normal(0,1) scale as the futility stopping threshold at interim analyses 1 and 2, respectively. Treatment A or B (or both) would be discontinued at the interim analysis 1 or 2 if the standardized difference in response rate between Treatment A (or B) and C (A minus C or B minus C) is at or below the respective futility threshold at the interim analysis. With the futility thresholds of -0.4 and 1.2 for the interim analysis 1 and 2, respectively, the probability of No-Go decision at the interim analyses is high for an inferior Treatment (55%-80% at interim analysis 1, and >98% at interim analysis 2); and is moderate for an ineffective Treatment (24% at interim analysis 1, 75% at interim analysis 2); and is low (approximately 5% or lower at interim analysis 1, and approximately 20% or lower at interim analysis 2) for a highly effective Treatment. The No-Go probabilities were comparable across all the simulated scenarios as described in Section 2.

APPENDIX 13
OPERATING CHARACTERISTICS OF NON-INFERIORITY TEST FOR TREATMENT A (OR B) RELATIVE TO TREATMENT C IN TERMS OF THE RATIO OF THE MORTALITY RATES

1. Introduction

The cumulative mortality rate over the 28 day period from dosing is a key secondary endpoint. Non-inferiority of Treatment A (or B) (Treatment) in comparison with Treatment C (Control) will be assessed based on the ratio of Treatment mortality relative to Control mortality. A multiplicity adjusted 2-sided confidence interval (CI) (97.5% or 95%, depending on the multiplicity adjustment) will be calculated for this ratio (Protocol Section 9.2.4.1.2) The CI will be used to assess the non-inferiority of Treatment in comparison to Control against the non-inferiority margin of 1.3. If the upper limit of the CI of ratio is equal to or less than 1.3, the non-inferiority of Treatment relative to Control is established.

This appendix provides a description of the operating characteristics of the approach to determine the non-inferiority as described above.

2. Simulation Study for Assessing Non-inferiority

The purpose of the simulation study was to evaluate the chance for establishing non-inferiority for a range of mortality rates for Treatment and Control, as well as the chance for rejection of non-inferiority, based on the non-inferiority margin of 30%.

A single parameter exponential distribution was assumed for the time-to-mortality variable of interest that would be simulated from the exponential distribution $F(t) = 1 - e^{-\lambda t}$. Since the mortality endpoint is the cumulative mortality over 28 days, the time variable "t" is fixed at 28 (days). For each pair of underlying mortality rates of Treatment and Control, 1000 studies were simulated. In each study, 330 observations of the time-to-mortality variable for each of Treatment and Control were simulated from the treatment specific exponential distribution determined by the underlying mortality rates of the treatment groups.

To be more specific, if a given cumulative mortality rate of Treatment over the 28 days after dosing was "x", then the single parameter λ of the exponential distribution function $F(t) = 1 - e^{-\lambda t} = x$ was selected to correspond to the specified mortality rate x at Day 28. Similarly, an exponential distribution was derived for the specified Control mortality rate at Day 28. Three hundred thirty observations were simulated from these exponential distributions up to t = 28 days for each Treatment and Control groups. Simulated mortality events exceeding Day 28 were censored at Day 28, thus each simulated random variate represents one participant's observed time-to-mortality outcome through Day 28. The cumulative mortality rate of Treatment and Control with the associated variance were estimated separately based on the 330 observations using the Kaplan-Meier method. The ratio of the Treatment to Control mortality rates at Day 28 and its accompanying variance

were calculated. The CI for this Day 28 mortality ratio with the multiplicity adjusted confidence level was calculated following the procedure presented for Estimand 4 in Protocol Section 9.2.4.1.2.

3. Simulation Results

The simulation outcomes were summarized in Table 16 and Table 17 to describe the operating characteristics of the assessment for the non-inferiority of Treatment relative to Control based on the ratio of the cumulative mortality of the two groups.

Table 16 provides the ranges of the underlying mortality rates of the two treatment groups with the row headers for Treatment and column headers for Control. The calculated ratio for each pair of the underlying mortality rates for Treatment and Control is presented in the body of the table. The entries of "1" on a diagonal are the ratios for equal mortality rates of the two treatments. The entries being < 1 below the diagonal with entries 1 represent the cases that the mortality of Treatment is lower than that of Control; while the entries being > 1 above the diagonal represent the cases that the mortality of Treatment is higher than that of Control.

For each pair of mortality rates of Treatment and Control in Table 16, 1000 studies were simulated each with 330 observations of time-to-mortality data for each treatment group following the procedure described in Section 2. The Day 28 mortality rate of each treatment group was estimated, and a 2-sided CI of the ratio of estimated mortality rates of Treatment relative to Control was calculated based on the simulated data of each study. Then the percentage of the studies with the upper limit of the CI that were ≤ 1.3 was determined out of the total of 1000 studies simulated for this pair of underlying mortality rates. These percentages are presented in Table 17. Although the confidence level of the CI's should be determined by the multiplicity adjustment as the non-inferiority would be assessed within the gatekeeping procedure, in this simulation the 2-sided confidence level of 97.5% was used for the calculation of all the CI's.

For example, for the underlying mortality rates of 6% and 8% of Treatment and Control, respectively, 97% of the 1000 simulated studies had the upper limit of the CI ≤ 1.3. This percentage estimates the probability of establishing non-inferiority of Treatment relative to Control for this pair of mortality rates corresponding to its row and column labels.

The entries highlighted in blue along the diagonal are cases of equal mortality rates between Treatment and Control. The values for these cases are reasonably high, indicating that there would be sufficient power for non-inferiority to be established for Treatment relative to Control. The power for the non-inferiority comparison is trending higher as the mortality rate for Treatment is trending lower relative to Control. Conversely, the power for non-inferiority is generally low for the cases that the ratio of mortalities of Treatment relative to Control exceeds 1.5.

Table 16 Multiplicative Ratios Between Treatment Mortality Relative to Control Mortality

Mortality Rate of CPI-006	Mortality Rate of Control								
	12%	11%	10%	9%	8%	7%	6%	5%	4%
16%	1.33	1.45	1.60	1.78	2.00	2.29	2.67	3.20	4.00
15%	1.25	1.36	1.50	1.67	1.88	2.14	2.50	3.00	3.75
14%	1.17	1.27	1.40	1.56	1.75	2.00	2.33	2.80	3.50
13%	1.08	1.18	1.30	1.44	1.63	1.86	2.17	2.60	3.25
12%	1.00	1.09	1.20	1.33	1.50	1.71	2.00	2.40	3.00
11%	0.92	1.00	1.10	1.22	1.38	1.57	1.83	2.20	2.75
10%	0.83	0.91	1.00	1.11	1.25	1.43	1.67	2.00	2.50
9%	0.75	0.82	0.90	1.00	1.13	1.29	1.50	1.80	2.25
8%	0.67	0.73	0.80	0.89	1.00	1.14	1.33	1.60	2.00
7%	0.58	0.64	0.70	0.78	0.88	1.00	1.17	1.40	1.75
6%	0.50	0.55	0.60	0.67	0.75	0.86	1.00	1.20	1.50
5%	0.42	0.45	0.50	0.56	0.63	0.71	0.83	1.00	1.25
4%	0.33	0.36	0.40	0.44	0.50	0.57	0.67	0.80	1.00
3%	0.25	0.27	0.30	0.33	0.38	0.43	0.50	0.60	0.75
2%	0.17	0.18	0.20	0.22	0.25	0.29	0.33	0.40	0.50

Table 17 **Estimated Power for Non-inferiority of Treatment Relative to Control in Terms of Mortality Ratio**

Mortality Rate of CPI-006	Mortality Rate of Control								
	12%	11%	10%	9%	8%	7%	6%	5%	4%
16%	0.44	0.29	0.15	0.08	0.03	0.00	0.00	0.00	0.00
15%	0.58	0.41	0.27	0.12	0.05	0.01	0.00	0.00	0.00
14%	0.71	0.57	0.38	0.20	0.10	0.03	0.01	0.00	0.00
13%	0.81	0.67	0.49	0.32	0.16	0.06	0.02	0.00	0.00
12%	0.89	0.81	0.61	0.44	0.27	0.12	0.03	0.01	0.00
11%	0.95	0.88	0.78	0.58	0.42	0.22	0.09	0.02	0.00
10%	0.97	0.96	0.88	0.74	0.57	0.36	0.17	0.07	0.01
9%	0.99	0.98	0.93	0.85	0.71	0.53	0.30	0.11	0.04
8%	1.00	0.99	0.97	0.93	0.82	0.65	0.44	0.22	0.08
7%	1.00	1.00	0.99	0.98	0.92	0.84	0.63	0.42	0.16
6%	1.00	1.00	1.00	0.99	0.97	0.92	0.82	0.58	0.34
5%	1.00	1.00	1.00	1.00	0.99	0.97	0.91	0.74	0.53
4%	1.00	1.00	1.00	1.00	1.00	1.00	0.97	0.91	0.77
3%	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.98	0.90
2%	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.99

APPENDIX 14
PROTOCOL AMENDMENT HISTORY

Table 18 Document History

Document History	Date of Issue
Version 003 (Amendment 2)	23-March-2021
Version 002 (Amendment 1)	11-January-2021
Version 001 (Original Protocol)	06-November-2020

Protocol

Protocol Title:	**Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients**
Protocol Number:	**CPI-006-003**
Regulatory Agency Identifier Number(s):	[redacted] **EudraCT: 2020-005305-54**
Compound Number:	**CPI-006**
Study Phase:	**3**
Sponsor Name:	**Corvus Pharmaceuticals**
Sponsor Address:	**863 Mitten Rd, Suite 102 Burlingame, CA 94010, USA**
Version Number:	**002**
Date Final:	**11 January 2021**

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	002

This clinical trial protocol was subject to critical review and has been approved by Corvus Pharmaceuticals.

[redacted]

Sponsor Signatory **Date**

[redacted]

Medical Monitor Name and Contact Information:

Name: [redacted]

Address: [redacted]

Email: [redacted]
Office Phone:
Cell Phone:

INVESTIGATOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	002

I have read and understood the current version of the protocol (as listed above). I agree to conduct this trial in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), all applicable regulatory requirements, and the general ethical principles outlined in the Declaration of Helsinki.

I agree to ensure that no deviation from, or changes to the protocol will take place without prior agreement from Corvus Pharmaceuticals and documented approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I will ensure that all staff members under my supervision involved in the conduct of this study are informed about the protocol and protocol amendments, the investigational products, and their study-related duties and functions.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational products and processes or methods of Corvus.

Investigator Signatory Name: **Title:**	**Date**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin converting enzyme 2
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the serum or plasma concentration-time curve
$AUC_{(0\text{-}169)}$	AUC from the start of infusion to 169 hours after the start of infusion
AUC_{last}	AUC from time zero to the time of the last quantifiable concentration
BCR	B cell receptor
$C_{(0)}$	the initial CPI-006 concentration measured 30 minutes after completion of the infusion
CBC	complete blood count
CCP	Covid-19 Convalescent Plasma
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum drug concentration in serum or plasma
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
DLT	dose-limiting toxicity
ELISA	enzyme-linked immunosorbent assay
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

Abbreviation	Definition
HIPAA	United States Health Insurance Portability and Accountability Act
HLA-DR	human leukocyte antigen – DR isotype
IC_{50}	concentration required for 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2, -6, -10	interleukin 2, 6, 10
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MERS	Middle East respiratory syndrome
NEWS2	National Early Warning Score 2
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed adverse effect level
O_2	oxygen
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PD1	programmed cell death 1 receptor

Abbreviation	Definition
PE	polyethylene
PES	polyethersulfone
PK	pharmacokinetic(s)
PO	by mouth (orally)
PO/PE	polyolefin/polyethylene
PT	prothrombin time
PVC	polyvinylchloride
RBC	red blood cell
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sickle cell disease
SoA	schedule of activities
SOB	shortness of breath
SOC	standard of care
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US/USA	United States of America
USP	United States Pharmacopeia
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Name of Sponsor: Corvus Pharmaceuticals, Inc.

Investigational Product: CPI-006

Title of Study: Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients

Phase of Development: 3

Number of Participants: Approximately 1000 evaluable participants for an estimated total of 330 evaluable participants per treatment group

Study Centers: Multicenter

Study Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the proportion of participants alive and respiratory failure free during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who are alive and free from respiratory deterioration defined as follows per the 8-point ordinal scale (Appendix 6): o Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 o Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Key Secondary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale)

Objectives	Endpoints
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28
• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of ≥ 50% of the Covid-19 -attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline
Additional Secondary	
• To compare the mortality rate due to any cause during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who died during the 28 days after dosing
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, Day of Discharge, Days 14, 21, and 28
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21, and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 (Appendix 7) consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)

Objectives	Endpoints
• To compare the medical interventions/procedures during the 28 days after dosing of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate of procedures including intubation • Rate and duration of mechanical ventilation • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices • Oxygenation free days during the 28 days after dosing • Rate of rehospitalization
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment -emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0
Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• To characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO_2 = oxygen saturation.

Study Design:

This is a Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) or antigen testing for SARS-CoV-2.

Approximately 1000 participants will be randomized at a 1:1:1 ratio to the 3 treatment arms and stratified by the following factors:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg (Treatment A - maximum dose of 200 mg) or 1 mg/kg (Treatment B - maximum dose of 100 mg) intravenously (IV) on Day 1. A placebo will be given at the same schedule as the active drug for participants who receive the control (Treatment C). Participants, investigators, and Corvus will be blinded to the treatment allocation. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies, or any other approved treatment) per those guidelines at the

discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an interactive response technology (IRT) system to obtain the participant number. Every participant that signs the informed consent form (ICF) must be assigned with a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the National Early Warning Score 2 (NEWS2), Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if a participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 10% (approximately 100) of participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when 25%, 40%, 60%, and 80% (approximately 250, 400, 600, and 800, respectively) of participants have completed the Day 28 assessments. The analysis with 25% of participants is the first interim analysis for futility evaluation, and the analysis with 60% of participants is the second interim analysis for both efficacy and futility evaluation.

Study enrollment will be paused after 10% of the participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, the review of the futility analysis, study enrollment will also be paused at this time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for

enrollment for the subsequent reviews after the futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data.

The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

Eligibility: Hospitalized mild to moderately symptomatic Covid-19 patients. Participants may have controlled pre-existing conditions such as cancer and diabetes. Participants will receive standard care for Covid-19.

Test Product, Dose and Administration: CPI-006 single dose at either 1 mg/kg or 2 mg/kg given by IV infusion over 10-15 minutes.

Rationale:

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary redistribution in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients. The high anti-SARS-CoV-2 titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 27 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This Phase 3 study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in participants who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with

CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

Overall Design:

This is a randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized participants with Covid-19. An iDMC will monitor safety, efficacy, and conduct of the study. All participants will be followed for 28 days for production of anti-SARS-CoV-2 antibodies followed by an optional period of 5 months. While in the hospital, participants will receive standard of care monitoring including vital signs every 4-6 hours, or per institutional guidelines and safety assessments. Safety and other disease assessments will be conducted at Days 3, 7, 14, 21, and 28. Discharged participants will be asked to attend post-hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed.

Treatment Groups and Duration:

Participants meeting study entry criteria will be randomized in a 1:1:1 ratio to receive either Treatment A (CPI-006 2 mg/kg plus SOC) or Treatment B (CPI-006 1mg/kg plus SOC) or Treatment C (placebo plus SOC). Participants randomized to Treatment A will receive a single dose of CPI-006 at 2 mg/kg given by IV infusion plus SOC (maximum dose of 200 mg). Participants randomized to Treatment B will receive a single dose of CPI-006 at 1 mg/kg given by IV infusion plus SOC (maximum dose of 100 mg). A placebo will be given at the same schedule as the active drug for participants randomized to Treatment C. All participants will be managed per physician using best SOC for Covid-19 patients. No dose modifications will be allowed.

Statistical Methods:

Hypothesis

The primary hypothesis is that Treatment A will improve the proportion of participants alive and respiratory failure free during the 28 days after dosing based on the 8-point ordinal scale in comparison to Treatment C in mild to moderately symptomatic Covid-19 hospitalized participants.

The first secondary hypothesis is that Treatment A will shorten the time to recovery during the 28 days after dosing based on the 8-point ordinal scale in comparison to Treatment C in mild to moderately symptomatic Covid-19 hospitalized participants.

The second secondary hypothesis is that Treatment A will shorten the time to clinical improvement by at least 2 points during the 28 days after dosing on the 8-point ordinal scale in comparison to Treatment C.

The third secondary hypothesis is that Treatment A will increase the level of IgG targeting the RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 more than Treatment C, as measured

by the area under the IgG level curve above the baseline, calculated over Days 1 (the baseline), 7, 14, 21, 28, and Day of Discharge.

The fourth secondary hypothesis is that Treatment A will shorten the time to resolution of ≥ 50% of the Covid-19-attributable symptoms: fever, cough, sore throat, headache, muscle pain, and/or shortness of breath, reported at baseline in comparison to Treatment C.

The above 5 hypotheses are also applied to the comparison of Treatment B to Treatment C.

Sample Size

Approximately 1000 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1:1 ratio between Treatment A, Treatment B, and Treatment C within each of the strata defined by:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - CKD
    - SCD
    - Organ transplantation
    - Cancer

With approximately 300 participants per treatment arm, there would be an approximately 85% power to show a statistically significant superiority of Treatment A over Treatment C in the proportion of participants alive and respiratory failure free during the 28 days after dosing at an overall 1-sided α level of 0.025 when the true proportion of Treatment A is 92% and that of Treatment C is 84%. The same sample size and power statement also holds for the comparison between Treatment B and C.

An additional 10% of participants will be enrolled to cover the loss-of-follow-up.

Populations for Analyses

For purposes of analyses, the following populations are defined in Table 1.

Table 1 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study and analyzed according to treatment assigned at randomization.
Efficacy	All participants who receive any amount of study drug (CPI-006 or placebo) and have post-baseline efficacy assessment based on the 8-point ordinal scale. The participants will be analyzed according to the treatment actually received.
Safety	All participants who receive any amount of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

Statistical Methods

The primary objective of the study is to determine the difference between the 3 treatments in time to recovery during the 28 days after dosing.

Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (See Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.

Statistical Design

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis and will be performed when approximately 25% (250) of participants have been enrolled into the study with 28 days of follow-up time. Safety and efficacy will be analyzed for futility evaluation.

The second interim analysis is also a non-binding futility and efficacy analysis and will be performed when approximately 60% (600) of participants have completed Day 28 assessments. Comparison between Treatment A and C, and between Treatment B and C, with respect to the primary efficacy endpoint will be made. Should the comparison demonstrate a statistically significant superiority of Treatment A over Treatment C, Corvus may file the results to regulatory authorities for drug approval. The study will continue its course beyond the interim analysis and collect all the planned safety, efficacy, PK, and PD data.

At both interim analyses, unblinded analyses will be provided by a separate unblinded statistician to the iDMC for making the futility decision.

As part of the second interim analysis, Corvus may request the iDMC to assess the primary efficacy endpoint and its conditional power of establishing a significant treatment effect at the final analysis based on the interim data. The total sample size of the study may be increased with the recommendation by iDMC. The sample size adaptation plan and increase

rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the first interim analysis.

The primary analysis of the study is the final analysis. Safety and efficacy analyses will be performed when all the participants of the study have completed the Day 28 assessments.

The 5 endpoints listed below will be tested according to their hierarchical priority defined as they are ordered at both the second interim analysis and final analysis.

The primary efficacy endpoint, the proportion of participants who are alive and respiratory failure free during the 28 days after dosing, as defined above.

Time to recovery during the 28 days after dosing as defined above by the 8-point ordinal scale.

Time to improvement by at least 2 points on the 8-point ordinal scale during the 28 days after dosing.

The change in the level of IgG targeting RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 from baseline measured by the area under the IgG level curve above the baseline over Days 1, 7, 14, 21, 28 and Day of Discharge.

The time to resolution of ≥ 50% of the Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or short of breath reported at baseline.

At the second interim analysis, the superiority of Treatment A over C will be tested with respect to the above 5 endpoints following the hierarchical priority. If all the 5 endpoints reach statistical significance, then the superiority of Treatment B over C will be tested with respect to the 5 endpoints following the hierarchical priority.

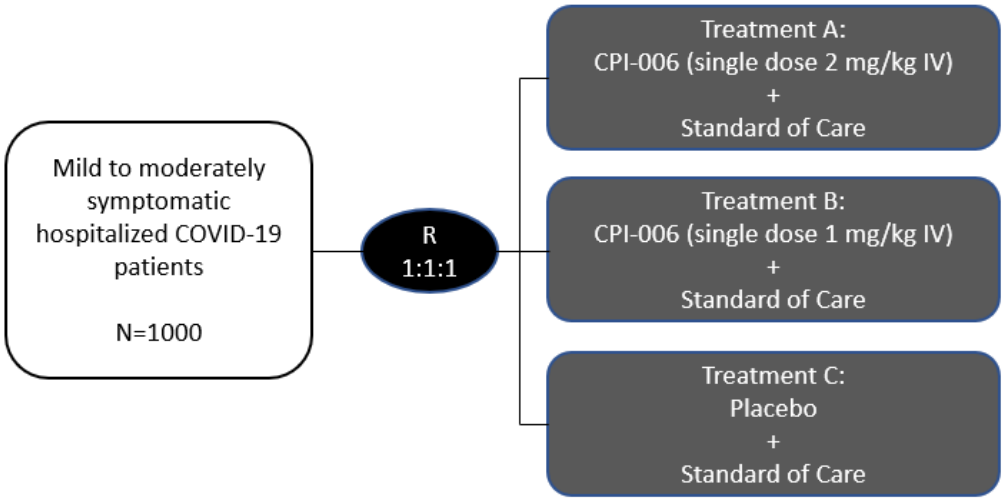
At the final analysis, the above endpoints which either are not tested or tested but fail to reach statistical significance at the interim analysis will be tested following the hierarchical priority for the superiority of Treatment A over C, then Treatment B over C.

For planning purpose for the study, the endpoints would be tested at a 1-sided α of 0.0038 at the second interim analysis and tested at a 1-sided α of 0.0238 at the final analysis. The α levels are determined by the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary assuming a 60% information fraction at the interim analysis. However, when the interim and final analyses are performed, the actual α levels will be determined based on the actual information fraction at the interim analysis.

The mortality rate due to all causes is also a secondary endpoint of the study and will be provided at both interim analyses and final analysis. The 95% 2-sided CI will also be calculated for all 3 treatments.

1.2. SCHEMA

Figure 1 Study Schematic



IV = intravenous; R = randomization

1.3. SCHEDULE OF ACTIVITIES (SOA)

For the schedule of activities, please see Appendix 1, Table 6.

2. INTRODUCTION

2.1. STUDY RATIONALE

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary redistribution in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients. The high anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are

supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 27 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This Phase 3 study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in participants who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

The Covid-19 pandemic is not yet under control and there is fear that infections could spread and/or recur in a seasonal manner, even if controlled now or with vaccination efforts. There is also the possibility of viral mutation or emergence of other virulent coronaviruses. Based on encouraging preliminary data, CPI-006 may improve the magnitude, duration, and diversity of antibody responses to SARS-CoV-2 and improve clinical outcome. It also may result in prolonged immunity to SARS-CoV-2, its variants, and related coronaviruses. It is also possible that experience gained with treating Covid-19 with CPI-006 could be applied to treatment of other infectious diseases including future viral pandemics, and potential use in conjunction with vaccination of healthy participants.

2.2. BACKGROUND

Since its emergence in Hubei province, China in December of 2019, the novel coronavirus (2019-nCoV, Covid-19) has become a global health crisis (Wu et al, 2020; Chan et al, 2020). There is an urgent need for therapies that can improve survival, clinical outcomes, and reduce the requirements for intensive supportive care and prolonged hospitalization (Huang et al, 2020). There are efforts underway to re-purpose direct acting antivirals targeting the ribonucleic acid (RNA)-dependent RNA polymerase including remdesivir and favipiravir both of which are being actively studied in multiple clinical trials. Similarly, inhibitors of the virally encoded proteases are being evaluated. To compliment therapeutic approaches there is an intense effort underway to develop vaccines. A number of approaches to vaccine development have begun clinical trials or are planned. To support vaccine strategies, there is a growing understanding of the key viral/host interaction required for viral entry and replication (Du et al, 2009). Indeed, it is increasingly clear that the virally encoded spike protein binds to angiotensin converting enzyme 2 (ACE2) on target cells to facilitate entry and replication. The spike protein is a multidomain viral envelop glycoprotein which

contains a receptor binding domain (RBD) in subunit 1 of the spike protein (Wrapp et al, 2020). This RBD directly interacts with N-terminal domain of ACE2. This interaction is absolutely required and initiates a sequence of steps leading to efficient viral infection. Thus, antibodies that disrupt this key interaction may be effective in viral neutralization and clearance. A recent publication from Zhang and colleagues have identified neutralizing antibodies from 8 Covid-19 infected patients that bind to the RBD of the spike protein and are neutralizing (Yuan et al, 2020). This provides evidence that neutralizing antibody responses to SARS-CoV-2 are possible and may provide clinical benefit in patients with Covid-19 and protection from disease in healthy subjects. Indeed, the U.S. Food and Drug Administration (FDA) has given emergency use authorization for the use of Covid-19 Convalescent Plasma (CCP) and monoclonal antibodies for the treatment of Covid-19. Clinical studies with CCP suggest that higher titers of neutralizing antibody provide superior clinical benefit to recipients (Joyner et al, 2020; Rasheed et al 2020). These findings support the value of anti-viral antibodies in eradicating viral infection in patients, lessening disease severity, improving clinical course and potentially reducing transmission.

CD73 is an adhesion molecule that was initially found to be important for lymphocyte trafficking and T cell activation (Resta & Thompson, 1997). It also functions as an ectoenzyme that converts adenosine monophosphate (AMP) to immunosuppressive adenosine. Several companies are developing anti-CD73 antibodies to inhibit production of adenosine and thereby augment immune response in patients with cancer. These antibodies have been designed primarily to block enzymatic activity. Corvus has designed a novel anti-CD73 antibody with agonistic, immunomodulatory properties that binds CD73 resulting in activation of immune cells such as B cells, and results in antibody production in vitro (Luke et al, 2019a). This antibody, CPI-006, is under investigation in a Phase 1b trial (NCT03454451) in advanced cancer as monotherapy and in combination with other immunotherapies such as anti- programmed cell death 1 receptor (PD1). Over 90 participants have received doses of this antibody ranging from 1 mg/kg to 24 mg/kg given IV every 21 days. Treatment has been safe and tolerable, with chills and rigor seen during antibody infusion, that are managed by premedication with acetaminophen and diphenhydramine.

CPI-006 is a humanized FcγR binding-deficient monoclonal antibody. In vitro studies have revealed binding to CD73 and direct effects on B cells, morphologic transformation to plasmablasts and induction of IgM and IgG secretion (Luke et al, 2019b). In vivo administration to patients with cancer has shown rapid and temporary drop in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in HLA-DR expression. Molecular studies of the BCR in treated patients have demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in patients with cancer have demonstrated production of anti-tumor antibodies in some patients.

CPI-006 is under investigation in a Phase 1 trial (NCT04464395) in mild to moderately symptomatic hospitalized Covid-19 patients. The results from the study (CPI-006-002) shows IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained overtime. Similar results were observed in anti-SARS-CoV-2 IgA titers. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days for the 1.0 mg/kg and 3.0 mg/kg cohorts, and 28 days for the 5.0 mg/kg cohort in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase for all isotypes toward each antigen from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. An increase of IgG titer toward spike protein was observed from 1.0 mg/kg to 3.0 mg/kg at Day 28. High and durable neutralizing titers were observed in subjects where ID_{50} values up to 23,000 were measured using a functional pseudovirus neutralizing antibody assay. Neutralizing titers were observed to persist at least 84 days following onset of symptoms in the ongoing trial. Immunophenotyping of peripheral blood mononuclear cells (PBMCs) at baseline and at 14, 28, or 56 days after treatment provided preliminary evidence that CPI-006 increased the frequency of memory B cells in 7 evaluated participants. An increased frequency of memory/effector $CD4^{POS}$ and $CD8^{POS}$ T cells was also observed in 5 ($CD4^{POS}$) and 6 ($CD8^{POS}$) evaluable participants. CPI-006 has been well tolerated in participants with Covid-19 in this study. No DLTs or treatment-related AEs have been reported in the study. The AEs reported in the study were due to the underlying Covid-19 or comorbidities.

In this Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized participants with Covid-19. Approximately 1000 participants will be randomized in a 1:1:1 fashion to receive Treatment A (CPI-006 at 2 mg/kg plus SOC) or Treatment B (CPI-006 at 1 mg/kg plus SOC) or Treatment C (matching placebo plus SOC). Standard of care will be per institutional guidelines. Corvus will assess if administering CPI-006 to participants with Covid-19 along with SOC can lead to clinical benefit and enhance humoral immune response to the SARS-CoV-2. The production of neutralizing antibodies would be expected to shorten disease interval and improve clinical outcome, and treatment is expected to be safe. Therefore, CPI-006 treatment is expected to have a positive benefit/risk profile (see Section 2.4.1).

2.3. CPI-006 NONCLINICAL EVALUATION

CPI-006 recognizes and binds human CD73 with high affinity (KD values of 0.64–7.1 nM), inhibits CD73 catalytic activity (mean concentration required for 50% inhibition [IC_{50}]

values of 2.1 nM and 4.0 nM for human and cynomolgus monkey CD73), and has downstream biological effects on T cells as evidenced by restoration of CD3+ T cell proliferation in the presence of AMP. CPI-006 also binds to and inhibits cynomolgus monkey CD73, but not mouse or rat CD73, supporting the use of cynomolgus monkeys for studies of the pharmacokinetics (PK) and toxicology of CPI-006.

Complete CD73 occupancy on CD8+ T cells in peripheral blood samples from cynomolgus monkeys by CPI-006 was observed at all doses of CPI-006. Complete CD73 occupancy was also observed in the axillary lymph nodes, indicating successful solid tissue penetration by CPI-006 with full coverage at least 24 hours after the final dose.

An in vitro cytokine release assay was conducted with CPI-006 to evaluate the potential for CPI-006 to induce an immune response resulting in production of multiple cytokines (cytokine storm). The results demonstrated that CPI-006 did not directly induce cytokine (interferon gamma [IFN-γ], interleukin 2 [IL-2], interleukin 6 [IL-6], interleukin 10 [IL-10], and tumor necrosis factor alpha [TNF-α]) release from fresh human PBMCs at 0.1-10 µg/mL of CPI-006.

Safety of CPI-006 was evaluated in male and female cynomolgus monkeys in two toxicity studies. In the first, a dose range finding study, CPI-006 was administered over 15-minutes by IV infusion at doses up to 120 mg/kg CPI-006, weekly (5 doses) for 31 days. The second, was a Good Laboratory Practice (GLP)-compliant toxicity study in which doses up to 100 mg/kg CPI-006 were administered by IV infusion over 60 minutes, weekly (5 doses) for 28 days. Toxicokinetics, safety pharmacology, and local tolerance assessments were built into the GLP compliant toxicity study. CPI-006 administered by IV infusion was well tolerated in both studies up to, and including, the highest doses administered. No definitive CPI-006-related changes were observed in the animals. No-observed adverse effect levels (NOAEL) were the highest doses administered, 120 mg/kg and 100 mg/kg CPI-006. Additional nonclinical information is provided in the Investigational Brochure for CPI-006.

2.4. SUMMARY OF CLINICAL EXPERIENCE WITH CPI-006

In CPI-006-001 oncology study, CPI-006 has been administered as a single agent and in combination with ciforadenant (an A2a receptor antagonist), and /or pembrolizumab (a blocking anti-PD-1 antibody). CPI-006 has been well tolerated when administered every 3 weeks as monotherapy and in combination with ciforadenant and/or pembrolizumab.

As of 20 Oct 2020, 35 participants have been treated with CPI-006 (every 3 weeks) monotherapy at doses up to 24 mg/kg, and no maximum tolerated dose was established. The most common adverse reactions were infusion related reactions (IRRs), primarily chills and rigors. These IRRs were non-serious, mild to moderate in severity (Grade 1-2), transient and did not lead to discontinuation. The IRRs have been observed during (or immediately after) Cycle 1, Day 1 and are uncommon at subsequent infusions of CPI-006. To mitigate the risk of IRRs, premedication with diphenhydramine (50 mg orally [PO]) and acetaminophen 500–

1000 mg PO (or equivalents) was required prior to infusion of CPI-006 at Cycle 1, Day 1 and has shown a decreased rate and intensity of IRRs.

As of 29 Dec 2020, in the ongoing Phase 1 CPI-006-002 study, 27 hospitalized participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3 mg/kg to 5 mg/kg with follow-up data. CPI-006 was well tolerated. IRRs have not been observed with CPI-006 infusion. No DLTs or treatment related AEs have been reported. The safety data in this Phase 1 study is reviewed on an ongoing basis by an Independent Data Monitoring Committee (iDMC).

2.4.1. Benefit/Risk Assessment

This study proposes to administer single doses of CPI-006 to hospitalized mild or moderately symptomatic participants with Covid-19.

Study treatment will be administered in the hospital and participants will be monitored closely. CD73 is expressed on endothelial cells and it is possible that negative effects or exacerbation of disease could be seen in participants with Covid-19. However, data from the GLP general toxicity study did not show any CPI-006 related changes in coagulation parameters (Section 4.3). Data from 27 participants with Covid-19in the CPI-006-002 study did not indicate any effect of CPI-006 on systemic inflammatory response or coagulopathy. In addition, data from over 90 participants in study CPI-006-001 in participants with cancer did not show any CPI-006 related systemic inflammatory response or coagulopathy. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. The benefit of therapy to participants who receive Treatment A or Treatment B is the development of neutralizing antibodies which could lead to more rapid clinical improvement, avoidance of complications of Covid-19 disease, and the potential for longer lasting immunity.

Participants enrolled in Treatment C will receive standard of care (SOC) per institutional guidelines. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. Overall data will be used to assess any difference between the participants who receive Treatment A, Treatment B, and Treatment C in terms of clinical outcome and anti-SARS-CoV-2 levels.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the proportion of participants alive and respiratory failure free during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who are alive and free from respiratory deterioration defined as follows per the 8-point ordinal scale (Appendix 6): o Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 o Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6
Key Secondary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale)
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28
• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of ≥ 50% of the Covid-19 -attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline
Additional Secondary	
• To compare the mortality rate due to any cause during the 28 days after dosing with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Proportion of participants who died during the 28 days after dosing
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, Day of Discharge, Days 14, 21, and 28

Objectives	Endpoints
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21, and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 (Appendix 7) consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)
• To compare the medical interventions/procedures during the 28 days after dosing of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate of procedures including intubation • Rate and duration of mechanical ventilation • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices • Oxygenation free days during the 28 days after dosing • Rate of rehospitalization
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment-emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0

Objectives	Endpoints
Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• To characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = Standard of Care; SpO_2 = oxygen saturation.

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a Phase 3, randomized, 3-arm, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) participants with Covid-19. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) or antigen testing for SARS-CoV-2.

Approximately 1000 participants will be randomized at a 1:1:1 ratio to the 3 treatment arms and stratified by the following factors:

- Region of the world (North America [US and Canada] vs. Latin America vs. Europe/Middle East/Africa)
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg (Treatment A – maximum dose of 200 mg) or 1 mg/kg (Treatment B – maximum dose of 100 mg) intravenously (IV) on Day 1. A placebo will be given at the same schedule as the active drug for participants who receive the control (Treatment C). Participants, investigators, and Corvus will be blinded to the treatment allocation. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies, or any other approved treatment) per those guidelines at the discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an

interactive response technology (IRT) system to obtain the participant number. Every participant that signs the informed consent form (ICF) must be assigned with a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. SARS-CoV-2 PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if the participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 10% (approximately 100) of participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when 25%, 40%, 60%, and 80% (approximately 250, 400, 600, and 800, respectively) of participants have completed the Day 28 assessments. The analysis with 25% of participants is the first interim analysis for futility evaluation, and the analysis with 60% of participants is the second interim analysis for both efficacy and futility evaluation. Safety and efficacy data will be analyzed for the iDMC review at both interim analyses.

Study enrollment will be paused after 10% of the participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, the review of the futility analysis, study enrollment will also be paused at this time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for enrollment for the subsequent reviews after the futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data.

The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting. Further details on the iDMC are provided in Section 9.4.8.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

CPI-006 activates B cells in vitro leading to B cell differentiation and secretion of immunoglobulins. Studies in patients with cancer have demonstrated differentiation of B cells into plasmablasts, trafficking from blood and return of memory B cells to blood. The in vitro and in vivo effects indicate that CPI-006 stimulates B cell differentiation, antigen driven clonal selection and differentiation into antibody producing cells. Novel anti-tumor antibodies have been produced in some treated patients with cancer. B cell receptor molecular studies have demonstrated the emergence of novel B cell clones in the blood of CPI-006 treated patients with cancer. No changes in total serum immunoglobulins have been seen to date (Willingham et al., 2020). It is believed that the activation of B cells and enhancement of antibody production will lead to a more robust humoral immune response to SARS-CoV-2 and provide clinical benefits such as shorter disease duration, less disease severity, fewer complications, and greater long-term immunity.

In Study CPI-006-002 (in mild to moderate hospitalized participants with Covid-19), IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable participants within 7 days of a single infusion of low doses of CPI-006 and were sustained over time. Similar results were observed in anti-SARS-CoV-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels has been observed in participants. Fourteen of 22 evaluable participants had low pre-treatment antibody titers despite relatively long durations of symptoms in some participants. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days for the 1.0 mg/kg and 3.0 mg/kg cohorts, and 28 days for the 5.0 mg/kg cohort in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase for all isotypes toward each antigen from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. An increase of IgG titer toward spike protein was observed from 1.0 mg/kg to 3.0 mg/kg at Day 28. High and durable neutralizing titers were observed in subjects where ID_{50} values up to 23,000 were measured using a functional pseudovirus neutralizing antibody assay. Neutralizing titers were observed to persist at least 84 days following onset of symptoms in the ongoing trial. No changes in total serum immunoglobulins have been seen to date.

4.3. JUSTIFICATION FOR DOSE

Two active doses of CPI-006, 1.0 mg/kg up to a maximum dose of 100 mg or 2.0 mg/kg up to a maximum dose of 200 mg, were selected based on safety, PD, and PK parameters. Safety is summarized in the CPI-006 Investigational Brochure and in Section 2.3 and Section 2.4.

In the GLP general toxicity study in cynomolgus monkeys, CPI-006 was administered by 60-minute IV infusion once weekly for 5 consecutive weeks at dose levels of 10, 30, or 100 mg/kg, followed by a 28-day recovery period. CPI-006 doses of up to 100 mg/kg/week (5 total doses) were well tolerated. CD73 is expressed weakly on endothelial cells. No CPI-006-related changes in hematologic coagulation parameters, which included prothrombin time (PT) activated partial thromboplastin time (aPTT), or fibrinogen, occurred during the study. The NOAEL was the highest dose administered, 100 mg/kg/week, corresponding to maximum drug concentration in serum or plasma (C_{max}) of 3,560 and 3,280 µg/mL and AUC from the start of infusion to 169 hours after the start of infusion ($AUC_{(0-169)}$) of 167,000 and 186,000 hr•µg/mL, for males and females, respectively. The C_{max} and AUC from time zero to the time of the last quantifiable concentration (AUC_{last}) for the GLP repeat dose cynomolgus monkey toxicity study are 60 and 66 times higher, respectively, than the C_{max} and AUC_{last} after a single administration of 3 mg/kg to humans in the CPI-006-001 study. Safety margins are anticipated to be even greater for the 1 mg/kg and 2 mg/kg doses selected for the subject protocol.

In clinical study CPI-006-001, 93 participants with advanced cancers received repeated IV infusions ranging from 1 mg/kg to 24 mg/kg CPI-006 once every 3 weeks until disease progression. CPI-006 was administered as a single agent or in combination with other oncology therapies. No DLTs were observed for CPI-006 at doses below 24 mg/kg in the dose escalation portion of the study. A DLT was observed in a single participant who received 24 mg/kg CPI-006 (Grade 3 hyponatremia in a participant with NSCLC who had a history of hyponatremia). The 24 mg/kg cohort was expanded, and no more DLTs were reported. Thus, a maximum tolerated dose was not established, and the 24 mg/kg cohort was defined as maximum administered dose per protocol.

A covariate analysis was performed using serum CPI-006 levels, participant demographics, vital signs, laboratory values, and concomitant medications data from 93 participants who received 1-24 mg/kg CPI-006 in the CPI-006-001 study. Clearance was strongly associated with participant body weight, indicating a body weight-adjusted dose is preferred over a fixed dose. CPI-006 showed non-linear PK and modeling with clearance being a linear function of dose. The fit of the model to the data was excellent. Area under the curve (AUC) after a dose of 24 mg/kg is 453-fold higher than the AUC after a dose of 1 mg/kg and it is estimated to be 31-fold higher than the area under the serum concentration-time curve (AUC) after a dose of 2 mg/kg. The serum CPI-006 concentration 30 minutes after infusion was not modeled for a dose of 2 mg/kg, but the geometric mean 30-minute serum CPI-006 concentration after administration of 24 mg/kg was 11.6 times higher than after administration of 3 mg/kg, and 40.2 times higher than after administration of 1 mg/kg, indicating a more than dose proportional increase in C_{max} over the range of doses.

In clinical study CPI-006-002, a single dose, dose escalation study, 27 participants hospitalized for mild to moderate Covid-19 symptoms were treated with a single IV infusion of CPI-006 ranging from 0.3 mg/kg to 5.0 mg/kg in combination with SOC. CPI-006 was

well tolerated in all participants with no DLTs or treatment-related AEs reported in the study. Safety was monitored in the study by an iDMC.

The preliminary geometric mean 30-minute serum CPI-006 concentrations in study CPI-006-002 (n = 3 per cohort) for the 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg cohorts are 1.9 μg/mL, 9.3 μg/mL, and 56.4 μg/mL, respectively. The 30-minute serum CPI-006 concentrations are similar to those for samples collected from the corresponding 1 mg/kg and 3 mg/kg cohorts at the same time in the CPI-006-001 oncology study. CPI-006 is rapidly cleared from serum and is undetectable (serum concentration < 50 ng/mL) 1-7 days after a 1 mg/kg IV infusion or 14-21 days after a 3 mg/kg infusion. In CPI-006-002, the relationship between clearance and weight was less well defined; however, there was a small statistical preference for a model in which clearance was weight-proportional, presumably because of fewer subject for whom PK data are available and the larger variability in this group of participants.

Serum IgG and IgM antibody titers against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable participants in CPI-006-002 within 7 days of a single infusion of CPI-006. Similar results were observed in serum anti-SARS-CoV-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels was observed in these participants. Thirteen of 17 evaluable participants had low pre-CPI-006 infusion antibody titers despite relatively long durations of symptoms in some participants. In participants receiving 0.3 mg/kg CPI-006, all 4 evaluable participants achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these participants, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were observed in antibody responses to the RBD. At doses higher than 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved for at least 84 days, 56 days, and 28 days for the 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg cohorts, respectively. Peak serum anti-SARS-CoV-2 titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase from 1.0 mg/kg to 5.0 mg/kg at the evaluable time points suggesting that the peak pharmacodynamic effect occurred in the range of 1.0-3.0 mg/kg CPI-006. In addition, the duration of sustained high antibody titers appeared optimum in the 1.0 mg/kg-3.0 mg/kg cohorts and was not improved at 5.0 mg/kg.

Immunophenotyping of peripheral blood from participants enrolled in clinical study CPI-006-001 demonstrated that doses greater than 1 mg/kg are sufficient to activate B cells, resulting in a temporary redistribution to lymphoid tissues and corresponding increase in the frequency of memory B cells returning to circulation. A similar increase in the frequency of memory B cells was observed in Covid-19 patients tested in the CPI-006-002 trial, including participants receiving 0.3 mg/kg CPI-006. In vitro, CPI-006 induced B cell activation is dose-dependent with concentrations of 1 μg/mL achieving near maximal induction of CD69. This initial activation leads to a morphologic transformation of B cells into plasmablasts and secretion of IgM and IgG in vitro. These levels of CPI-006 also result in increased expression of various markers involved in antigen presentation e.g. HLA-DR, CD86. A dose of 1 mg/kg is sufficient to sustain CPI-006 serum concentrations above 1 μg/ml for up to 48 hours and a dose of 2 mg/kg to sustain CPI-006 serum concentrations up to 1 week.

In summary, a dose of 1 mg/kg appeared to be sufficient to achieve the maximum level of IgG and IgM anti-SARS-CoV-2 titers in serum. Immunophenotyping of peripheral blood in participants from CPI-006-001 suggested that a higher dose may be required to activate B cells, resulting in a temporary redistribution to lymphoid tissues and corresponding increase in the frequency of memory B cells returning to circulation. Thus, a dose of 2 mg/kg was selected for investigation.

4.4. END OF STUDY DEFINITION

A participant in this study is considered to have completed the study if he/she has completed all study visits including Day 28 study assessments. The study visits beyond Day 28 will be optional for exploratory endpoint of antibody levels at Days 56, 84, and 168.

The end of the study is defined as the date that the last expected study visit is completed for all participants.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Participants must be ≥ 18 years of age at the time of signing the informed consent.
2. Confirmed positive by PCR or antigen test for SARS-CoV-2 within 72 hours before randomization.
3. Onset of symptoms not more than 7 days prior to randomization.
4. Participant capable of understanding the study and giving informed consent. Participant capable of signing and dating the written ICF. Participant must understand and agree to comply with planned study procedures for the duration of the study. The study visits beyond Day 28 will be optional and require a separate consent.
5. Hospitalized for Covid-19 illness for ≤72 hours with mild to moderate Covid-19 symptoms including:
    - Mild: Symptoms of Covid-19 including fever, rhinorrhea, mild cough, sore throat, headache, muscle pain, malaise but not requiring supplemental oxygen
    - Moderate: Lower respiratory symptoms: shortness of breath (SOB) or signs of pneumonia or lung infiltrates based on X-ray or computed tomography (CT) scan < 50% present
6. Maintains O_2 saturation of at least 93% on room air or supplemental O_2, including high-flow and non-invasive ventilation at randomization (Categories 4, 5, or 6 per 8-point ordinal scale; see Appendix 6).
7. Adequate organ function, as defined by:
    - CBC: ANC >1000/mm^3, platelets>75,000mm^3, Hgb >9 gm/100 cc
    - Calculated creatinine clearance based on ideal body weight per Cockcroft-Gault formula or 24-hour urine ≥ 30 mL/min

- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN)
- D-dimer < 10,000 ng/mL

8. Eligible participants of child-bearing age (male or female) must agree to use adequate contraception for a total of 6 weeks after study treatment administration (Appendix 5). Female participants or the female partners of male participants who become pregnant during the study or within the protocol-specified period after their last CPI-006 administration should immediately inform their treating physicians.

5.2. EXCLUSION CRITERIA

1. Signs of acute respiratory distress syndrome (ARDS) or respiratory failure necessitating mechanical ventilation at the time of screening (and randomization) or anticipated impending need for mechanical ventilation.
2. History of severe chronic respiratory disease and requirement for long-term oxygen therapy.
3. Any uncontrolled active systemic infection or hemodynamic instability requiring admission to an intensive care unit (ICU).
4. Participants with malignant tumor receiving treatment, or other serious systemic diseases affecting life expectancy within 29 days of Screening.
5. Receipt of cancer chemotherapy or immunomodulatory drugs including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use equivalent to prednisone >10 gm/day, during preceding 2 months.

   Note: Steroids for treatment of Covid-19 are acceptable.
6. Patients who are participating in other clinical trials including participants in an extended access program.
7. Active deep vein thrombosis or pulmonary embolism as confirmed by the investigator within last 6 months.
8. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 48 hours of admission as confirmed by the investigator.
9. Any active uncontrolled co-morbid disease that might interfere with study conduct or interpretation of findings.
10. Known to be positive for HIV or positive test for chronic HBV infection (defined as positive hepatitis B surface antigen [HbsAg]) or positive test for hepatitis C antibody.
11. Convalescent plasma (CCP) or anti-SARS-CoV-2 monoclonal antibodies administered less than 24 hours prior to randomization. Participants must have recovered from any adverse events related to CCP treatment. Received chloroquine or hydroxychloroquine within last 7 days or during the study.
12. Pregnancy or breast feeding.

13. Persons under legal protection or currently incarcerated.

5.3. LIFESTYLE CONSIDERATIONS

Blood, sperm, and ova donations are restricted for at least 6 weeks after CPI-006 administration.

5.3.1. Meals and Dietary Restrictions

No dietary restrictions.

5.3.2. Activity

No required restrictions.

5.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Reasons for screen failure will be recorded.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. STUDY TREATMENT ADMINISTERED

A summary of study treatment information is provided in Table 2.

Table 2 Study Treatment

Study Treatment Name:	**CPI-006 Injection, 200 mg/20 mL**	**CPI-006 Placebo**
Dosage formulation:	10 mg/mL with 20 mM histidine, 9 % sucrose, 0.01 % (w/v) polysorbate 80, pH 5.5.	(5% Dextrose Injection, USP [5% dextrose (glucose)[a]])
Unit dose strength (s)	200 mg / 20 mL (10 mg/mL)	5% Dextrose
Route of administration	IV	IV
Dose[b]	Treatment Group A: 2 mg/kg up to a maximum of 200 mg -or- Treatment Group B: 1 mg/kg up to a maximum of 100 mg	Treatment Group C: Placebo (no CPI-006)

Dosing instructions:	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP (5% dextrose [glucose]). CPI-006 Injection is diluted with 5% Dextrose Injection, USP (5% dextrose [glucose]).	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP (5% dextrose [glucose]).
Packaging and labeling	Study Treatment will be provided in a sterile, single-use vial with a rubber stopper and a blue cap. One vial is packaged inside a carton. Each vial will be labeled as required per country requirement.	Not Applicable
Manufacturer	Manufactured for Corvus Pharmaceuticals, Inc. by Vetter Development Services USA, Inc.	Placebo will be purchased by the clinical institution from commercial vendors approved by that institution

Abbreviations: IV = intravenous; US/USA = United States of America; USP= United States Pharmacopeia
[a] 5% Dextrose Injection, USP will be used at clinical sites within the United States; similar sterile, low-endotoxin grades of 5% dextrose (glucose) that are commercially available and meet local or compendial laws and regulations may be substituted outside of the US.
[b] The CPI-006 dose for participants who weigh more than 100 kg will be limited to a fixed dose of 200 mg in the 2 mg/kg dose group (Treatment A), or a fixed dose of 100 mg for the 1 mg/kg dose group (Treatment B).

6.2. STUDY TREATMENT: PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. 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.
2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment 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 site staff.
3. The unblinded site staff preparing the study treatment is responsible for study treatment accountability, log of receipt, inventory, reconciliation, dispensing, return of study treatment, destruction of study treatment and record maintenance (i.e., receipt, reconciliation, and final disposition records). The study treatment logs and records must be kept current and blinded from others (e.g. investigators, site staff, participants, Sponsor and contract research organization (CRO) staff with oversight of study conduct). Study treatment logs must be kept in a secure location with access limited only to the unblinded staff members.

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

6.2.1. Handling and Storage

6.2.1.1. CPI-006 Injection

CPI-006 Injection is provided as a sterile solution in a single use vial that delivers up to 200 mg of active ingredient in 20 mL (10 mg/mL). CPI-006 vials will be stored at 2°C to 8°C and protected from direct light. Excursions up to 25°C are allowed up to 3 days. Refer to the product labeling for product storage.

The prepared CPI-006 can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared CPI-006.

Do not freeze CPI-006 vials or diluted CPI-006 infusion solution.

6.2.1.2. Placebo

The placebo, 5% Dextrose Injection, USP will be purchased by each clinical site within the United States. Either 5% Dextrose Injection, USP or a similar sterile, low-endotoxin grade of 5% dextrose (glucose) that is commercially available and meets local or compendial laws and regulations may be substituted outside of the US. The placebo should be handled and stored according to manufacturer's specifications.

The prepared placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

Do not freeze the placebo.

6.2.2. Preparation and Dispensing

Refer to the Pharmacy Manual for detailed instructions on how to prepare study treatment for administration. Study treatment will be prepared using aseptic techniques and dispensed by an appropriately qualified and experienced member of the study staff (e.g., pharmacist, pharmacy assistant, or pharmacy technician) who is unblinded to study treatment (see blinding plan in the pharmacy manual). A second staff member will verify the dispensing and preparation. The identity of the study treatment should not be revealed by markings on labels or the infusion bag or infusion set except for a blinded randomization code.

CPI-006 infusion will be prepared using aseptic techniques by withdrawing the appropriate amount of CPI-006 Injection, 10 mg/mL from a vial into a sterile syringe. The contents of the syringe will be emptied into a sterile polyolefin/polyethylene (PO/PE) or polyvinyl chloride

(PVC) infusion bag and diluted with 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose). Apply gentle mixing by inverting the IV bag; avoid shaking the IV bag.

Placebo will be prepared using aseptic techniques. The placebo infusion is 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) in a sterile polyolefin/ polyethylene (PE) or polyvinyl chloride (PVC) infusion bag. After it is prepared, the placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at room temperature (15°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

6.2.3. Administration

Administration of study treatment will be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and infusion-experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Site staff administering the study treatment will be blinded to the treatment (active or placebo) being administered. Participants will receive a single dose of study treatment by IV infusion on Day 1 of the study. Study treatment must be infused through an in-line filter. Infusion lines should be made of PO/PE or PVC, equipped with a 0.2 μm or 0.22 μm in-line polyethersulfone (PES) filter.

The infusion should be administered via a port as close to the participant's vein as possible to ensure that the full dose is administered in the allotted time. The total infusion time from start of infusion to completion of infusion will be 10-15 minutes. As soon as the infusion is complete, the infusion line used for the study treatment will be flushed with the greater of the priming volume of the infusion set or 30 mL of 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) solution. The same infusion rate used for the study treatment infusion will be used for the flush.

Infusion reactions are possible, thus appropriate drugs and medical equipment to treat acute infusion reactions must be immediately available and study personnel must be trained to recognize and treat infusion reactions. Premedication with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo is recommended for participants who are not receiving steroids for treatment of Covid-19. Oral premedication should be administered 30-60 minutes prior to the start of the CPI-006/placebo infusion. IV diphenhydramine should be administered 15-30 minutes prior to the start of the CPI-006/placebo infusion.

Study treatment administration details will be recorded on the CRF and will include at a minimum: participant number, randomization code, infusion start time and stop time, interruption stop and restart times, flush start and stop times.

6.2.4. Management of Infusion Reactions

Any CPI-006-associated infusion reactions should also be managed as shown in Table 3.

Table 3 CPI-006 Infusion-Related Reaction Management Guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; treatment not indicated	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Provide supportive care. Increase monitoring of vital signs as medically indicated. If symptoms do not improve within 1 hour, provide medical treatment until the participant is deemed medically stable in the opinion of the investigator. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g., from 10 mL/min to 5 mL/min).

NCI CTCAE Grade	Treatment
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Additional appropriate medical therapy may include but is not limited to: – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Narcotics – Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms have not subsided or worsen with reduced infusion rate, stop infusion. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g. from 10 mL/min to 5 mL/min). Otherwise, if symptoms do not resolve, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity with premedication and do not have symptom resolution within 2 hours of medical treatment should be permanently discontinued from further study drug treatment.

NCI CTCAE Grade	Treatment
Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: – Epinephrine[a] – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Corticosteroids – Narcotics – Oxygen – Vasopressors
Grade 4 Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - Epinephrine[a] - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Vasopressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Participant is permanently discontinued from further study drug treatment.

Abbreviations: : IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

[a] In cases of anaphylaxis, epinephrine should be used immediately.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be randomized to Treatment A, Treatment B, or Treatment C in a 1:1:1 ratio using an Interactive Response Technology (IRT). Before the study is initiated, the log-in information & directions for the IRT will be provided to each site.

Participants will receive a single IV administration of study treatment on Day 1 of the study.

Returned study treatment should not be redispensed to any participants.

6.3.2. Blinding

This is an observer blinded design, so investigators, site staff (except the unblinded pharmacy personnel preparing the study treatment), participants, Sponsor, and CRO staff with oversight of study conduct will remain blinded to treatment allocation throughout the course of the study. The IRT will provide the unblinded pharmacist(s) the randomized treatment arm assignment to be allocated to the participant at the administration visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

CPI-006 Injection is a clear colorless solution and will remain clear and colorless when diluted in 5% Dextrose Injection, USP or equivalent grade of 5% dextrose (glucose) solution. At full concentration, CPI-006 is slightly more viscous than water and may create minimal foam if vigorously shaken. Once diluted, CPI-006 is not visually distinguishable from the 5% Dextrose Injection, USP placebo.

To maintain the blind, an otherwise uninvolved staff member (e.g. pharmacist, pharmacy assistant, or pharmacy technician) will prepare and dispense the study treatment for administration such that the identity (active or placebo) of the treatment is blinded to all other site staff responsible for administration and study conduct throughout the study. The unblinded personnel are responsible for study treatment preparation and accountability only and will not participate in any other aspect of the study. The unblinded personnel will endeavor to ensure that there are no differences in time taken to dispense following randomization or preparation that might reveal the identity of the study treatment to investigators, site staff, participants, Sponsor and CRO staff.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.3. Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant'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 case report form, as applicable.

6.4. Study Treatment Compliance

Investigational Product will be administered on a single occasion by the investigator or qualified designee to participants who are hospitalized. Randomization code, treatment

volume, start and stop times for the study treatment infusion, flush volume, and start and stop times for the flush will be accurately recorded in the CRF.

The study site is responsible for ensuring that participants comply with the specified study windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Appendix 1 Schedule of Activities). If a participant does not complete a visit within the specified time, the visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (e.g. clinical laboratory testing, and immunologic testing, as applicable).

6.5. CONCOMITANT THERAPY

Investigators may prescribe any concomitant medications, procedures, or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.3.

Any medication or vaccine (including influenza vaccine and Covid-19 vaccine, which are both allowed concomitant medications), over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

6.5.1. Rescue Medicine

The study site will supply infusion reaction rescue medication that will be obtained locally by the clinical site. The following rescue medications may be used:

- Antihistamine such as diphenhydramine administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Analgesics such as acetaminophen administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Corticosteroids administered according to standard practices at the site/hospital for treating infusion related reactions
- The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the CRF

6.5.2. Permitted Concomitant Therapy

The following concomitant medications and vaccinations are allowed and will be recorded in the CRF:

- Therapies that are either approved or accepted as standard of care therapies for Covid-19 per site/institutional guidelines (e.g., remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies)
- Prophylactic or therapeutic anticoagulation
- Supportive care for management of Covid-19 symptoms and complications
- It is recommended that participants who are not being treated with steroids for Covid-19 be premedicated with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo (see Section 6.2.3).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.3. Prohibited Concomitant Therapy

The following medications are prohibited and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications, however, will not definitively require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol analysis set.

If a participant receives a prohibited concomitant medication, the investigator in consultation with the medical monitor will evaluate any potential impact on receipt of the study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data.

The following concomitant medications are prohibited:

- Chloroquine or hydroxychloroquine
- Cancer chemotherapy or immunomodulatory drugs including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use
- Investigational medication or device (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment and throughout the study unless the investigator, in consult with the Corvus medical monitor, feels medical necessity and that such participation would not affect the integrity of this trial.

The medical monitor should be contacted if there are any questions regarding concomitant therapies.

6.6. Dose Modification

No dose modifications for CPI-006 are allowed.

6.7. Study Treatment After the End of the Study

No study treatment will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

- Participant or participant's physician may elect to discontinue their participation in the study at any time. Reasons for withdrawal will be recorded on the CRF.
- All randomized participants will be followed for 28 days.
- Participants who consent to optional follow-up visits will be followed for 168 days.

7.1. DISCONTINUATION OF STUDY TREATMENT

A single dose of CPI-006/placebo is administered only on Day 1 for participants, thus there is no discontinuation from study treatment unless the participant does not receive full dose due to toxicity during the infusion. Standard of care will be administered to all participants at the discretion of the investigator per institutional guidelines.

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. LOST TO FOLLOW-UP

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
    - Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible,

3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Appendix 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) 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 time frame defined in the SoA.

Hospitalized participants will receive daily monitoring and testing while in the hospital including routine vital sign monitoring and labs per institutional standards. Once discharged, participants will be asked to attend post- hospitalization study visits as described in Section 4.1.

Follow-up visits after discharge could include, but are not limited to, clinic visits, outpatient hospital visits, home health visits or telehealth, depending on local or institutional standards. If no other method of follow-up is feasible, home visits may be used.

Study assessments will utilize local labs and procedures at the clinical sites except for the key secondary endpoint, anti-SARS-CoV-2 antibody levels and various exploratory endpoints such as neutralizing antibody levels and peripheral blood immunophenotyping which will be assessed by the central lab. Other exploratory endpoints such as BCR repertoire analysis and systemic cytokine/chemokine analysis will be performed by external vendors outside of the central lab. Results of tests conducted at central lab, are not considered as critical to the management of Covid-19 in participants and will not be reported to the investigator or participant.

The anti-RBD IgG level will be measured using an electrochemiluminescent immunoassay on serum specimens stored at -20°C. The method is based on reactivity to immunogenic viral protein where a recombinant form of viral RBD antigen is absorbed to the surface of a 96-well microtiter plate. Participant serum will be dispensed to the wells where antibodies recognizing the antigen are allowed to react before removal of unbound immunoglobulin

from the wells. Anti-RBD IgG bound to the viral protein will be detected using standard enzyme-linked immunosorbent assay (ELISA) techniques.

Immediate safety concerns should be discussed with the Sponsor directly upon occurrence or awareness to determine if the participant should continue or discontinue study treatment regardless of SoA assessments. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. SCREENING

Screening assessments and procedures are detailed in Appendix 1, Table 6.

8.2. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are detailed in Appendix 1, Table 6.

8.3. EFFICACY ASSESSMENTS

The following assessments will also be performed for all participants at the time points described in the SoA (Appendix 1, Table 6):

- Covid-19 Symptoms Assessment – Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath (Appendix 8)
- 8-point Ordinal Scale Assessment (Appendix 6)
- SARS-CoV-2 viral load
- PCR negativity
- NEWS2 Assessment (Appendix 7)
- Anti-RBD antibody titers will be measured in sera collected at the time points described in the SoA (Appendix 1, Table 6). Collection of the predose timepoint is critical for subsequent analysis. The assays will measure IgM, IgG and IgA levels targeting the RBD for key and additional secondary endpoints using the electrochemiluminescent immunoassay. The assays will be conducted at a centralized testing facility using validated methods.
- A viral PCR test by nasal swab will be obtained to demonstrate a negative test and viral load. Participants with positive PCR or antigen tests will have repeat PCR tests on subsequent visits until a negative test. This test will be conducted by the clinical lab at the investigator sites.
- Exploratory measurements will be conducted at Sponsor's research laboratories or through use of outside vendors including immunophenotyping analysis, immune cell

functional assays, BCR repertoire analysis, systemic cytokine/chemokine analysis, and, anti-SARS-CoV-2 antibody characterization, and anti-viral neutralization assays.

- Clinical assessments will include time to clinical improvement, time to resolution of the Covid-19 attributable symptoms, change in clinical status, rate of participants with clinical improvement, time to discharge, requirement for ICU, requirement for mechanical ventilation, rate of procedures including intubation, duration of mechanical ventilation, oxygenation free days in the first 28 days, and incidence and duration of new O_2 use during the study.

8.4. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Serum samples will be collected from each participant enrolled in the study for measurement of serum concentrations of CPI-006 as specified in the SoA (Appendix 1, Table 6). A maximum of 4 additional samples may be collected at time points during the study if warranted and agreed upon between the investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor.

The actual collection date and time (24-hour clock time) for each sample will be recorded.

Samples will be used to evaluate the PK of CPI-006. Each serum sample will be divided into 3 aliquots (1 each for PK, backup, and for potential analysis of anti-drug antibodies [ADA], and/or neutralizing antibodies [refer to Section 8.7.1 Immunogenicity Assessments]). Samples collected for analyses of serum CPI-006 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

At visits during which serum samples for the determination of PK, backup, ADA, and/or neutralizing antibodies of CPI-006 will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points, up to 4 time points, for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5. SAFETY ASSESSMENTS

The following assessments will also be performed for all participants at the time points described in the SoA (Appendix 1, Table 6):

- Incidence, type, and severity of AEs and SAEs assessed by NCI CTCAE v 5.0 to compare safety of CPI-006 plus SOC to placebo plus SOC.
- Safety assessments will be made using local lab testing (Appendix 3) for hematology, chemistry, coagulation, inflammatory markers and serum quantitative immunoglobulins.
- Routine physical exams.
- Vital signs (pulse rate, blood pressure, respiratory rate, temperature and blood oxygen saturation) including at start, at conclusion and at approximately 2 hours after completion of the CPI-006/placebo infusion.

8.6. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, or surrogate).

The investigator and any qualified 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 participant to discontinue the administration of CPI-006/ placebo, or the study (see Section 7).

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by protocol-mandated procedures (e.g., study related procedures, discontinuation of medications) should be reported (see Appendix 4).

After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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

For participants with worsening of Covid-19, the clinical event(s) that mark the worsening should be reported as AE or an SAE (see definitions in Appendix 4). Investigators are not obligated to actively seek AEs or SAEs outside clinical practice after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time

after a participant 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 the Sponsor.

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.

8.6.2. Method of Detecting AEs and SAEs

The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event CRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 4.

For each AE recorded on the Adverse Event CRF, the investigator assesses seriousness, severity, and causality as per Appendix 4.

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

Reporting requirements for SAEs can be found in Appendix 4.

8.6.3. Follow-up of AEs and SAEs

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

8.6.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants 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, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigational Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.7. BIOMARKERS

Serum at baseline and at specified times will be stored at -20°C for use in various serology studies which include:

Key and Additional Secondary Endpoints

- Measurement of anti-RBD IgG, IgM, and IgA levels.

Exploratory Endpoints

- Measurement of neutralizing antibody levels that block association of viral RBD and human ACE2 assessed in a biochemical ELISA.
- Measurement of neutralizing antibody levels that block infection assessed in a pseudovirus assay, and in a live virus assay
- Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins.
- Additional exploratory serum assays may be conducted with extra serum not required for primary analysis.

Peripheral blood collected at baseline and at specified times will be analyzed while fresh or processed into PBMCs and cryopreserved for use in various studies including:

- Immunophenotyping using flow cytometry to evaluate the frequency of memory B cells and memory/effector T cells
- Functional B and T cell assays to evaluate ex vivo immune responses to SARS-CoV-2 antigens compared to controls.
- BCR repertoire analysis to evaluate effects of CPI-006 on B cell clonality and antibody isotype switching

8.7.1. Immunogenicity Assessments

Antibodies to CPI-006 may be evaluated in serum samples collected from participants according to the SoA. These samples may be tested by the Sponsor or Sponsor's designee.

Serum samples may be screened for antibodies binding to CPI-006 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to CPI-006 and/or further characterize the immunogenicity of CPI-006

The detection and characterization of antibodies to CPI-006 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for

detection of antibodies to study treatment may also be evaluated for CPI-006 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to CPI-006.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

The primary hypothesis is that Treatment A will improve the proportion of participants alive and respiratory failure free during the 28 days after dosing based on the 8-point ordinal scale in comparison to Treatment C in mild to moderately symptomatic Covid-19 hospitalized participants.

The first secondary hypothesis is that Treatment A will shorten the time to recovery during the 28 days after dosing based on the 8-point ordinal scale in comparison to Treatment C in mild to moderately symptomatic Covid-19 hospitalized participants.

The second secondary hypothesis is that Treatment A will shorten the time to clinical improvement by at least 2 points during the 28 days after dosing on the 8-point ordinal scale in comparison to Treatment C.

The third secondary hypothesis is that Treatment A will increase the level of IgG targeting the RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 more than Treatment C, as measured by the area under the IgG level curve above the baseline, calculated over Days 1 (the baseline), 7, 14, 21, 28, and Day of Discharge.

The fourth secondary hypothesis is that Treatment A will shorten the time to resolution of ≥ 50% of the Covid-19-attributable symptoms: fever, cough, sore throat, headache, muscle pain, and/or shortness of breath, reported at baseline in comparison to Treatment C.

The above 5 hypotheses are also applied to the comparison of Treatment B to Treatment C.

9.2. SAMPLE SIZE DETERMINATION

Approximately 1000 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1:1 ratio between Treatment A, Treatment B and Treatment C (approximately 330 per arm) within each of the strata defined by:

- Region of the world (North America [(US and Canada] vs. Latin America vs. Europe/Middle East/Africa).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma

- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Obesity (body mass index ≥ 30 kg/m^2)
- Diabetes (Type 1, Type 2, or gestational)
- Liver disease
- CKD
- SCD
- Organ transplantation
- Cancer

With approximately 300 participants per treatment arm, there would be an approximately 85% power to show a statistically significant superiority of Treatment A over Treatment C in the proportion of participants alive and respiratory failure free during the 28 days after dosing at an overall 1-sided α level of 0.025 when the true proportion of Treatment A is 92% and that of Treatment C is 84%. The same sample size and power statement also holds for the comparison between Treatment B and C. An additional 10% of participants will be enrolled to cover the loss-of-follow-up.

9.3. POPULATION FOR ANALYSES

For purposes of analyses, the following populations are defined in Table 4.

Table 4 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study and analyzed according to treatment assigned at randomization.
Efficacy	All participants who receive any amount of study drug (CPI-006 or placebo) and have post-baseline efficacy assessment based on the 8-point ordinal scale. The participants will be analyzed according to the treatment actually received.
Safety	All participants who receive any amount of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

9.4. STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be developed and finalized before the first interim analysis (the futility analysis, see Section 9.4.6) and will describe the study populations to be included in the analyses. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Approach

Unless otherwise specified, the following general analysis will be performed. Continuous variables will be summarized using the following descriptive statistics: number of observed

values, mean, standard deviation, median, and minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Time-to-event variables, when appropriate, will be summarized by the median with 95% confidence intervals (CI) and the 25% and 75% quartiles. Kaplan-Meier curves will be provided. The baseline value for analysis variable is the last measurement before administration of study treatments.

9.4.2. Demographic and Participant Characteristics

Demographic information such as age, gender, race, body weight, and participant characteristics such as baseline disease severity, symptoms, and comorbidities will be listed and summarized.

9.4.3. Efficacy Analyses

All efficacy analyses will be performed based on the ITT Population.

Table 5 Efficacy Analyses

Endpoint	Statistical Analysis
Primary	The primary efficacy endpoint is the proportion of participants who are alive and free from respiratory deterioration during the 28 days after dosing defined as follows per the 8-point ordinal scale (Appendix 6): • Deterioration to Categories 6, 7, or 8 for a participant who entered the trial at Categories 4 or 5 • Deterioration to Categories 7 or 8 for a participant who entered the trial at Category 6 The superiority of Treatment A over C with respect to the primary efficacy endpoint will be analyzed using the Cochran-Mantel-Haenszel test statistic adjusted by the stratification factors. The proportion in each group will also be presented with a 95% confidence interval (CI) using the Clopper-Pearson method. The difference in proportions between the two treatments and its 95% CI for the treatment group comparison will be presented. The superiority of Treatment B over C with respect to the primary efficacy endpoint will be tested using the same statistical method.
Secondary	The following secondary endpoints will be compared between Treatment A and C, and between Treatment B and C. The detailed analysis methods will be described in SAP. **Key Secondary Endpoint**: • Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale: o Not hospitalized, no limitations on activities. o Not hospitalized, limitation on activities and/or requiring home oxygen; o Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care. The superiority of Treatment A over C with respect to this endpoint will be analyzed using the log-rank test adjusted by the stratification factors with deaths due to all causes censored at Day 28. The superiority of Treatment B over C will be analyzed using the same method.

	• Time to clinical improvement determined by ≥ 2 points improvement in the 8-point ordinal scale during the 28 days after dosing. The endpoint will be analyzed by the same method as for the time to recovery. • The change in the level of IgG targeting RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 from baseline measured by the area under the IgG level curve above the baseline. The endpoint will be analyzed by analysis of variance method adjusted by the stratification factors. • Time to resolution of ≥ 50% of the Covid-19 attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline. Explicitly, the resolution of ≥ 50% of symptoms means the resolution of 1 of 1 symptom, 1 of 2 symptoms, 2 of 3 symptoms, 2 of 4 symptoms, 3 of 5 symptoms, or 3 of 6 symptoms that are reported at baseline. The endpoint will be analyzed by the same method as for the time to recovery. **Other Secondary Endpoints:** • Mortality rate due to any cause during the 28 days after dosing. • Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Day of Discharge and Days 3, 7, 14, 21, and 28. • Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Day of Discharge and Days 3, 7, 14, 21, and 28. • Change from baseline in level of IgM targeting the RBD at Days 7, 14, 21, and 28. • Change from baseline in the SARS-CoV-2 viral load at Days 7, 14, 21, and 28 • Time to PCR negativity, and percentage of participants with PCR negative at Days 7, 14, 21, and 28 • Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. • Rate of procedures including intubation. • Rate and duration of mechanical ventilation. • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices during the trial • Oxygenation free days in the first 28 days after dosing • Rate of rehospitalization
Exploratory	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline in level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) trimeric spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of discharge and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84 and 168 • PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

9.4.4. Safety Analyses

The safety analyses will include all participants in the Safety Population.

Safety will be assessed through summaries of AEs (including SAEs), changes in laboratory test results, physical examination findings, and vital signs.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0) to categorize each AE by System Organ Class and Preferred Term. The number of participants who experienced at least 1 AE; treatment-related AE; severe (Grade 3 or higher) AE, SAE; and the number of participants withdrawn from treatment due to AEs will be summarized. The incidence of AEs will be presented overall, by System Organ Class and Preferred Term, by intensity (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5), by severity, by relationship to study treatment or if treatment-emergent, and by treatment. Individual listings of AEs will be provided. Study treatment related AEs will be listed individually.

Laboratory tests will be listed and summarized for each test. Lab values will be graded according to the NCI-CTCAE criteria and summarized.

Deaths and related information will be listed.

9.4.5. Exploratory Analyses

PK, pharmacodynamic (PD), and biomarker exploratory analyses will be described in the SAP, finalized before database lock.

9.4.6. Interim and Final Analyses

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis and will be performed when approximately 25% (250) of participants have been enrolled into the study with 28 days of follow-up time. Safety and efficacy will be analyzed for futility evaluation.

The second interim analysis is also a non-binding futility and efficacy analysis and will be performed when approximately 60% (600) of participants have been enrolled with 28 days of follow-up time. Comparison between Treatment A and C, and between Treatment B and C, with respect to the efficacy endpoints will be made at this interim analysis. Should the comparison demonstrate a statistically significant superiority of Treatment A over Treatment C with respect to the primary efficacy endpoint, Corvus may file the results to regulatory authorities for drug approval. The study will continue its course beyond the interim analysis and collect all the planned safety, efficacy, PK, and PD data.

At both interim analyses, unblinded analyses will be provided by a separate unblinded statistician to the iDMC for making the futility decision.

As part of the second interim analysis, Corvus may request the iDMC to assess the primary efficacy endpoint and its conditional power of establishing a significant treatment effect at the final analysis based on the interim data. The total sample size of the study may be

increased with the recommendation by iDMC. The sample size adaptation plan and increase rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the first interim analysis.

The primary analysis of the study is the final analysis. Safety and efficacy analyses will be performed when all the participants of the study have completed the Day 28 assessments.

9.4.7. Hierarchical Testing

The 5 hypotheses listed in Section 9.1 will be tested according to their hierarchical priority defined as they are ordered at both the second interim analysis and final analysis.

At the second interim analysis, the 5 hypotheses for the superiority of Treatment A over C will be tested following their hierarchical priority. If the results of the tests for all the 5 hypotheses reach statistical significance, then the 5 hypotheses for the superiority of Treatment B over C will be tested following the hierarchical priority.

At the final analysis, the hypotheses that are either not tested or tested but fail to reach statistical significance for the superiority of Treatment A over C at the interim analysis will be tested following the hierarchical priority. If all the hypotheses are tested to be significant, then the hypotheses that are either not tested or tested but fail to reach statistical significance for the superiority of Treatment B over C at the interim analysis will be tested following the hierarchical priority.

For planning purpose for the study, the hypotheses are tested at a 1-sided α of 0.0038 at the second interim analysis and tested at a 1-sided α of 0.0238 at the final analysis. The α levels are determined by the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary assuming a 60% information fraction at the interim analysis. However, when the interim and final analyses are performed, the actual α levels will be determined based on the actual information fraction at the interim analysis.

The mortality rate due to all causes during the 28 days after dosing is also a secondary endpoint and will be provided at both interim analyses and final analysis. The 95% 2-sided CI will also be calculated for all 3 treatments.

9.4.8. Independent Data Monitoring Committee (iDMC)

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 10% (approximately 100) of participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur when 25%, 40%, 60%, and 80% (approximately 250, 400, 600, and 800, respectively) of participants have completed the Day 28 assessments. The analysis with 25% of participants is the first interim analysis for futility evaluation, and the analysis with 60% of participants is the second interim analysis for both efficacy and futility evaluation. Safety and efficacy data will be analyzed for the iDMC review at both interim analyses.

Study enrollment will be paused after 10% of the participants are enrolled. Enrollment will only be re-initiated following iDMC recommendation. For the second iDMC review, the review of the futility analysis (first interim analysis), study enrollment will also be paused at this time. Enrollment will only be re-initiated following iDMC recommendation. The study will not be paused for enrollment for the subsequent reviews after the futility analysis. However, the iDMC may request a pause in enrollment at any time during the study based on the safety and efficacy data. In addition, the iDMC is available for ad hoc reviews for safety concerns. The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

iDMC membership includes:

- Three clinicians experienced in care/management of Covid-19 and an unblinded independent statistician (all voting members)

10. REFERENCES

Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-523.

Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV –- a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226-36

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with Covid-19: initial three-month experience. MedRxiv. 2020.

Luke JJ, Merchan J; Harshman L, et al. Immunobiology and clinical activity of CPI-006, an anti-CD73 antibody with immunomodulating properties in a Phase 1/1b trial in advanced cancers. J. Immunother. Cancer 2019b Nov;7(suppl.1) 282.

Luke JJ, Powderly JD, Merchan JR, et al. Immunobiology, preliminary safety, and efficacy of CPI-006, an anti-CD73 antibody with immune modulating activity, in a phase 1 trial in advanced cancers. J. Clin. Oncol. 2019a 37(15 suppl.).

Rasheed AM, Ftak DF, Hashim HA, et al. The therapeutic effectiveness of Convalescent plasma therapy on treating Covid-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. medRxiv. 2020.

Resta R, Thompson LF. T cell signaling through CD73. Cell Signal. 1997 Feb;9(2):131-9.

Royal College of Physicians. National early warning score (NEWS) 2. Standardising the assessment of acute-illness severity in the NHS. 2017.

Willingham SB, Criner G, Hill C, et al. Characterization and Phase 1 Trial of a B Cell Activating Anti-CD73 Antibody for the Immunotherapy of Covid-19. medRxiv. 2020.

World Health Organization. Coronavirus disease 2019 (Covid-19): situation report, 72.

Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367(6483):1260-1263.

Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Apr; 580(7803):E7.

Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. Science. 2020 Apr 3. pii: eabb7269

APPENDIX 1
SCHEDULE OF ACTIVITIES

Table 6 Schedule of Activities

Procedure	Screening (up to 3 days before Day 1) [a]	Day 1	Day 2 to X (during hospital stay) [b]	Day 7 (if participant remains in the hospital) [c]	Day of Hospital Discharge [c]	Day 7 (if participant is discharged from hospital) [d]	Day 14 [c, d, e]	Day 21 [c, d, e]	Early Termination D28 [d]	Optional Assessment		
										Day 56 [d]	Day 84 [d]	Day 168 [d]
Informed Consent	X											
Inclusion and Exclusion Criteria	X											
Demography	X											
Physical Examination	X											
Limited Physical Exam		X	X	X	X				X			
Medical History	X											
Covid-19 Symptoms Assessment [f]	X	X	X	X	X	X	X	X	X			
National Early Warning Score 2 Assessment	X	X	X	X	X				X			
8-point Ordinal Scale Assessment	X	X	X	X	X		X [g]	X [g]	X			
Vital Signs [h]	X	X	X	X	X				X			
Hematology Panel [i]	X	X	X	X	X				X			
Chemistry Panel [j]	X	X	X	X	X				X			
Serum Quantitative Immunoglobulins [j]	X	X			X				X			
Serum Ferritin	X	X	X	X	X				X			
Coagulation Test (PT, aPTT, INR)	X	X	X	X	X				X			
D-dimer	X	X	X	X	X				X			

Procedure	Screening (up to 3 days before Day 1)[a]	Day 1	Day 2 to X (during hospital stay)[b]	Day 7 (if participant remains in the hospital)[c]	Day of Hospital Discharge[c]	Day 7 (if participant is discharged from hospital)[d]	Day 14[c, d, e]	Day 21[c, d, e]	Early Termination D28[d]	Optional Assessment		
										Day 56[d]	Day 84[d]	Day 168[d]
Fibrinogen	X	X	X	X	X				X			
Pregnancy Test[k]	X								X			
SARS-CoV-2 PCR Test[l]	X	X		X	X							
Viral load sample (for Central Lab)		X	X[m]	X	X		X	X	X			
Influenza and RSV PCR Test	X											
C-Reactive Protein	X	X	X	X	X				X			
Anti-SARS-CoV-2 Serum Antibody Test Blood Sample (Central Lab)[n]		X[n] (pre-dose)		X	X		X	X	X	(X)	(X)	(X)
Exploratory Biomarker Blood Samples		X[o]			X		X		X			
PK[n] and Immunogenicity Serum Samples	See Table 7 for details											
Treatment Administration		X										
Adverse Event Review[p]		<==========							==========>			
Serious Adverse Event Review[p]	<==========								==========>			
Concomitant Medication Review	<==========								==========>			
Covid-19 Medical Intervention Review[q]	<==========								==========>			

NOTE: Procedures indicated with parentheses "(X)" are conditional. Refer to the appropriate footnote for details.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; NEWS2 = National Early Warning Score 2 Assessment; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RSV = Respiratory Syncytial Virus; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Screening and Day 1 testing can be combined, providing they are separated by less than 24 hours and there are no signs of changes in the participant's status.

[b] Participants will be monitored daily while in the hospital for a minimum of 48 hours after study treatment administration. Participants will be monitored with vital signs including blood oxygen saturation every 4-6 hours or per institutional standards. Laboratory assessment will be taken daily or per institutional standards and should include but are not limited to hematology panel, chemistries, ferritin, CRP, LDH, D-dimer, fibrinogen, PT, aPTT and INR. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital.

[c] All participants will have samples collected for viral load, anti-SARS-CoV-2 serum antibody test, and exploratory biomarkers on day of discharge. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Participants who are discharged before Day 7, do not need a Day 7 sample collection but will be assessed for Covid-19 symptoms.

[d] Day 7 can be ± 1 day, Day 14, and Day 21 can be ± 2 days, Day 28 can be + 7 days. Day 56, Day 84, and Day 168 can be ± 5 days.

[e] All efforts should be made to have the blood draws and exams done and assessments completed. When needed a telemedicine or home health visit can replace a clinical visit for the post-hospitalization visits.

[f] Assessment of Covid-19 symptoms (per Appendix 8) should happen daily during the hospital stay. In the post- hospitalization setting, assessment of symptoms should happen on Day 7 (for those discharged before Day 7), Day 14, Day 21 and Day 28. Day 7, Day 14, and Day 21 assessments can be a telemedicine or phone call visit.

[g] If the participant is hospitalized, the assessment should be conducted in the hospital. If discharged and participant is at home, assessment may be conducted over the phone.

[h] Vital signs includes pulse, blood pressure, temperature, respiratory rate, and oxygen saturation by pulse oximeter. Height and weight collected at screening only. On Day 1 vital signs will be collected pre-dose, at completion of treatment administration (at the end of the flush) (+ 15 minute window), and 2 hours post-dose (± 15 minutes window).

[i] Hematology panel should include the parameters detailed in protocol Appendix 3.

[j] Chemistry panel should include the parameters detailed in protocol Appendix 3 and serum quantitative immunoglobulins (Screening, Day 1, day of discharge and Day 28).

[k] Pregnancy test (serum or urine) for women of child-bearing potential only (Appendix 5).

[l] Participants must have a confirmed positive PCR or antigen test for SARS-CoV-2 within 72 hours of randomization (screening sample). PCR test will also be obtained on Days 1 and 7, while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally.

[m] Viral load sample to be collected on Day 3 while hospitalized as well as day 1 (pre-dose), Day of discharge, Day 7 (if hospitalized), 14, 21 and 28.

[n] Anti-SARS-CoV-2 serum antibody test blood sample to be collected pre-dose administration. Anti-SARS-CoV-2 serum antibody samples will be collected to be assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if participant remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the post-hospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

[o] Exploratory biomarker samples on Day 1 will be collected pre-dose and 4 hours post-dose (± 30 min).

[p] After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by protocol-mandated procedures will be reported. After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

[q] Review of medical interventions/ procedures for management of Covid-19 such as intubation, ventilation, and supplemental oxygen and rehospitalization.

Table 7 PK, ADA, and Neutralizing Antibody Sampling Schedule

Sample[a]	Collection Timepoint	PK Variance	ADA and Neutralizing Antibody Only
1	pre-dose	-1 hour-0 hours	X (collected as part of PK)
2	0.5 hours	± 5 min	
3	2 hours	± 30 min	
4	4 hours	± 30 min	
5	8 hours	± 2 hours	
6	24 hours	± 6 hours	
7	48 hours	± 8 hours	
8	Day 28		X

Abbreviation: ADA = anti-drug antibodies; min = minutes; PK = pharmacokinetics
[a] Time post CPI-006 infusion and line flush except for pre-dose sample

APPENDIX 2
REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- In accordance with applicable laws and regulations, protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- 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 site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor 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 study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants 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 participant.

The ICF will address the use of remaining mandatory samples. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

Sites will be allowed to use all processes approved by their IRB to ensure safety of staff and patients from Covid-19, while maintaining appropriate consent procedures for the duration of this study.

DATA PROTECTION

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant 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.

COMMITTEES STRUCTURE

The objectives of the iDMC are to evaluate interim clinical and safety data to protect participant welfare and to provide recommendations regarding study conduct. Details of iDMC responsibilities and procedures are specified in the iDMC charter.

DISSEMINATION OF CLINICAL STUDY DATA

Clinical Study Reports, periodic safety reports, and clinical study summary reports will be disclosed after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.

Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

Publication planning and other activities related to non-promotional, peer-reviewed publications will be conducted to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies should be through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

DATA QUALITY ASSURANCE

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing CRF verification to confirm that data entered into the CRF by authorized site personnel are accurate and complete; that the safety

and rights of participants 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.

- U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. No records may be transferred to another location or party without written notification to the Sponsor.

SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the CRF 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 study monitoring plan.

STUDY TERMINATION

Potential reasons for closing the study include:

- Unsatisfactory subject enrollment
- Potentially unacceptable risk to study subjects
- Decision to modify clinical development plan
- Decision by the regulatory authority

In the event of a decision to close the study, the Sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed explanation of the reason for closure. The Sponsor and investigator will ensure that the safety of the subjects is protected and that IRB/IEC reporting continues per the requirements of the IRB/IEC and applicable local laws or requirements.

SITE CLOSURE

The Sponsor or designee reserves the right to close a study site at any time for any reason at the sole discretion of the Sponsor. Potential reasons for closing a site include:

- Investigator noncompliance

- Unsatisfactory subject recruitment and enrollment
- Lack of adherence to protocol procedures, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision by the regulatory authority

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or confirmed as destroyed and a study-site closure visit has been performed.

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

PUBLICATION POLICY

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 3
CLINICAL LABORATORY TESTS

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.

Table 8 Protocol-Required Safety Laboratory Assessments

Chemistry	Hematology	Serum Quantitative Immunoglobulins	Inflammatory Biomarkers	Coagulation Testing
BUN (Blood Urea Nitrogen)	Platelet Count	IgA	C-reactive protein	PT
Potassium	RBC Count	IgG	Ferritin	aPTT
Creatinine	Hemoglobin	IgM		INR
Sodium	Hematocrit			D-dimer
Glucose	RBC (Red Blood Cell) indices: MCV MCH % Reticulocytes			Fibrinogen
Calcium				
Bilirubin (total & direct)				
Protein (total)				
LDH (Lactate Dehydrogenase)	WBC count (White Blood Cell) with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils			
AST				
ALT				

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell.

APPENDIX 4
ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, 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 or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, is accompanied by clinical symptoms, results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), results in a medical treatment (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
  - 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.
- For worsening of Covid-19 symptoms, the clinical event(s) that mark the worsening should be reported as AE or an SAE.
- If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event CRF.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Deaths that occur within 28 days after study treatment (CPI-006) should be reported as an SAE.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- "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
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., 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 (e.g., hospitalization for signs/symptoms of the progression of disease under study). Hospitalization or ICU admissions due to Covid-19, worsening of Covid-19 in the 28 days during this study, or pulmonary conditions attributable to Covid-19 infection are considered efficacy-related endpoints. Therefore, Covid-19-related hospitalization or ICU admission is excluded from this definition.

A 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 participant 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 **Any adverse event that causes prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event).** • For this study, the subjects will be hospitalized for Covid-19 treatment so initial hospitalization will not be considered as an SAE. Complications that occur during hospitalization are AEs/SAEs. If a complication prolongs hospitalization (or requires admission to ICU) or fulfills any other serious criteria, the event is serious. **An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:** • Hospitalization for respite care • Planned hospitalization required by the protocol (e.g., for the Covid-19 treatment).

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 (e.g., 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 participant or may require medical or surgical treatment to prevent 1 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 (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- 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. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF
- If vomiting results in severe dehydration, both events should be reported separately on the CRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the CRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF

All AEs should be recorded separately on the Adverse Event CRF if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient or participant evaluation timepoints. Such events should be recorded with each severity change on the Adverse Event CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported, with each subsequent change in severity recorded on the same AE CRF with the exception of a non-serious event becoming serious. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious.). A new AE should be recorded as serious in the CRF with the date the event became serious recorded as the start date and completing all data fields related to SAEs.

- A recurrent AE is one that resolves between patient or participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event CRF.

Assessment of Intensity

The guidelines outlined below will be used for assessing the severity of AEs. The severity/intensity of AEs and SAEs will be graded based upon the participant's symptoms according to the NCI CTCAE v5.

AEs that are not defined in the NCI CTCAE v5 should be evaluated for severity/intensity according to the following scale:

Table 9 Assessment of Severity of Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or treatment not indicated
2	Moderate; minimal, local, or non-invasive treatment indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living.[b,c] An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
4	Life-threatening consequences or urgent treatment indicated [d]
5	Death related to AE [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE per the definition of SAE in (see section above).

[d] Grade 4 and 5 events must be reported as SAEs per the definition of SAE (see section above).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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 Investigational Brochure (IB) 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 Sponsor. 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 Sponsor.
- 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

- Treatment related AEs and SAEs should be followed up until resolution or until the AE is stable.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor 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 participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE Reporting to Corvus via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Corvus will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone or email.

SAE Reporting via Paper Report Forms

The primary mechanism for reporting an SAE to Sponsor will be through EDC. If EDC is down or not available, then the paper SAE report form can be used for SAE reporting.

Events That Occur Prior to the Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment (non-treatment emergent), **only SAEs caused by protocol-mandated procedures** should be reported in EDC using the EDC SAE form. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event CRF and submit the report via the paper report form. All other non-treatment emergent AEs should be reported in the Medical History CRF.

Events That Occur after Study Treatment Initiation

- After initiation of study treatment, all AEs and SAEs will be reported for 28 days following stopping of study treatment and until participants complete the study. The site will enter the SAE data into the EDC SAE report form.

Adverse Events That Occur after the Adverse Event Reporting Period are described in the following section.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, then the site can report this information in EDC (see next section) or to the Sponsor's designee by telephone on the number listed in a section below.

If EDC is unavailable, then the paper Clinical Trial Serious Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators below. Please note that email is preferred over fax and phone.

Note: For Ex-US country-specific safety fax and phone numbers, refer to the study manual.

- 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 CRF pages within the designated reporting time frames.

APPENDIX 5
CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

WOMAN OF CHILDBEARING POTENTIAL (WOCBP) AND OF FERTILE MEN

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

1. Women in the following categories are not considered WOCBP
2. Premenarchal
    a. Premenopausal female with 1 of the following:
        i. Documented hysterectomy
        ii. Documented bilateral salpingectomy
        iii. Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the participant'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 hormonal 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.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

CONTRACEPTION GUIDANCE:

MALE PARTICIPANTS

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following for 6 weeks after study treatment.

- 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 Table 1 of this appendix when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 6 weeks after study treatment.

FEMALE PARTICIPANTS

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10.

In addition, female participants must refrain from donating ova for the duration of the study and for 6 weeks after study treatment.

Table 10 Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent [b]

Failure rate of <1% per year when used consistently and correctly.

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [c]

- Oral
- Intravaginal
- Transdermal

Progestogen only hormonal contraception associated with inhibition of ovulation

- Oral
- Injectable

Highly Effective Contraceptive Methods That Are User Independent [c]

- Implantable progestogen only hormonal contraception associated with inhibition of ovulation[c]
- IUD
- IUS
- Bilateral tubal occlusion

Vasectomized partner

A vasectomized partner is a highly effective contraception 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 defined as 6 weeks after receiving 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 participant.

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system; WOCBP = woman of childbearing potential

[a] Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhea method (LAM) are not considered acceptable methods of contraception. A male and female condom should not be used together as friction between the two can result in either product failing.

[b] 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 participants participating in clinical studies.

[c] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 6 weeks corresponding to time needed to eliminate study treatment after the last dose of study treatment. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.

PREGNANCY TESTING:

- WOCBP should only be included after a negative (urine or serum) pregnancy test at screening
- Additional pregnancy testing is required at end of study or at early termination (see Appendix 1 – Schedule of Activities)

COLLECTION OF PREGNANCY INFORMATION:

MALE PARTICIPANTS WITH PARTNERS WHO BECOME PREGNANT

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

FEMALE PARTICIPANTS WHO BECOME PREGNANT

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. 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 post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

APPENDIX 6
8-POINT ORDINAL SCALE FOR CLINICAL IMPROVEMENT

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

APPENDIX 7
NEWS2 SCORING SYSTEM

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

National Early Warning Score (NEWS) 2

APPENDIX 8
EXAMPLE OF AN ASSESSMENT OF 14 COMMON COVID-19-RELATED SYMPTOMS: ITEMS AND RESPONSE OPTIONS

Example items *For items 1–10, sample item wording could be: "What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you **vomit (throw up)** in the last **24 hours**?**	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?**	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

APPENDIX 9
PROTOCOL AMENDMENT HISTORY

Table 11 Document History

Document History	Date of Issue
Version 002 (Amendment 1)	11-January-2021
Version 001 (Original Protocol)	06-November-2020

Protocol

Protocol Title:	**Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients**
Protocol Number:	**CPI-006-003**
Regulatory Agency Identifier Number(s):	[redacted] **EudraCT: 2020-005305-54**
Compound Number:	**CPI-006**
Study Phase:	**3**
Sponsor Name:	**Corvus Pharmaceuticals**
Sponsor Address:	**863 Mitten Rd, Suite 102 Burlingame, CA 94010**
Version Number:	**001**
Date Final:	**06 November 2020**

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	001

This clinical trial protocol was subject to critical review and has been approved by Corvus Pharmaceuticals.

[redacted]

Sponsor Signatory **Date**

[redacted]

Medical Monitor Name and Contact Information:

Name:	[redacted]
Address:	[redacted]
Email:	[redacted]
Office Phone:	
Cell Phone:	

INVESTIGATOR SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients
Protocol Number:	CPI-006-003
Version Number:	001

I have read and understood the current version of the protocol (as listed above). I agree to conduct this trial in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), all applicable regulatory requirements, and the general ethical principles outlined in the Declaration of Helsinki.

I agree to ensure that no deviation from, or changes to the protocol will take place without prior agreement from Corvus Pharmaceuticals and documented approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I will ensure that all staff members under my supervision involved in the conduct of this study are informed about the protocol and protocol amendments, the investigational products, and their study-related duties and functions.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational products and processes or methods of Corvus.

Investigator Signatory Name: **Title:**	**Date**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin converting enzyme 2
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the serum or plasma concentration-time curve
$AUC_{(0\text{-}169)}$	AUC from the start of infusion to 169 hours after the start of infusion
AUC_{last}	AUC from time zero to the time of the last quantifiable concentration
BCR	B cell receptor
C(0)	the initial CPI-006 concentration measured 30 minutes after completion of the infusion
CBC	complete blood count
CCP	Covid-19 Convalescent Plasma
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum drug concentration in serum or plasma
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
DLT	dose-limiting toxicity
EAP	extended access program
ELISA	enzyme-linked immunosorbent assay
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
HIPAA	United States Health Insurance Portability and Accountability Act
HLA-DR	human leukocyte antigen – DR isotype
IC_{50}	concentration required for 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2, -6, -10	interleukin 2, 6, 10
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IV	Intravenous(ly)
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MERS	Middle East respiratory syndrome
NEWS2	National Early Warning Score 2
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed adverse effect level
O_2	oxygen
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PD1	programmed cell death 1 receptor

PE	polyethylene
PES	polyethersulfone
PK	pharmacokinetic(s)
PO	by mouth (orally)
PO/PE	polyolefin/polyethylene
PT	prothrombin time
PVC	polyvinylchloride
RBC	red blood cell
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sickle cell disease
SoA	schedule of activities
SOB	shortness of breath
SOC	standard of care
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TNF-α	tumor necrosis factor alpha
TTD	time to death
ULN	upper limit of normal
US/USA	United States of America
USP	United States Pharmacopeia
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Name of Sponsor: Corvus Pharmaceuticals, Inc.

Investigational Product: CPI-006

Title of Study: Phase 3, Randomized, Placebo Controlled, Double-blind, Multicenter, Stratified Study of CPI-006 Plus Standard of Care Versus Placebo Plus Standard of Care in Mild to Moderately Symptomatic Hospitalized Covid-19 Patients

Phase of Development: 3

Number of Participants: Approximately 620 evaluable participants for an estimated total of 310 evaluable participants per treatment group

Study Centers: Multicenter

Study Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
Key Secondary	
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale)
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28
• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of ≥ 50% of the Covid-19 -attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline

Additional Secondary	
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, Day of Discharge, Days 14, 21, and 28
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21 and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)
• To compare the medical interventions/procedures including intubation, mechanical ventilation, and supplemental O_2 use, rehospitalization of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate of procedures including intubation • Rate and duration of mechanical ventilation • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices during the trial • Oxygenation free days in the first 28 days • Rehospitalization
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment -emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0
• To compare TTD of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to death during the first 28 days

Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• Characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; O_2 = oxygen; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = Standard of Care; SpO_2 = oxygen saturation; TTD = time to death

Study Design:

This is a Phase 3, randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) Covid-19 patients. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) testing.

Participants will be randomized at a 1:1 ratio to the 2 treatment arms and stratified by the following factors:

- Region of the world (North America vs. Latin America vs. Europe).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg up to a maximum dose of 200 mg intravenously (IV) on Day 1 in the participants randomized to receive treatment (Treatment A). A placebo will be given at the same schedule and same volume as the active drug for participants to receive the control (Treatment B). Participants, investigators, and Corvus will not be aware of the treatment the participants receive. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir or any other approved treatment) per those guidelines at the discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator in consult with the Corvus medical monitor feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an interactive response technology (IRT) system to obtain the participant number. Every participant that signs the informed consent form (ICF) must be assigned with a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site

in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the National Early Warning Score 2 (NEWS2), Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if patient remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the posthospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 50 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur after every 150 participants have completed the Day 28 assessments. In addition, the iDMC is available for ad hoc reviews for safety concerns. The study will not stop enrollment awaiting these iDMC reviews, although the iDMC may recommend temporary or permanent cessation of enrollment based on their safety and/or efficacy reviews. The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

Eligibility: Hospitalized mild to moderately symptomatic Covid-19 patients. Participants may have preexisting conditions such as cancer and diabetes. Participants will receive standard care for Covid-19.

Test Product, Dose and Administration: CPI-006 single dose at 2 mg/kg given by IV infusion over 10-15 minutes.

Rationale:

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to cancer patients has shown rapid and temporary redistribution in circulating B cells with

return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients has demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in cancer patients have demonstrated production of anti-tumor antibodies in some patients. The high anti-SARS-CoV-2 titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 20 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable patients within 7 days of a single infusion of low doses of CPI-006. Similar results were observed in anti-SARS-Cov-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in patients who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

Overall Design:

This is a randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized Covid-19 patients. An iDMC will monitor safety, efficacy, and conduct of the study. All participants will be followed for 28 days for production of anti-SARS-CoV-2 antibodies followed by an optional period of 5 months. While in the hospital, participants will receive standard of care monitoring including vital signs every 4-6 hours, or per institutional guidelines and safety assessments. Safety and other disease assessments will be conducted at Days 3, 7, 14, 21, and 28. Discharged participants will be asked to attend post-hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed.

Treatment Groups and Duration:

Participants meeting study entry criteria will be randomized in a 1:1 ratio to receive either Treatment A (CPI-006 plus SOC) or Treatment B (placebo plus SOC). Participants randomized to Treatment A will receive a single dose of CPI-006 at 2 mg/kg given by IV infusion plus SOC. A placebo will be given at the same schedule and same volume as the

active drug for participants randomized to Treatment B. All participants will be managed per physician using best SOC for Covid-19 patients. No dose modifications will be allowed.

Statistical Methods:

Hypothesis

The primary hypothesis is that treatment with CPI-006 plus SOC (Treatment A) will shorten the time to recovery during the 28 days after dosing based on the 8-point ordinal scale in comparison to placebo plus SOC (Treatment B) in mild to moderately symptomatic Covid-19 hospitalized participants.

The first secondary hypothesis is that treatment A will shorten the time to clinical improvement by at least 2 points during the 28 days after dosing on the 8-point ordinal scale in comparison to treatment B.

The second secondary hypothesis is that Treatment A will increase the level of IgG targeting the RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 more than Treatment B, as measured by the area under the IgG level curve above the baseline, calculated over Days 1 (the baseline), 7, 14, 21, 28, and Day of Discharge.

The third secondary hypothesis is that Treatment A will shorten the time to resolution of ≥ 50% of the Covid-19-attributable symptoms: fever, cough, sore throat, headache, muscle pain, and/or shortness of breath, reported at baseline. Explicitly, the resolution of ≥ 50% of symptoms means the resolution of 1 of 1 symptom, 1 of 2 symptoms, 2 of 3 symptoms, 2 of 4 symptoms, 3 of 5 symptoms, or 3 of 6 symptoms that are reported at baseline.

Sample Size

Approximately 620 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1 ratio between Treatment A and Treatment B within each of the strata defined by:

- Region of the world (North America vs. Latin America vs. Europe).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - CKD
    - SCD
    - Organ transplantation
    - Cancer

With 520 observed recoveries in the 2 treatment groups, there would be an approximately 83% power to show a statistically significant superiority of Treatment A over Treatment B in recovery rate at an overall 1-sided α level of 0.025 when the true recovery rate ratio of Treatment A to Treatment B is 1.296, assuming an exponential distribution for time to recovery for each treatment.

With a total of approximately 620 participants, it is estimated that 520 recoveries will be observed after 5.5 months assuming that the median time to recovery is 5.4 days and 7 days of Treatments A and B, respectively. The all-cause death rate is assumed to be 6% over the 28-day period.

Populations for Analyses

For purposes of analyses, the following populations are defined in Table 1.

Table 1 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study.
Efficacy	All participants who take at least 1 dose of study treatment (CPI-006 or placebo) and have at least 1 post-baseline assessment based on the 8-point ordinal scale.
Safety	All participants who take at least 1 dose of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

Statistical Methods

The primary objective of the study is to determine the difference between the 2 treatments in time to recovery during the 28 days after dosing.

Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (See Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.

Statistical Design

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis when approximately 150 participants have been enrolled into the study with 28 days of follow up time. Safety and efficacy will be the focus of the evaluation. Unblinded safety and efficacy data will be reviewed by the iDMC.

The second interim analysis will be performed when approximately 310 (60% of the 520) recovery events have been observed in the 2 treatment arms based on the Efficacy Population. Comparison between Treatment A and Treatment B with respect to the time to

recovery will be made using a modified version of stratified log-rank test correcting for competing risk of all-cause death. Should the comparison demonstrate a statistically significant superiority of Treatment A over Treatment B, Corvus may file the results to regulatory authorities for drug approval. The study will continue its course beyond the interim analysis and collect all the planned safety efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) data.

As part of the second interim analysis, Corvus may request the iDMC to assess the recovery rates and the conditional power of the study based on the interim data. The total sample size of the study may be increased with the recommendation by iDMC. The sample size adaptation plan and increase rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the second interim analysis.

The primary analysis of the study is the final analysis in the time to recovery during the 28 days after dosing and will be performed when approximately 520 recovery events have been observed in the 2 treatment arms based on the ITT Population. Comparison between Treatment A and Treatment B with respect to the time to recovery will be made using a modified version of stratified log-rank test correcting for competing risk of all-cause death. The efficacy stopping boundaries at the second interim and final analyses will be derived based on the time and number of recovery events using the Lan-Demets O'Brien and Fleming-like α spending function.

All the enrolled participants will be follow-up to Day 28 and further to the optional visits. Corvus may perform the primary analysis when all the enrolled participants have completed Day 28 visit and include all participants' data for the primary analysis, if the iDMC recommends doing so at the second interim analysis. In this case, the analysis when 520 recovery events are observed will not be performed.

The following are the three key secondary endpoints with their hierarchical priority as ordered for statistical testing:

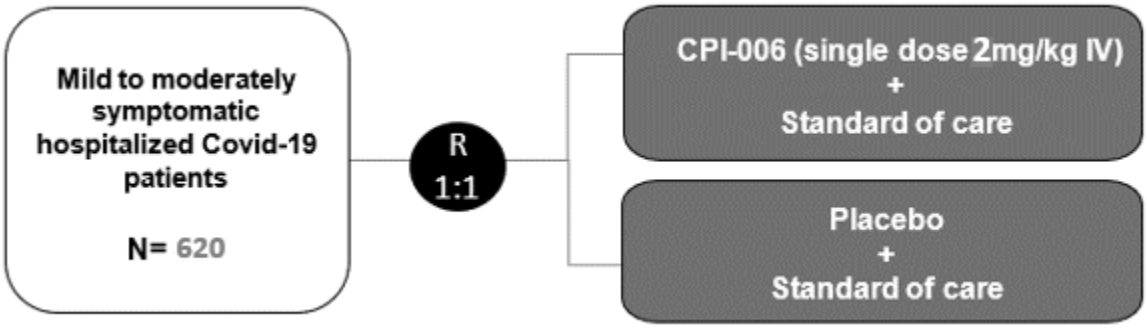
- Time to improvement by at least two points on the 8-point ordinal scale during the 28 days after dosing;
- The change in the level of IgG targeting RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 from baseline measured by the area under the IgG level curve above the baseline over Days 1, 7, 14, 21, 28 and Day of Discharge;
- The time to resolution of ≥ 50% of the Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or short of breath reported at baseline.

In the case that a statistical significance is achieved in the time to recovery in comparison of Treatments A and B, the three secondary endpoints will be tested according to their hierarchical priority. This hierarchical procedure will be applied to the second interim analysis and to the final analysis. The α level for the comparison in the secondary endpoints will be the same α level as for the comparison in the time to recovery.

TTD is also a secondary endpoint of the study. TTD will be described at the final analysis which will be performed up to 6 months after the primary analysis and will be based on the ITT Population. The purpose of the analysis is to show a favorable trend of TTD with Treatment A over Treatment B. The Kaplan-Meier product limit curves of TTD and the 2-sided 95% confidence interval (CI) for the median TTD will be computed for each arm. A hazard ratio and a 2-sided 95% CI of the ratio will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors.

1.2. SCHEMA

Figure 1 Study Schematic



R = randomization

1.3. SCHEDULE OF ACTIVITIES (SOA)

For the schedule of activities, please see Appendix 1, Table 6.

2. INTRODUCTION

2.1. STUDY RATIONALE

CPI-006 is a humanized immunoglobulin G (IgG) fragment crystallizable (Fc) receptor binding deficient monoclonal antibody that activates B cells leading to the production of immunoglobulin M (IgM) and IgG antibodies (Luke et al, 2019b). In vivo administration to cancer patients has shown rapid and temporary redistribution in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in human leukocyte antigen – DR isotype (HLA-DR) expression. Molecular studies of the B cell receptor (BCR) in treated patients has demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in cancer patients have demonstrated production of anti-tumor antibodies in some patients. The high anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) titer seen in a patient with Covid-19 following treatment with CPI-006 for lung cancer are

supportive of the hypothesis that CPI-006 may enhance anti-viral antibody response. CPI-006 is therefore under development for Covid-19 since neutralizing antibodies and the generation of immune memory are critical for eliminating infections with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. In the ongoing Phase 1 CPI-006-002 study, 20 participants with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3mg/kg to 5 mg/kg. CPI-006 was well tolerated with no treatment related AEs or dose-limiting toxicities (DLTs) reported. IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable patients within 7 days of a single infusion of low doses of CPI-006. Similar results were observed in anti-SARS-Cov-2 immunoglobulin A (IgA) titers. This increase in antibody titers provides the rationale to develop CPI-006 for treatment of Covid-19. This study evaluates clinical benefit, safety, and the anti-SARS-CoV-2 antibody production in patients who are hospitalized with mild to moderately symptomatic Covid-19 treated with CPI-006. Treatment with CPI-006 may also result in prolonged immunity to SARS-CoV-2 and related viruses (Willingham et al., 2020).

The Covid-19 pandemic is not yet under control and there is fear that infections could spread and/or recur in a seasonal manner, even if controlled now. There is also the possibility of viral mutation or emergence of other virulent coronaviruses. Vaccines are in development but it is not yet clear if such an approach will be effective in controlling Covid-19. Based on encouraging preliminary data, CPI-006 may improve the magnitude, duration, and diversity of antibody responses to SARS-CoV-2 and improve clinical outcome. It also may result in prolonged immunity to SARS-CoV-2, its variants and related coronaviruses. It is also possible that experience gained with treating Covid-19 with CPI-006 could be applied to treatment of other infectious diseases including future viral pandemics, and potential use in conjunction with vaccination of healthy participants.

2.2. BACKGROUND

Since its emergence in Hubei province, China in December of 2019, the novel coronavirus (2019-nCoV, Covid-19) has become a global health crisis (Wu et al, 2020; Chan et al, 2020). There is an urgent need for therapies that can improve survival, clinical outcomes, and reduce the requirements for intensive supportive care and prolonged hospitalization (Huang et al, 2020). There are efforts underway to re-purpose direct acting antivirals targeting the ribonucleic acid (RNA)-dependent RNA polymerase including remdesivir and favipiravir both of which are being actively studied in multiple clinical trials. Similarly, inhibitors of the virally encoded proteases are being evaluated. To compliment therapeutic approaches there is an intense effort underway to develop vaccines. A number of approaches to vaccine development have begun clinical trials or are planned. To support vaccine strategies, there is a growing understanding of the key viral/host interaction required for viral entry and replication (Du et al, 2009). Indeed, it is increasingly clear that the virally encoded spike protein binds to angiotensin converting enzyme 2 (ACE2) on target cells to facilitate entry and replication. The spike protein is a multidomain viral envelop glycoprotein which

contains a receptor binding domain (RBD) in subunit 1 of the spike protein (Wrapp et al, 2020). This RBD directly interacts with N-terminal domain of ACE2. This interaction is absolutely required and initiates a sequence of steps leading to efficient viral infection. Thus, antibodies that disrupt this key interaction may be effective in viral neutralization and clearance. A recent publication from Zhang and colleagues have identified neutralizing antibodies from 8 Covid-19 infected patients that bind to the RBD of the spike protein and are neutralizing (Yuan et al, 2020). This provides evidence that neutralizing antibody responses to SARS-CoV-2 are possible and may provide clinical benefit in patients with Covid-19 and protection from disease in healthy subjects. Indeed, the U.S. Food and Drug Administration (FDA) has given emergency use authorization for the use of Covid-19 Convalescent Plasma (CCP) for the treatment of Covid-19. Clinical studies with CCP suggest that higher titers of neutralizing antibody provide superior clinical benefit to recipients (Joyner et al, 2020; Rasheed et al 2020) These findings support the value of anti-viral antibodies in eradicating viral infection in patients, lessening disease severity, improving clinical course and potentially reducing transmission.

CD73 is an adhesion molecule that was initially found to be important for lymphocyte trafficking and T cell activation (Resta & Thompson, 1997). It also functions as an ectoenzyme that converts adenosine monophosphate (AMP) to immunosuppressive adenosine. Several companies are developing anti-CD73 antibodies to inhibit production of adenosine and thereby augment immune response in patients with cancer. These antibodies have been designed primarily to block enzymatic activity. Corvus has designed a novel anti CD73 antibody with agonistic, immunomodulatory properties that binds CD73 resulting in activation of immune cells such as B cells, and results in antibody production in vitro (Luke et al, 2019a). This antibody, CPI-006, is under investigation in a Phase 1b trial (NCT03454451) in advanced cancer as monotherapy and in combination with other immunotherapies such as anti- programmed cell death 1 receptor (PD1). Over 90 patients have received doses of this antibody ranging from 1mg/kg to 24 mg/kg given IV every 21 days. Treatment has been safe and tolerable, with chills and rigor seen during antibody infusion, that are managed by premedication with acetaminophen and diphenhydramine.

CPI-006 is a humanized FcγR binding-deficient monoclonal antibody. In vitro studies have revealed binding to CD73 and direct effects on B cells, morphologic transformation to plasmablasts and induction of IgM and IgG secretion (Luke et al, 2019b). In vivo administration to cancer patients has shown rapid and temporary drop in circulating B cells with return of memory B cell phenotype. Immune markers demonstrate activation of B cells, expression of CD69 and increases in HLA-DR expression. Molecular studies of the BCR in treated patients has demonstrated that CPI-006 stimulates the generation of B cell clones with new BCRs. These findings indicate that CPI-006 is activating B cells, causing their trafficking to lymphoid tissues and potentially their further differentiation into antibody producing cells. Further studies in cancer patients have demonstrated production of anti-tumor antibodies in some patients.

CPI-006 is under investigation in a Phase1 trial (NCT04464395) in mild to moderately symptomatic hospitalized Covid-19 patients. The results from the study (CPI-006-002) shows IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or receptor binding domain (RBD) increased in all evaluable patients within 7 days of a single infusion of low doses of CPI-006. Similar results were observed in anti-SARS-Cov-2 IgA titers. In patients receiving 0.3 mg/kg CPI-006, all four evaluable patients achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these patients, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to -84 days, 56 days, and 14 days for the 1.0 mg/kg, 3.0 mg/kg and 5.0 mg/kg cohorts, respectively in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. Immunophenotying of peripheral blood mononuclear cells (PBMCs) at baseline and at 14 -or 18-days after treatment provided preliminary evidence that CPI-006 increased the frequency of memory B cells in 2 evaluated patients. An increased frequency of memory/effector $CD4^{POS}$ and $CD8^{POS}$ T cells was also observed in 3 evaluable patients. CPI-006 has been well tolerated in Covid-19 patients in this study. No DLTs or treatment related AEs have been reported in the study. The AEs reported in the study were due to the underlying Covid-19 or comorbidities.

In this Phase 3, randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus standard of care (SOC) versus placebo plus SOC in mild to moderately symptomatic hospitalized Covid-19 patients, Corvus will assess if administering CPI-006 to Covid-19 patients along with standard of care can lead to clinical benefit and enhance humoral immune response to the SARS-CoV-2. The production of neutralizing antibodies would be expected to shorten disease interval and improve clinical outcome, and treatment is expected to be safe. Therefore, CPI-006 treatment is expected to have a positive benefit/risk profile.

2.3. CPI-006 NONCLINICAL EVALUATION

CPI-006 recognizes and binds human CD73 with high affinity (KD values of 0.64–7.1 nM), inhibits CD73 catalytic activity (mean concentration required for 50% inhibition [IC_{50}] values of 2.1 nM and 4.0 nM for human and cynomolgus monkey CD73), and has downstream biological effects on T cells as evidenced by restoration of CD3+ T cell proliferation in the presence of AMP. CPI-006 also binds to and inhibits cynomolgus monkey CD73, but not mouse or rat CD73, supporting the use of cynomolgus monkeys for studies of the pharmacokinetics (PK) and toxicology of CPI-006.

Complete CD73 occupancy on CD8+ T cells in peripheral blood samples from cynomolgus monkeys by CPI-006 was observed at all doses of CPI-006. Complete CD73 occupancy was also observed in the axillary lymph nodes, indicating successful solid tissue penetration by CPI-006 with full coverage at least 24 hours after the final dose.

An in vitro cytokine release assay was conducted with CPI-006 to evaluate the potential for CPI-006 to induce an immune response resulting in production of multiple cytokines (cytokine storm). The results demonstrated that CPI-006 did not directly induce cytokine (interferon gamma [IFN-γ], interleukin 2 [IL-2], interleukin 6 [IL-6], interleukin 10 [IL-10], and tumor necrosis factor alpha [TNF-α]) release from fresh human PBMCs at 0.1-10 μg/mL of CPI-006.

Safety of CPI-006 was evaluated in male and female cynomolgus monkeys in two toxicity studies. In the first, a dose range finding study, CPI-006 was administered over 15-minutes by IV infusion at doses up to 120 mg/kg CPI-006, weekly (5 doses) for 31 days. The second, was a Good Laboratory Practice (GLP)-compliant toxicity study in which doses up to 100 mg/kg CPI-006 were administered by IV infusion over 60 minutes, weekly (5 doses) for 28 days. Toxicokinetics, safety pharmacology, and local tolerance assessments were built into the GLP compliant toxicity study. CPI-006 administered by IV infusion was well tolerated in both studies up to, and including, the highest doses administered. No definitive CPI-006-related changes were observed in the animals. No-observed adverse effect levels (NOAEL) were the highest doses administered, 120 mg/kg and 100 mg/kg CPI-006. Additional nonclinical information is provided in the Investigator Brochure for CPI-006.

2.4. SUMMARY OF CLINICAL EXPERIENCE WITH CPI-006

In CPI-006-001 oncology study, CPI-006 has been administered as a single agent and in combination with ciforadenant (an A2a receptor antagonist), and /or pembrolizumab (a blocking anti-PD-1 antibody). CPI-006 has been well tolerated when administered every 3 weeks as monotherapy and in combination with ciforadenant and/or pembrolizumab.

As of 20 Oct 2020, 35 patients have been treated with CPI-006 (every 3 weeks) monotherapy at doses up to 24mg/kg, and no maximum tolerated dose was established. The most common adverse reactions were infusion related reactions (IRRs); primarily chills and rigors. These IRRs were non-serious, mild to moderate in severity (Grade 1-2), transient and did not lead to discontinuation. The IRRs have been observed during (or immediately after) Cycle 1, Day 1 and are uncommon at subsequent infusions of CPI-006. To mitigate the risk of IRRs, premedication with diphenhydramine (50 mg orally [PO]) and acetaminophen 500–1000 mg PO (or equivalent) was required prior to infusion of CPI-006 at Cycle 1, Day 1 and has shown a decreased rate and intensity of IRRs.

As of 20 Oct 2020, in the ongoing Phase 1 CPI-006-002 study, 20 hospitalized patients with mild to moderate Covid-19 have received a single dose of CPI-006 at doses ranging from 0.3mg/kg to 5 mg/kg with follow up data. CPI-006 was well tolerated. IRRs have not been observed with CPI-006 infusion. No DLTs or treatment related AEs have been reported. The safety data in this study is reviewed on an ongoing basis by an Independent Data Monitoring Committee (iDMC).

2.4.1. Benefit/Risk Assessment

This study proposes to administer single doses of CPI-006 to hospitalized mild or moderately symptomatic patients with Covid-19.

Study treatment will be administered in the hospital and participants will be monitored closely. CD73 is expressed on endothelial cells and it is possible that negative effects or exacerbation of disease could be seen in Covid-19 patients. However, data from the GLP general toxicity study did not show any CPI-006 related changes in coagulation parameters (Section 4.3). Data from 20 Covid-19 participants in the CPI-006-002 study did not indicate any effect of CPI-006 on systemic inflammatory response or coagulopathy. In addition, data from over 90 participants in study CPI-006-001 in cancer patients did not show any CPI-006 related systemic inflammatory response or coagulopathy. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. The benefit of therapy to participants who receive Treatment A is the development of neutralizing antibodies which could lead to more rapid clinical improvement, avoidance of complications of Covid-19 disease, and the potential for longer lasting immunity.

Participants enrolled in Treatment B will receive standard of care (SOC) per institutional guidelines. The participant follow-up and monitoring involve routine procedures not associated with significant health risk. Overall data will be used to assess any difference between the participants who receive Treatment A and Treatment B in terms of clinical outcome and anti-SARS-CoV-2 levels.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the time to recovery of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies 1 of the following 3 categories from the 8-point ordinal scale (Appendix 6): 1) Not hospitalized, no limitations on activities.; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
Key Secondary	
• To compare the time to clinical improvement of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to clinical improvement (≥ 2 points improvement in the 8-point ordinal scale)
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgG targeting the RBD at Days 7, 14, 21, and 28

• To compare the time to improvement of Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and shortness of breath	• Time to resolution of ≥ 50% of the Covid-19 -attributable symptoms (see Appendix 8) including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline
Additional Secondary	
• To compare the clinical status of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Days 3, 7, Day of Discharge, Days 14, 21, and 28
• To compare the percentage of participants with clinical improvement with CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Days 3, 7, 14, 21, and 28
• To compare the change from baseline in the level of antibodies targeting the RBD of SARS-CoV-2	• Change from baseline level of IgM targeting the RBD at Days 7, 14, 21 and 28
• To compare the change from baseline in the SARS-CoV-2 viral load	• Change from baseline in the SARS-CoV-2 viral load at Days 3, 7, 14, 21, and 28
• To compare time to PCR negativity, and percentage of participants with PCR negative of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to PCR negativity • Percentage of participants with PCR negative at Days 7, 14, 21, and 28
• To compare the change from Baseline in NEWS2 of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. NEWS2 consists of: Physiological Parameters: respiration rate (per minute), SpO_2 Scale 1 (%), SpO_2 Scale 2 (%), use of air or oxygen, systolic blood pressure (mmHg), pulse (per minute), consciousness, and temperature (°C)
• To compare the medical interventions/procedures including intubation, mechanical ventilation, and supplemental O_2 use, rehospitalization of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Rate of procedures including intubation • Rate and duration of mechanical ventilation • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices during the trial • Oxygenation free days in the first 28 days • Rehospitalization
• To compare the safety of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Incidence, type, and severity of treatment -emergent adverse events of CPI-006 plus SOC compared to placebo plus SOC assessed by NCI CTCAE v 5.0

• To compare TTD of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Time to death during the first 28 days
Exploratory	
• To compare changes from baseline in Covid-19-related lab assessments of CPI-006 plus SOC versus placebo plus SOC in hospitalized participants with mild to moderately symptomatic Covid-19 infection	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28 • Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of Discharge, and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84, and 168
• Characterize the pharmacokinetics of CPI-006 in hospitalized participants with Covid-19 infection	• PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

Abbreviations: aPTT = activated partial thromboplastin time; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NEWS2 = National Early Warning Score 2; O_2 = oxygen; PCR = polymerase chain reaction; PK = pharmacokinetic; RBD = receptor binding domain; PT = prothrombin time; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = Standard of Care; SpO_2 = oxygen saturation; TTD = time to death

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a Phase 3, randomized, placebo controlled, double-blind, multicenter, stratified study of CPI-006 plus SOC versus placebo plus SOC in mild to moderately symptomatic hospitalized adult (≥ 18 years) Covid-19 patients. Covid-19 disease will be confirmed by polymerase chain reaction (PCR) testing.

Participants will be randomized at a 1:1 ratio to the 2 treatment arms and stratified by the following factors:

- Region of the world (North America vs. Latin America vs. Europe).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease
    - Chronic kidney disease (CKD)
    - Sickle cell disease (SCD)
    - Organ transplantation
    - Cancer

CPI-006 will be administered at a dose of 2 mg/kg up to a maximum dose of 200 mg intravenously (IV) on Day 1 in the participants randomized to receive treatment (Treatment A). A placebo will be given at the same schedule and same volume as the active drug for participants to receive the control (Treatment B). Participants, investigators, and Corvus will not be aware of the treatment the participants receive. All participants will receive supportive care according to the SOC of the trial hospital. If a hospital has a written policy or guideline, participants will receive treatment (including remdesivir or any other approved treatment) per those guidelines at the discretion of the investigator. Chloroquine/hydroxychloroquine are not allowed as SOC. Participation in any other investigational treatment during the first 28 days after randomization will not be allowed unless the investigator in consult with the Corvus medical monitor feels medical necessity and that such participation would not affect the integrity of this trial.

After the participant's initial eligibility is established and informed consent has been obtained, the study site must enroll the participant into the study by logging in to an interactive response technology (IRT) system to obtain the participant number. Every participant that signs the informed consent form (ICF) must be assigned with a participant

number in IRT. Specific instructions for using IRT will be provided to the investigational site in the IRT Manual. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by Corvus.

All participants will undergo a series of efficacy, safety, and laboratory assessments. Participants will be assessed daily during their hospitalization. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. SARS-CoV-2 PCR test will be obtained on Days 1, 7, 14, 21, and 28 while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally. Samples will be collected for viral load that will be assessed at a central lab. Anti-SARS-CoV-2 antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if patient remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the posthospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 50 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur after every 150 participants have completed the Day 28 assessments. In addition, the iDMC is available for ad hoc reviews for safety concerns. The study will not stop enrollment awaiting these iDMC reviews, although the iDMC may recommend temporary or permanent cessation of enrollment based on their safety and/or efficacy reviews. The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting. Further details on the iDMC are provided in Section 9.4.7.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

CPI-006 activates B cells in vitro leading to B cell differentiation and secretion of immunoglobulins. Studies in cancer patients have demonstrated differentiation of B cells into plasmablasts, trafficking from blood and return of memory B cells to blood. The in vitro and in vivo effects indicate that CPI-006 stimulates B cell differentiation, antigen driven clonal selection and differentiation into antibody producing cells. Novel anti-tumor antibodies have been produced in some treated cancer patients. B cell receptor molecular studies have demonstrated the emergence of novel B cell clones in the blood of CPI-006 treated cancer patients. No changes in total serum immunoglobulins have been seen to date (Willingham et al., 2020). It is believed that the activation of B cells and enhancement of

antibody production will lead to a more robust humoral immune response to SARS-CoV-2 and provide clinical benefits such as shorter disease duration, less disease severity, fewer complications, and greater long-term immunity.

In Study CPI-006-002 (in mild moderate hospitalized Covid-19 participants), IgG and IgM antibody titers measured against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable patients within 7 days of a single infusion of low doses of CPI-006. Similar results were observed in anti-SARS-Cov-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels has been observed in patients. Thirteen of 17 evaluable patients had low pre-treatment antibody titers despite relatively long durations of symptoms in some patients. In patients receiving 0.3 mg/kg CPI-006, all four evaluable patients achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these patients, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were seen in antibody responses to RBD. At doses above 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days, 56 days and 14 days for the 1.0 mg/kg, 3.0 mg/kg and 5.0 mg/kg cohorts, respectively in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points. High and durable neutralization titers were observed in subjects where values up to 9000 that persist beyond 56 days following onset of symptoms were measured using a functional pseudovirus neutralizing antibody assay. No changes in total serum immunoglobulins have been seen to date.

4.3. JUSTIFICATION FOR DOSE

A single dose of 2 mg/kg up to a maximum of 200 mg (2 mg/kg in patients ≥100 kg) was selected based on safety, pharmacodynamic, and pharmacokinetic parameters. Safety is summarized in the CPI-006 investigator brochure and in Section 2.3 and Section 2.4. In clinical study CPI-006-002, 20 patients hospitalized for mild to moderate COVID-19 symptoms were treated with a single intravenous infusion of CPI-006 ranging from 0.3 mg/kg to 5.0 mg/kg. Half of the patients in the study received an infusion of 3 mg/kg or 5 mg/kg. CPI-006 was well tolerated in all patients with no DLTs or treatment related AEs reported in the study. Safety was monitored in the study by an iDMC. Ninety-three patients with advanced cancers enrolled in CPI-006-001 received repeated intravenous infusions of CPI-006 once every 3 weeks until disease progression. CPI-006 was administered as a single agent, in combination with ciforadenant, Corvus' experimental adenosine 2A receptor antagonist, pembrolizumab, a commercially available anti-PD1 inhibitor, or the triple combination of CPI-006, ciforadenant, and pembrolizumab. No dose-limiting toxicities (DLTs) were observed for CPI-006 administered as a single agent or in combination at doses below 24 mg/kg in the dose escalation portion of the study. A DLT was observed in a single patient who received 24 mg/kg CPI-006 (Grade 3 hyponatremia in a NSCLC patient with history of hyponatremia). This cohort was further expanded with no more DLTs reported. A maximum tolerated dose was not established and after completion of the 24 mg/kg cohort,

this dose was maximum administered dose per protocol. Overall, CPI-006 was well tolerated at all doses studied including repeated doses up to 12 times higher than the 2 mg/kg dose.

A covariate analysis was performed using serum CPI-006 levels, patient demographics, vital signs, laboratory values, and concomitant medications data from 93 patients who received 1-24 mg/kg CPI-006 in the CPI-006-001 oncology study. In CPI-006-001, clearance was strongly associated with patient body weight indicating a body weight adjusted dose is preferred over a fixed dose. CPI-006 showed non-linear PK, modeling with clearance being a linear function of dose and fit of the model to the data was excellent. In CPI-006-001, AUC after a dose of 24 mg/kg is estimated to be 31-fold higher than the area under the serum or plasma concentration-time curve (AUC) after a dose of 2 mg/kg. The serum CPI-006 concentration 30 minutes after infusion was not modeled for a dose of 2 mg/kg, but the geometric mean 30-minute serum CPI-006 concentration after administration of 24 mg/kg was 11.6 times higher than after administration of 3 mg/kg.

The preliminary geometric mean 30-minute serum CPI-006 concentrations in study CPI-006-002 (n = 3 per cohort) for the 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg cohorts are 1.9 μg/mL, 9.3 μg/mL, and 56.4 μg/mL, respectively. The 30-minute serum CPI-006 concentrations are similar to those for samples collected from the corresponding 1 mg/kg and 3 mg/kg cohorts at the same time in the CPI-006-001 oncology study. CPI-006 is rapidly cleared from serum and is undetectable (serum concentration < 50 ng/mL) 1-7 days after a 1 mg/kg intravenous infusion or 14-21 days after a 3 mg/kg infusion. In CPI-006-002, the relationship between clearance and weight was less defined (there was a small statistical preference for a model in which clearance was weight-proportional), presumably the result of the small number of subjects for whom PK data are presently available and larger variability in this critically-ill group of patients.

In the GLP general toxicity study in cynomolgus monkeys, CPI-006 was administered by 60-minute IV infusion once weekly for 5 consecutive weeks at dose levels of 10, 30, or 100 mg/kg, followed by a 28-day recovery period. CPI-006 doses of up to 100 mg/kg/week (5 total doses) were well tolerated. CD73 is expressed weakly on endothelial cells. No CPI-006-related changes in hematologic coagulation parameters, which included prothrombin time (PT) activated partial thromboplastin time (aPTT), or fibrinogen, occurred during the study. The NOAEL was the highest dose administered, 100 mg/kg/week, corresponding to maximum drug concentration in serum or plasma (C_{max}) of 3,560 and 3,280 μg/mL and AUC from the start of infusion to 169 hours after the start of infusion ($AUC_{(0-169)}$) of 167,000 and 186,000 hr•μg/mL, for males and females, respectively. The C_{max} and AUC from time zero to the time of the last quantifiable concentration (AUC_{last}) for the GLP repeat dose cynomolgus monkey toxicity study are 60 and 66 times higher, respectively, than the C_{max} and AUC_{last} after a single administration of 3 mg/kg to humans in the CPI-006-001 study. Safety margins are anticipated to be at least as high or higher after administration of single dose of 2 mg/kg to patients.

IgG and IgM antibody titers against the SARS-CoV-2 spike protein and/or RBD increased in all evaluable patients in CPI-006-002 within 7 days of a single infusion of CPI-006. Similar results were observed in anti-SARS-Cov-2 IgA titers. No correlation between duration of Covid-19 symptoms and pre-treatment serum antibody levels was observed in patients. Thirteen of 17 evaluable patients had low pre-CPI-006 infusion antibody titers despite relatively long durations of symptoms in some patients. In patients receiving 0.3 mg/kg CPI-006, all four evaluable patients achieved high IgG titers to spike protein that were sustained for at least 84 days after onset of symptoms. In these patients, IgM titers peaked at 14 days and remained elevated at the last measured timepoint of 84 days. Similar kinetics were observed in antibody responses to the RBD. At doses higher than 0.3 mg/kg, durable high titers of IgG and IgM to spike protein and RBD were achieved out to 84 days, 56 days and 14 days for the 1.0 mg/kg, 3.0 mg/kg and 5.0 mg/kg cohorts, respectively in the ongoing study. Peak titers increased from 0.3 mg/kg to 1.0 mg/kg CPI-006 but did not appear to increase from 1.0 mg/kg to 3.0 mg/kg or from 3.0 mg/kg to 5.0 mg/kg at the evaluable time points, suggesting that the peak pharmacodynamic effect occurred in the range of 1.0-3.0 mg/kg CPI-006.

Immunophenotyping of peripheral blood from patients enrolled in clinical study CPI-006-001 demonstrated that doses greater than 1 mg/kg are sufficient to activate B cells, resulting in a temporary redistribution to lymphoid tissues and corresponding increase in the frequency of memory B cells returning to circulation. A similar increase in the frequency of memory B cells was observed in Covid-19 patients tested in the CPI-006-002 trial, including patients receiving 0.3 mg/kg CPI-006. In vitro, CPI-006 induced B cell activation is dose-dependent with concentrations of 1 μg/mL achieving near maximal induction of CD69. This initial activation leads to a morphologic transformation of B cells into plasmablasts and secretion of IgM and IgG in vitro. These levels of CPI-006 also result in increased expression of various markers involved in antigen presentation e.g. HLA-DR, CD86. A dose of 1mg/kg is sufficient to sustain CPI-006 serum concentrations above 1 ug/ml CPI-006 for 24 to 48 hours after administration.

In summary, A single dose of 2 mg/kg CPI-006 up to a maximum of 200 mg was selected based on a good safety profile, maximum pharmacodynamic effect, and good pharmacokinetic parameters. This dose is expected to ensure that maximal pharmacodynamically active levels of 1μg/ml are achieved. CPI-006 repeatedly administered once every 3 weeks by IV infusion was demonstrated to be well tolerated in 93 patients in oncology study CPI-006-001 and after a single administration of up to 5 mg/kg to 20 COVID-19 patients in study CPI-006-002. Clearance decreases with increasing dose and is weight proportional in CPI-006-001 and likely CPI-006-002. CPI-006 clears rapidly in the dose-range studied for Covid-19 patients. After a single administration of 3 mg/kg or less, serum CPI-006 is undetectable in 3 weeks or less. In CPI-006-002, a dose response in pharmacodynamic measures was observed between 0.3 and 1.0 mg/kg and no further improvement was observed above 1.0 mg/kg. A dose of 2 mg/kg was selected to ensure

sufficient exposure to CPI-006 for maximum pharmacodynamic effect, rapid clearance, and substantial safety margins.

4.4. END OF STUDY DEFINITION

A participant in this study is considered to have completed the study if he/she has completed all study visits including Day 28 study assessments. The study visits beyond Day 28 will be optional for exploratory endpoint of antibody levels at Days 56, 84, and 168.

The end of the study is defined as the date that each participant enrolled in the study completes his/her last study visit or discontinues from the study.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Participants must be ≥ 18 years of age at the time of signing the informed consent.
2. Confirmed positive by PCR test for SARS-CoV-2 within 72 hours before randomization.
3. Onset of symptoms not more than 7 days prior to randomization.
4. Understand and agree to comply with planned study procedures for the duration of the study. The study visits beyond Day 28 will be optional and require a separate consent.
5. Hospitalized for Covid-19 illness for ≤72 hours with mild to moderate Covid-19 symptoms including:
    - Mild: Symptoms of Covid-19 including fever, rhinorrhea, mild cough, sore throat, headache, muscle pain, malaise but not requiring supplemental oxygen
    - Moderate: Lower respiratory symptoms: shortness of breath (SOB) or signs of pneumonia or lung infiltrates based on X-ray or computed tomography (CT) scan < 50% present
6. Maintains O_2 saturation of at least 93% on room air or supplemental O_2 at randomization.
7. Adequate organ function, as defined by:
    - CBC: ANC >1000/mm^3, platelets>75,000mm^3, Hgb>9 gm/100 cc
    - Calculated creatinine clearance based on ideal body weight per Cockcroft-Gault formula or 24-hour urine ≥ 30 mL/min
    - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5 x upper limit of normal (ULN)
    - D-dimer < 10,000 ng/mL
8. Eligible participants of child-bearing age (male or female) must agree to use at least 1 medically accepted method of contraception (e.g., barrier contraceptives [condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables,

combination oral contraceptives, transdermal patches, or contraceptive rings], or intrauterine devices), or agree to abstinence for 6 weeks. Female participants or the female partners of male participants who become pregnant during the study or within the protocol-specified period after their last CPI-006 administration should immediately inform their treating physicians.

5.2. EXCLUSION CRITERIA

1. Signs of acute respiratory distress syndrome (ARDS) or respiratory failure necessitating mechanical ventilation at the time of screening (and randomization) or anticipated impending need for mechanical ventilation.
2. History of severe chronic respiratory disease and requirement for long-term oxygen therapy.
3. Any uncontrolled active systemic infection or hemodynamic instability requiring admission to an intensive care unit (ICU).
4. Patients with malignant tumor receiving treatment, or other serious systemic diseases affecting life expectancy within 29 days of Screening.
5. Receipt of cancer chemotherapy or immunomodulatory drugs including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use equivalent to prednisone >10 gm/day, during preceding 2 months.

   Note: Steroids for treatment of Covid-19 is acceptable.
6. Patients who are participating in other clinical trials including participants in an extended access program (EAP).
7. Active deep vein thrombosis or pulmonary embolism as confirmed by the investigator within last 6 months.
8. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours of admission as confirmed by the investigator.
9. Any active uncontrolled co-morbid disease that might interfere with study conduct or interpretation of findings.
10. Known to be positive for HIV or positive test for chronic HBV infection (defined as positive hepatitis B surface antigen [HBsAg]) or positive test for hepatitis C antibody.
11. Convalescent plasma (CCP) or anti-SARS-CoV-2 monoclonal antibodies administered less than 24 hours prior to randomization. Patient must have recovered from any adverse events related to CCP treatment. Received chloroquine or hydroxychloroquine within last 7 days or during the study.
12. Pregnancy or breast feeding.

5.3. LIFESTYLE CONSIDERATIONS

Blood, sperm, and ova donations are restricted for at least 6 weeks after CPI-006 administration.

5.3.1. Meals and Dietary Restrictions

No dietary restrictions.

5.3.2. Activity

No required restrictions.

5.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Reasons for screen failure will be recorded.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment (s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. STUDY TREATMENT ADMINISTERED

A summary of study treatment information is provided in Table 2.

Table 2 Study Treatment

Study Treatment Name:	**CPI-006 Injection, 200 mg/20 mL**	**CPI-006 Placebo**
Dosage formulation:	10 mg/mL with 20 mM histidine, 9 % sucrose, 0.01 % (w/v) polysorbate 80, pH 5.5.	(5% Dextrose Injection, USP[a])
Unit dose strength (s)	200 mg / 20 mL (10 mg/mL)	5% Dextrose
Route of administration	IV	IV
Dose[b]	2 mg/kg up to a maximum of 200 mg	Placebo (no CPI-006)
Dosing instructions:	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP. CPI-006 Injection is diluted with 5% Dextrose Injection, USP	IV Infusion over 10-15 minutes, on Day 1 followed by infusion line flush with 5% Dextrose Injection, USP.
Packaging and labeling	Study Treatment will be provided in a sterile, single-use vial with a rubber stopper and a blue cap. One vial is packaged inside a carton. Each vial will be labeled as required per country requirement.	Not Applicable

Manufacturer	Manufactured for Corvus Pharmaceuticals, Inc. by Vetter Development Services USA, Inc.	Placebo will be purchased by the clinical institution from commercial vendors approved by that institution

Abbreviations: IV = intravenous; US/USA = United States of America; USP= United States Pharmacopeia
[a] 5% Dextrose Injection, USP will be used at clinical sites within the United States, similar sterile, endotoxin free, grades of 5% Dextrose Injection that are commercially available and meet local or compendial laws and regulations may be substituted outside of the US.
[b] The CPI-006 dose of 2 mg/kg up to a maximum dose of 200 mg, patients who are 100 kg or more will receive a dose of 200 mg.

6.2. STUDY TREATMENT: PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. 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.

2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment 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 site staff.

3. The unblinded site staff preparing the study treatment is responsible for study treatment accountability, log of receipt, inventory, reconciliation, dispensing, return of study treatment, destruction of study treatment and record maintenance (i.e., receipt, reconciliation, and final disposition records). The study treatment logs and records must be kept current and blinded from others (e.g. investigators, site staff, participants, Sponsor and contract research organization (CRO) staff with oversight of study conduct). Study treatment logs must be kept in a secure location with access limited only to the unblinded staff members.

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

6.2.1. Handling and Storage

6.2.1.1. CPI-006 Injection

CPI-006 Injection is provided as a sterile solution in a single use vial that delivers 200 mg of active ingredient in 20 mL (10 mg/mL). CPI-006 vials will be stored at 2°C to 8°C and protected from direct light. Excursions up to 25°C are allowed up to 3 days.

The prepared CPI-006 can be stored at 2°C to 8°C for up to 24 hours and/or stored at controlled room temperature (20°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared CPI-006.

Do not freeze CPI-006 vials or diluted CPI-006 infusion solution.

6.2.1.2. Placebo

The placebo, 5% Dextrose Injection, USP will be purchased by each clinical site within the United States. Either 5% Dextrose Injection, USP or a similar sterile, endotoxin free, grade of 5% Dextrose Injection that is commercially available and meets local or compendial laws and regulations may be substituted outside of the US. The placebo should be handled and stored according to manufacturer's specifications.

The prepared placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at controlled room temperature (20°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

Do not freeze the placebo.

6.2.2. Preparation and Dispensing

Refer to the Pharmacy Manual for detailed instructions on how to prepare study treatment for administration. Study treatment will be prepared using aseptic techniques and dispensed by an appropriately qualified and experienced member of the study staff (e.g. pharmacist, pharmacy assistant, or pharmacy technician) who is unblinded to study treatment (see blinding plan in the pharmacy manual). A second staff member will verify the dispensing and preparation. The identity of the study treatment should not be revealed by markings on labels or the infusion bag or infusion set except for a blinded randomization code.

CPI-006 infusion will be prepared using aseptic techniques by withdrawing the appropriate amount of CPI-006 Injection, 10 mg/mL from a vial into a sterile syringe. The contents of the syringe will be emptied into a sterile polyolefin/polyethylene (PO/PE) or polyvinyl chloride (PVC) infusion bag and diluted with 5% Dextrose Injection, USP or equivalent grade. Apply gentle mixing by inverting the IV bag; avoid shaking the IV bag.

Placebo will be prepared using aseptic techniques. The placebo infusion is 50 mL to 100 mL 5% Dextrose Injection, USP, in a sterile polyolefin/polyethylene (PE) or polyvinyl chloride (PVC) infusion bag, depending on the patient weight.

After it is prepared, the placebo can be stored at 2°C to 8°C for up to 24 hours and/or stored at controlled room temperature (20°C to 25°C) for up to 6 hours, including the infusion time. Avoid shaking the prepared placebo.

6.2.3. Administration

Administration of study treatment will be performed by an appropriately qualified, GCP-trained, and infusion-experienced member of the study staff (e.g. physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Site staff administering the study treatment will be blinded to the treatment (active or placebo) being administered. Participants will receive a single dose of study treatment by IV infusion on Day 1 of the study. The volume of the study treatment will be 50-100 mL depending on the dose to be administered. Study treatment must be infused through an in-line filter. Infusion lines should be made of PO/PE or PVC, equipped with a 0.2 μm or 0.22 μm in-line polyethersulfone (PES) filter.

The infusion should be administered via a port as close to the participant's vein as possible to ensure that the full dose is administered in the allotted time. The total infusion time from start of infusion to completion of infusion will be 10-15 minutes. As soon as the infusion is complete, the infusion line used for the study treatment will be flushed with the greater of the priming volume of the infusion set or 30 mL of 5% Dextrose Injection, USP. The same infusion rate used for the study treatment infusion will be used for the flush.

Infusion reactions are possible, thus appropriate drugs and medical equipment to treat acute infusion reactions must be immediately available and study personnel must be trained to recognize and treat infusion reactions. Premedication with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo is recommended for participants who are not receiving steroids for treatment of Covid-19. Oral premedication should be administered 30-60 minutes prior to the start of the CPI-006/placebo infusion. IV diphenhydramine should be administered 15-30 minutes prior to the start of the CPI-006/placebo infusion.

Study treatment administration details will be recorded on the CRF and will include at a minimum: patient number, randomization code, infusion start time and stop time, interruption stop and restart times, flush start and stop times.

6.2.4. Management of Infusion Reactions

Any CPI-006-associated infusion reactions should also be managed as shown in Table 3.

Table 3 CPI-006 Infusion-Related Reaction Management Guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; treatment not indicated	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Provide supportive care. Increase monitoring of vital signs as medically indicated. If symptoms do not improve $\geq$ 1 hour, provide medical treatment until the participant is deemed medically stable in the opinion of the investigator. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g., from 10 mL/min to 5 mL/min).

Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Reduce infusion rate (e.g., from 10 mL/min to 5 mL/min) or stop infusion rate as medically indicated. Additional appropriate medical therapy may include but is not limited to: – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Narcotics – Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms have not subsided or worsen with reduced infusion rate, stop infusion. If infusion is stopped and symptoms resolve within 2 hours. CPI-006 infusion may be restarted at 25%-50% of the original infusion rate (e.g. from 10 mL/min to 5 mL/min). Otherwise if symptoms do not resolve, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity with premedication and do not have symptom resolution within 2 hours of medical treatment should be permanently discontinued from further study drug treatment.

Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: – Epinephrine[a] – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Corticosteroids – Narcotics – Oxygen – Vasopressors
Grade 4 Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - Epinephrine[a] - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Vasopressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Participant is permanently discontinued from further study drug treatment.

Abbreviations: : IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

[a] In cases of anaphylaxis, epinephrine should be used immediately.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be randomized to Treatment A or Treatment B in a 1:1 ratio using an Interactive Response Technology (IRT). Before the study is initiated, the log-in information & directions for the IRT will be provided to each site.

Participants will receive a single IV administration of study treatment on Day 1 of the study.

Returned study treatment should not be re-dispensed to any participants.

6.3.2. Blinding

This is an observer blinded design, so investigators, site staff (except the unblinded pharmacy personnel preparing the study treatment), participants, Sponsor, and CRO staff with oversight of study conduct will remain blinded to treatment allocation throughout the course of the study. The IRT will provide the unblinded pharmacist(s) the randomized treatment arm assignment to be allocated to the participant at the administration visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

CPI-006 Injection is a clear colorless solution and will remain clear and colorless when diluted in 5% Dextrose Injection, USP. At full concentration, CPI-006 is slightly more viscous than water and may create minimal foam if vigorously shaken. Once diluted, CPI-006 is not visually distinguishable from the 5% Dextrose Injection, USP placebo.

To maintain the blind, an otherwise uninvolved staff member (e.g. pharmacist, pharmacy assistant, or pharmacy technician) will prepare and dispense the study treatment for administration such that the identity (active or placebo) of the treatment is blinded to all other site staff responsible for administration and study conduct throughout the study. The unblinded personnel are responsible for study treatment preparation and accountability only and will not participate in any other aspect of the study. The unblinded personnel will endeavor to ensure that there are no differences in time taken to dispense following randomization or preparation that might reveal the identity of the study treatment to investigators, site staff, participants, Sponsor and CRO staff.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.3. Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant'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 case report form, as applicable.

6.4. Study Treatment Compliance

Investigational Product will be administered on a single occasion by the investigator or qualified designee to participants who are hospitalized. Randomization code, treatment

volume, start and stop times for the study treatment infusion, flush volume, and start and stop times for the flush will be accurately recorded in the CRF.

The study site is responsible for ensuring that participants comply with the specified study windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Appendix 1 Schedule of Activities). If a participant does not complete a visit within the specified time, the visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (e.g. clinical laboratory testing, and immunologic testing, as applicable).

6.5. CONCOMITANT THERAPY

Investigators may prescribe any concomitant medications, procedures, or treatments deemed necessary to provide adequate supportive care except for those listed in Section 5.2.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

6.5.1. Rescue Medicine

The study site will supply infusion reaction rescue medication that will be obtained locally by the clinical site. The following rescue medications may be used:

- Antihistamine such as diphenhydramine administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Analgesics such as acetaminophen administered PO or IV according to standard practices at the clinical institution for treating infusion related reactions
- Corticosteroids administered according to standard practices at the site/hospital for treating infusion related reactions
- The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the CRF

6.5.2. Permitted Concomitant Therapy

The following concomitant medications and vaccinations are allowed and will be recorded in the CRF:

- Therapies that are either approved or accepted as standard of care therapies for Covid-19 per site/institutional guidelines (e.g. remdesivir, tocilizumab, steroids, convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies [see Section 5.3])

- Prophylactic or therapeutic anticoagulation
- Supportive care for management of Covid-19 symptoms and complications
- It is recommended that participants who are not being treated with steroids for Covid-19 be premedicated with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) or diphenhydramine 25–50 mg IV and acetaminophen 500–1000 mg PO (or equivalent dose of analgesic) prior to infusion of CPI-006/placebo (see Section 6.2.3).

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

6.5.3. Prohibited Concomitant Therapy

The following medications are prohibited. and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications, however, will not definitively require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol analysis set.

If a participant receives a prohibited concomitant medication, the investigator in consultation with the Medical Monitor will evaluate any potential impact on receipt of the study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data.

The following concomitant medications are prohibited:

- Chloroquine or hydroxychloroquine
- Cancer chemotherapy or immunomodulatory drugs including (but not limited to) biologics such as anti-CD20, anti-TNF, anti-IL6; alkylating agents (e.g., cyclophosphamide); antimetabolites (e.g., azathioprine); or chronic corticosteroid use
- Investigational medication or device (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment and throughout the study unless the investigator in consult with the Corvus medical monitor feels medical necessity and that such participation would not affect the integrity of this trial.

6.6. Dose Modification

No dose modifications for CPI-006 are allowed.

6.7. Treatment After the End of the Study

No study treatment will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

- Participant or participant's physician may elect to discontinue their participation in the study at any time. Reasons for withdrawal will be recorded on the CRF.
- All randomized participants will be followed for 28 days.
- Participants who consent to optional follow up visits will be followed for 168 days.

7.1. DISCONTINUATION OF STUDY TREATMENT

A single dose of CPI-006/placebo is administered on Day 1 only for participants, thus there is no discontinuation from study treatment unless patient does not receive full dose due to toxicity during the infusion. Standard of care will be administered to both treatments at the discretion of the investigator per institutional guidelines.

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. LOST TO FOLLOW UP

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
    - Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Appendix 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) 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 time frame defined in the SoA.

Hospitalized participants will receive daily monitoring and testing while in the hospital including routine vital sign monitoring and labs per institutional standards. Once discharged, participants will be asked to attend post- hospitalization study visits as described in Section 4.1.

Follow up visits after discharge could include, but are not limited to, clinic visits, outpatient hospital visits, home health visits or telehealth, depending on local or institutional standards. If no other method of follow-up is feasible, home visits may be used.

Study assessments will utilize local labs and procedures at the clinical sites except for the key secondary endpoint, anti-SARS-CoV-2 antibody levels and various exploratory endpoints such as neutralizing antibody levels and peripheral blood immunophenotyping which will be assessed by the central lab. Other exploratory endpoints such as BCR repertoire analysis and systemic cytokine/chemokine analysis will be performed by external vendors outside of the central lab. Results of tests conducted at central lab, are not considered as critical to the management of Covid-19 in participants and will not be reported to the investigator or patient.

The anti-RBD IgG level will be measured using an electrochemiluminescent immunoassay on serum specimens stored at -20°C. The method is based on reactivity to immunogenic viral protein where a recombinant form of viral RBD antigen is absorbed to the surface of a 96-well microtiter plate. Participant serum will be dispensed to the wells where antibodies recognizing the antigen are allowed to react before removal of unbound immunoglobulin from the wells. Anti-RBD IgG bound to the viral protein will be detected using standard enzyme-linked immunosorbent assay (ELISA) techniques.

Immediate safety concerns should be discussed with the Sponsor directly upon occurrence or awareness to determine if the participant should continue or discontinue study treatment regardless of SoA assessments. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. SCREENING

Screening assessments and procedures are detailed in Appendix 1, Table 6.

8.2. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are detailed in Appendix 1, Table 6.

8.3. EFFICACY ASSESSMENTS

The following assessments will also be performed for both treatments at the time points described in the SoA (Appendix 1, Table 6):

- Covid-19 Symptoms Assessment – Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath (Appendix 8)
- 8-point Ordinal Scale Assessment (Appendix 6)
- SARS-CoV-2 viral load
- PCR negativity
- NEWS2 Assessment (Appendix 7)
- Anti-RBD antibody titers will be measured in sera collected at the time points described in the SoA (Appendix 1, Table 6). Collection of the predose timepoint is critical for subsequent analysis. The assays will measure IgM, IgG and IgA levels targeting the RBD for key and additional secondary endpoints using the electrochemiluminescent immunoassay. The assays will be conducted at a centralized testing facility using validated methods.
- A viral PCR test by nasal swab will be obtained to demonstrate a negative test and viral load. Participants with positive PCR tests will have repeat tests on subsequent visits until a negative test. This test will be conducted by the clinical lab at the investigator sites.
- Exploratory measurements will be conducted at Sponsor's research laboratories or through use of outside vendors including immunophenotyping analysis, immune cell functional assays, BCR repertoire analysis, systemic cytokine/chemokine analysis, and, anti-SARS-CoV-2 antibody characterization, and anti-viral neutralization assays.

- Clinical assessments will include time to clinical improvement, time to resolution of the Covid-19 attributable symptoms, change in clinical status, rate of participants with clinical improvement, time to discharge, requirement for ICU, requirement for mechanical ventilation, time to death (TTD), rate of procedures including intubation, duration of mechanical ventilation, oxygenation free days in the first 28 days, and incidence and duration of new O_2 use during the study.

8.4. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Serum samples will be collected from each patient enrolled in the study for measurement of serum concentrations of CPI-006 as specified in the SoA (Appendix 1, Table 6). A maximum of 4 additional samples may be collected at time points during the study if warranted and agreed upon between the investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor.

The actual collection date and time (24-hour clock time) for each sample will be recorded.

Samples will be used to evaluate the PK of CPI-006. Each serum sample will be divided into 3 aliquots (1 each for PK, backup, and for potential analysis of anti-drug antibodies [ADA], and/or neutralizing antibodies [refer to Section 8.7.1 Immunogenicity Assessments]). Samples collected for analyses of serum CPI-006 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

At visits during which serum samples for the determination of PK, backup, ADA, and/or neutralizing antibodies of CPI-006 will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points, up to 4 timepoints, for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5. SAFETY ASSESSMENTS

The following assessments will also be performed for both treatments at the time points described in the SoA (Appendix 1, Table 6):

- Incidence, type, and severity of AEs and SAEs assessed by NCI CTCAE v 5.0 to compare safety of CPI-006 plus SOC to placebo plus SOC.

- Safety assessments will be made using local lab testing (Appendix 3) for hematology, chemistry, coagulation, inflammatory markers and serum quantitative immunoglobulins.
- Routine physical exams.
- Vital signs (pulse rate, blood pressure, respiratory rate, temperature and blood oxygen saturation) including at start, at conclusion and at approximately 2 hours after completion of the CPI-006/placebo infusion.

8.6. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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, study treatment or that caused the participant to discontinue the administration of CPI-006/placebo, or the study (see Section 7).

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated treatment (e.g., study related procedures, discontinuation of medications) should be reported (see Appendix 4).

After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

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

For participants with worsening of Covid-19, the clinical event (s) that mark the worsening should be reported as AE or an SAE (see definitions in Appendix 4). Investigators are not obligated to actively seek AE or SAE outside clinical practice after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant 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 the Sponsor.

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

8.6.2. Method of Detecting AEs and SAEs

The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event CRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 4.

For each AE recorded on the Adverse Event CRF, the investigator assesses seriousness, severity, and causality as per Appendix 4.

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

Reporting requirements for SAEs can be found in Appendix 4.

8.6.3. Follow-up of AEs and SAEs

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

8.6.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants 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 (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., 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.

8.7. BIOMARKERS

Serum at baseline and at specified times will be stored at -20°C for use in various serology studies which include:

Key and Additional Secondary Endpoints

- Measurement of anti-RBD IgG, IgM and IgA levels.

Exploratory Endpoints

- Measurement of neutralizing antibody levels that block association of viral RBD and human ACE2 assessed in a biochemical ELISA.
- Measurement of neutralizing antibody levels that block infection assessed in a pseudovirus assay, and in a live virus assay
- Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) spike, nucleocapsid, and membrane proteins.
- Additional exploratory serum assays may be conducted with extra serum not required for primary analysis.

Peripheral blood collected at baseline and at specified times will be analyzed while fresh or processed into PBMCs and cryopreserved for use in various studies including:

- Immunophenotyping using flow cytometry to evaluate the frequency of memory B cells and memory/effector T cells
- Functional B and T cell assays to evaluate ex vivo immune responses to SARS-CoV-2 antigens compared to controls.
- BCR repertoire analysis to evaluate effects of CPI-006 on B cell clonality and antibody isotype switching

8.7.1. Immunogenicity Assessments

Antibodies to CPI-006 may be evaluated in serum samples collected from participants according to the SoA. These samples may be tested by the Sponsor or Sponsor's designee.

Serum samples may be screened for antibodies binding to CPI-006 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to CPI-006 and/or further characterize the immunogenicity of CPI-006

The detection and characterization of antibodies to CPI-006 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for

detection of antibodies to study treatment may also be evaluated for CPI-006 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to CPI-006.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

The primary hypothesis is that treatment with CPI-006 plus SOC (Treatment A) will shorten the time to recovery during the 28 days after dosing based on the 8-point ordinal scale in comparison to placebo plus SOC (Treatment B) in mild to moderately symptomatic Covid-19 hospitalized participants.

The first secondary hypothesis is that treatment A will shorten the time to clinical improvement by at least 2 points during the 28 days after dosing on the 8-point ordinal scale in comparison to treatment B.

The second secondary hypothesis is that Treatment A will increase the level of IgG targeting the RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 more than Treatment B, as measured by the area under the IgG level curve above the baseline, calculated over Days 1 (the baseline), 7, 14, 21, 28, and Day of Discharge.

The third secondary hypothesis is that Treatment A will shorten the time to resolution of ≥ 50% of the Covid-19-attributable symptoms: fever, cough, sore throat, headache, muscle pain, and/or shortness of breath, reported at baseline. Explicitly, the resolution of ≥ 50% of symptoms means the resolution of 1 of 1 symptom, 1 of 2 symptoms, 2 of 3 symptoms, 2 of 4 symptoms, 3 of 5 symptoms, or 3 of 6 symptoms that are reported at baseline.

9.2. SAMPLE SIZE DETERMINATION

Approximately 620 hospitalized participants with mild to moderately symptomatic Covid-19 will be enrolled. The participants will be randomized in a 1:1 ratio between Treatment A and Treatment B within each of the strata defined by:

- Region of the world (North America vs. Latin America vs. Europe).
- Age (< 65 vs. ≥ 65)
- Comorbidities (0 vs. at least 1) based on the following list:
    - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, COPD, or cystic fibrosis) or moderate to severe asthma
    - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
    - Obesity (body mass index ≥ 30 kg/m^2)
    - Diabetes (Type 1, Type 2, or gestational)
    - Liver disease

- CKD
- SCD
- Organ transplantation
- Cancer

With 520 observed recoveries in the 2 treatment groups, there would be an approximately 83% power to show a statistically significant superiority of Treatment A over Treatment B in recovery rate at an overall 1-sided α level of 0.025 when the true recovery rate ratio of Treatment A to Treatment B is 1.296, assuming an exponential distribution for time to recovery for each treatment.

With a total of approximately 620 participants, it is estimated that 520 recoveries will be observed after 5.5 months assuming that the median time to recovery is 5.4 days and 7 days of Treatments A and B, respectively. The all-cause death rate is assumed to be 6% over the 28-day period.

9.3. POPULATION FOR ANALYSES

For purposes of analyses, the following populations are defined in Table 4.

Table 4 Population Definitions

Population	Description
Intent-to-treat (ITT)	All participants who are randomized into the study.
Efficacy	All participants who take at least 1 dose of study treatment (CPI-006 or placebo) and have at least 1 post-baseline assessment based on the 8-point ordinal scale.
Safety	All participants who take at least 1 dose of study treatment (CPI-006, placebo, or SOC).
Pharmacokinetic	All participants who receive CPI-006 and had at least 1 post-treatment blood sample collected

9.4. STATISTICAL ANALYSES

The SAP will be developed and finalized before the second interim analysis (see Section 9.4.6) and will describe the study populations to be included in the analyses. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Approach

Unless otherwise specified, the following general analysis will be performed. Continuous variables will be summarized using the following descriptive statistics: number of observed values, mean, standard deviation, median, and minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Time-to-event variables, when appropriate, will be summarized by the median with 95% confidence intervals (CI) and

the 25% and 75% quartiles. Kaplan-Meier curves will be provided. The baseline value for analysis variable is the last measurement before administration of study treatments.

9.4.2. Demographic and Participant Characteristics

Demographic information such as age, gender, race, body weight, and participant characteristics such as baseline disease severity, symptoms, and comorbidities will be listed and summarized.

9.4.3. Efficacy Analyses

All efficacy analyses will be performed based on the Efficacy Population.

Table 5 Efficacy Analyses

Endpoint	Statistical Analysis
Primary	The primary efficacy endpoint is the time to recovery during the 28 days after dosing. Day of recovery is defined as the first day on which the participant satisfies one of the following three categories from the eight-point ordinal scale: • Not hospitalized, no limitations on activities. • Not hospitalized, limitation on activities and/or requiring home oxygen; • Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care Treatment A and B will be compared by the time to recovery.
Secondary	The following endpoints will be compared between Treatment A and B: Key Secondary Endpoint: • Time to clinical improvement determined by ≥ 2 points improvement in the 8-point ordinal scale during the 28 days after dosing. • The change in the level of IgG targeting RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 from baseline measured by the area under the IgG level curve above the baseline. • Time to resolution of ≥ 50% of the Covid-19 attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or shortness of breath reported at baseline. Other Secondary Endpoints • Change in clinical status, defined by the change in the 8-point ordinal scale from baseline at Day of Discharge and Days 3, 7, 14, 21, and 28. • Percentage of participants with clinical improvement (≥ 2 points improvement in the 8-point ordinal scale) at Day of Discharge and Days 3, 7, 14, 21, and 28. • Change from baseline in level of IgM targeting the RBD at Days 7, 14, 21 and 28. • Change from baseline in the SARS-CoV-2 viral load at Days 7, 14, 21, and 28 • Time to PCR negativity, and percentage of participants with PCR negative at Days 7, 14, 21, and 28 • Change from Baseline in NEWS2 at Days 3 and 7, Day of Discharge, and Day 28. • Rate of procedures including intubation. • Rate and duration of mechanical ventilation. • Rate and duration of supplemental oxygen, non-invasive ventilation, or high flow oxygen devices during the trial • Oxygenation free days in the first 28 days. • Time to death during the first 28 days.

	• Hematology, chemistry, CRP, and ferritin assessments on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized); Day of Discharge; and Day 28 (return to clinic if discharged) • PT, INR, aPTT, fibrinogen, and D-dimer on Days 1, 3, 5, 7, 14, 21, 28 (while hospitalized), and Day of Discharge • Change from baseline in level of IgA targeting the RBD at Days 7, 14, 21, and 28 • Changes in IgG, IgM, or IgA antibodies targeting other SARS-CoV-2 antigens including (but not limited to) trimeric spike, nucleocapsid, and membrane proteins • Change from baseline in the frequency and function of memory B cells in the peripheral blood at Days 14 and 28
Exploratory	• Changes from baseline in the frequency or function of memory/effector T cells in the peripheral blood at Days 14 and 28 • B cell receptor repertoire analysis at baseline, Day 14, and Day 28 • Systemic cytokine and chemokine levels at baseline and Days 7 (while hospitalized), Day of discharge and Day 28 • Neutralizing antibody levels on Days 1 and 28 using a biochemical ELISA, a pseudovirus neutralization assay, and a PRNT50 live virus assay • Change from baseline level of IgG and IgM targeting the RBD at Days 56, 84 and 168 • PK characteristics including covariate analysis to determine which variables, if any, influence exposure of CPI-006

9.4.4. Safety Analyses

The safety analyses will include all participants in the Safety Population.

Safety will be assessed through summaries of AEs (including SAEs), changes in laboratory test results, physical examination findings, and vital signs.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0) to categorize each AE by System Organ Class and Preferred Term. The number of participants who experienced at least 1 AE; treatment-related AE; severe (Grade 3 or higher) AE, SAE; and the number of participants withdrawn from treatment due to AEs will be summarized. The incidence of AEs will be presented overall, by System Organ Class and Preferred Term, by intensity (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5), by severity, by relationship to study treatment or if treatment-emergent, and by treatment. Individual listings of AEs will be provided. Study treatment related AEs will be listed individually.

Laboratory tests will be listed and summarized for each test. Lab values will be graded according to the NCI-CTCAE criteria and summarized.

Deaths and related information will be listed.

9.4.5. Exploratory Analyses

PK, pharmacodynamic (PD), and biomarker exploratory analyses will be described in the SAP, finalized before database lock.

9.4.6. Interim Analyses

Two formal interim analyses are planned for this study. The first interim analysis is a non-binding futility analysis when approximately 150 participants have been enrolled into the study with 28 days of follow up time. Safety and efficacy will be the focus of the evaluation. Unblinded safety and efficacy data will be reviewed by the iDMC.

The second interim analysis will be performed when approximately 310 (60% of the 520) recovery events have been observed in the 2 treatment arms based on the Efficacy Population. Comparison between Treatment A and Treatment B with respect to the time to recovery will be made using a modified version of stratified log-rank test correcting for competing risk of all-cause death. Should the comparison demonstrate a statistically significant superiority of Treatment A over Treatment B, Corvus may file the results to regulatory authorities for drug approval. The study will continue its course beyond the interim analysis and collect all the planned safety efficacy, PK, and PD data.

As part of the second interim analysis, Corvus may request the iDMC to assess the recovery rates and the conditional power of the study based on the interim data. The total sample size of the study may be increased with the recommendation by iDMC. The sample size adaptation plan and increase rule will be detailed in the statistical analysis plan and provided to the regulatory authority before the second interim analysis.

The primary analysis of the study is the final analysis in the time to recovery during the 28 days after dosing and will be performed when approximately 520 recovery events have been observed in the 2 treatment arms based on the intent-to-treat (ITT) Population. Comparison between Treatment A and Treatment B with respect to the time to recovery will be made using a modified version of stratified log-rank test correcting for competing risk of all-cause death. The efficacy stopping boundaries at the second interim and final analyses will be derived based on the time and number of recovery events using the Lan-Demets O'Brien and Fleming-like α spending function.

All the enrolled participants will be followed-up to Day 28 and further to the optional visits. Corvus may perform the primary analysis when all the enrolled participants have completed the Day 28 visit and include all participants' data for the primary analysis, if the iDMC recommends doing so at the second interim analysis. In this case, the analysis when 520 recovery events are observed will not be performed.

The following are the three key secondary endpoints with their hierarchical priority as ordered for statistical testing:

- Time to improvement by at least two points on the 8-point ordinal scale during the 28 days after dosing;
- The change in the level of IgG targeting RBD of SARS-CoV-2 over Days 7, 14, 21, and 28 from baseline measured by the area under the IgG level curve above the baseline over Days 1, 7, 14, 21, 28 and Day of Discharge;

- The time to resolution of ≥ 50% of the Covid-19-attributable symptoms including fever, cough, sore throat, headache, muscle pain, and/or short of breath reported at baseline.

In the case that a statistical significance is achieved in the time to recovery in comparison of Treatments A and B, the three secondary endpoints will be tested according to their hierarchical priority. This hierarchical procedure will be applied to the second interim analysis and to the final analysis. The α level for the comparison in the secondary endpoints will be the same α level as for the comparison in the time to recovery.

TTD is also a secondary endpoint of the study. TTD will be described at the final analysis which will be performed up to 6 months after the primary analysis and will be based on the ITT Population. The purpose of the analysis is to show a favorable trend of TTD with Treatment A over Treatment B. The Kaplan-Meier product limit curves of TTD and the 2-sided 95% confidence interval for the median TTD will be computed for each arm. A hazard ratio and a 2-sided 95% confidence interval of the ratio will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors.

9.4.7. Independent Data Monitoring Committee (iDMC)

An iDMC will be formed to monitor safety and efficacy of the study treatment at pre-specified timepoints including futility and interim analysis timepoints. The iDMC will review the unblinded safety data from the first 50 participants after completion of the Day 28 assessments. Subsequent iDMC reviews will occur after every 150 participants have completed the Day 28 assessments. In addition, the iDMC is available for ad hoc reviews for safety concerns. The study will not stop enrollment awaiting these iDMC reviews, although the iDMC may recommend temporary or permanent cessation of enrollment based on their safety and/or efficacy reviews. The protocol team will review blinded pools of AE/SAE data every 2 weeks. If there are a significant number of unexpected AEs, the iDMC will be asked to review unblinded safety and efficacy data in an ad hoc meeting.

iDMC membership includes:

- Three clinicians experienced in care/management of Covid-19 (voting members) and an unblinded non-voting independent statistician

10. REFERENCES

Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-523.

Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV –- a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226-36

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with Covid-19: initial three-month experience. MedRxiv. 2020.

Luke JJ, Merchan J; Harshman L, et al. Immunobiology and clinical activity of CPI-006, an anti-CD73 antibody with immunomodulating properties in a Phase 1/1b trial in advanced cancers. J. Immunother. Cancer 2019b Nov;7(suppl.1) 282.

Luke JJ, Powderly JD, Merchan JR, et al. Immunobiology, preliminary safety, and efficacy of CPI-006, an anti-CD73 antibody with immune modulating activity, in a phase 1 trial in advanced cancers. J. Clin. Oncol. 2019a 37(15 suppl.).

Rasheed AM, Ftak DF, Hashim HA, et al. The therapeutic effectiveness of Convalescent plasma therapy on treating Covid-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. medRxiv. 2020.

Resta R, Thompson LF. T cell signaling through CD73. Cell Signal. 1997 Feb;9(2):131-9.

Royal College of Physicians. National early warning score (NEWS) 2. Standardising the assessment of acute-illness severity in the NHS. 2017.

Willingham SB, Criner G, Hill C, et al. Characterization and Phase 1 Trial of a B Cell Activating Anti-CD73 Antibody for the Immunotherapy of Covid-19. medRxiv. 2020.

World Health Organization. Coronavirus disease 2019 (Covid-19): situation report, 72.

Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367(6483):1260-1263.

Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Apr; 580(7803):E7.

Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. Science. 2020 Apr 3. pii: eabb7269

APPENDIX 1
SCHEDULE OF ACTIVITIES

Table 6 Schedule of Activities

Procedure	Screening (up to 3 days before Day 1)[a]	Day 1	Day 2 to X (during hospital stay)[b]	Day 7 (if patient remains in the hospital)[c]	Day of Hospital Discharge[c]	Day 7 (if patient is discharged from hospital)[d]	Day 14[c, d, e]	Day 21[c, d, e]	Early Termination D28[d]	Optional Assessment		
										Day 56[d]	Day 84[d]	Day 168[d]
Informed Consent	X											
Inclusion and Exclusion Criteria	X											
Demography	X											
Physical Examination	X											
Limited Physical Exam		X	X	X	X				X			
Medical History	X											
Covid-19 Symptoms Assessment[f]	X	X	X	X	X	X	X	X	X			
National Early Warning Score 2 Assessment	X	X	X	X	X				X			
8-point Ordinal Scale Assessment	X	X	X	X	X		X[g]	X[g]	X			
Vital Signs[h]	X	X	X	X	X				X			
Hematology Panel[i]	X	X	X	X	X				X			
Chemistry Panel[j]	X	X	X	X	X				X			
Serum Quantitative Immunoglobulins[j]	X	X			X				X			
Serum Ferritin	X	X	X	X	X				X			
Coagulation Test (PT, aPTT, INR)	X	X	X	X	X				X			
D-dimer	X	X	X	X	X				X			

Procedure	Screening (up to 3 days before Day 1) [a]	Day 1	Day 2 to X (during hospital stay)[b]	Day 7 (if patient remains in the hospital)[c]	Day of Hospital Discharge [c]	Day 7 (if patient is discharged from hospital)[d]	Day 14[c, d, e]	Day 21[c, d, e]	Early Termination D28[d]	Optional Assessment		
										Day 56[d]	Day 84[d]	Day 168[d]
Fibrinogen	X	X	X	X	X				X			
Pregnancy Test[k]	X								X			
SARS-CoV-2 PCR Test[l]	X	X		X	X							
Viral load sample (for Central Lab)		X	X[m]	X	X		X	X	X			
Influenza and RSV PCR Test	X											
C-Reactive Protein	X	X	X	X	X				X			
Anti-SARS-CoV-2 Serum Antibody Test Blood Sample (Central Lab)[n]		X[n] (pre-dose)		X	X		X	X	X	(X)	(X)	(X)
Exploratory Biomarker Blood Samples		X[o]			X		X		X			
PK[n] and Immunogenicity Serum Samples	See Table 7 for details											
Treatment Administration		X										
Adverse Event Review[p]		<==========							==========>			
Serious Adverse Event Review[p]	<==========								==========>			
Concomitant Medication Review	<==========								==========>			
Covid-19 Medical Intervention Review[q]	<==========								==========>			

NOTE: Procedures indicated with parentheses "(X)" are conditional. Refer to the appropriate footnote for details.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; NEWS2 = National Early Warning Score 2 Assessment; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RSV = Respiratory Syncytial Virus; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Screening and Day 1 testing can be combined, providing they are separated by less than 24 hours and there are no signs of changes in the participant's status.

[b] Participants will be monitored daily while in the hospital for a minimum of 48 hours after study treatment administration. Participants will be monitored with vital signs including blood oxygen saturation every 4-6 hours or per institutional standards. Laboratory assessment will be taken daily or per institutional standards and

should include but are not limited to hematology panel, chemistries, ferritin, CRP, LDH, D-dimer, fibrinogen, PT, aPTT and INR. Participants' clinical status based on the 8-point ordinal scale, the NEWS2, Covid-19 related signs/symptoms, and safety laboratory tests will be recorded every day while hospitalized including day of discharge from the hospital.

[c] All participants will have samples collected for viral load, anti-SARS-CoV-2 serum antibody test, and exploratory biomarkers on day of discharge. Discharged participants will be asked to attend post- hospitalization study assessments at Days 14, 21, and 28, if discharged before any of these assessments were completed. Participants who are discharged before Day 7, do not need a Day 7 sample collection but will be assessed for Covid-19 symptoms

[d] Day 7 can be ± 1 day, Day 14, and Day 21 can be ± 2 days, Day 28 can be ± 3 days. Day 56, Day 84, and Day 168 can be ± 5 days.

[e] All efforts should be made to have the blood draws and exams done and assessments completed. When needed a telemedicine or home health visit can replace a clinical visit for the post-hospitalization visits.

[f] Assessment of Covid-19 symptoms (per Appendix 8) should happen daily during the hospital stay. In the post- hospitalization setting, assessment of symptoms should happen on Day 7 (for those discharged before Day 7), Day 14, Day 21 and Day 28. Day 7, Day 14, and Day 21 assessments can be a telemedicine or phone call visit.

[g] If the patient is hospitalized, the assessment should be conducted in the hospital. If discharged and patient is at home, assessment may be conducted over the phone.

[h] Vital signs includes pulse, blood pressure, temperature, respiratory rate, and oxygen saturation by pulse oximeter. Height and weight collected at screening only. On Day 1 vital signs will be collected pre-dose, at completion of treatment administration (at the end of the flush) (+ 15 minute window), and 2 hours post-dose (± 15 minutes window).

[i] Hematology panel should include the parameters detailed in protocol Appendix 3.

[j] Chemistry panel should include the parameters detailed in protocol Appendix 3 and serum quantitative immunoglobulins (Screening, Day 1, day of discharge and Day 28).

[k] Pregnancy test (serum or urine) for women of child-bearing potential only (Appendix 5).

[l] Participants must have a confirmed positive test by PCR for SARS-CoV-2 within 72 hours of randomization (screening sample). PCR test will also be obtained on Days 1 and 7, while hospitalized; and on day of discharge (if discharged prior to Day 28) and will be tested locally.

[m] Viral load sample to be collected on Day 3 while hospitalized as well as day 1(pre-dose), Day of discharge, Day 7, 14, 21 and 28.

[n] Anti-SARS-CoV-2 serum antibody test blood sample to be collected pre-dose administration. Anti-SARS-CoV-2 serum antibody samples will be collected to assessed at a central lab on Day 1 before dosing, and on Days 7, 14, 21, and 28 if patient remains hospitalized as well as the day of hospital discharge. For participants who are discharged before Day 14, 21 and 28, a sample will be collected on day of discharge as well as the posthospitalization sample collection on Days 14, 21, and 28 that are not collected during the hospital stay. Participants who consent separately to the optional assessments for anti-SARS-CoV-2 serum antibody tests will be evaluated on Days 56, 84, and 168.

[o] Exploratory biomarker samples on Day 1 will be collected pre-dose and 4 hours post-dose (± 30 min).

[p] After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol- mandated procedures will be reported. After initiation of study treatment, all AEs and SAEs will be reported until completion of the study at Day 28.

[q] Review of medical interventions/ procedures for management of Covid-19 such as intubation, ventilation, and supplemental oxygen and rehospitalization.

Table 7 PK, ADA, and Neutralizing Antibody Sampling Schedule

Sample[a]	Collection Timepoint	Variance
1	pre-dose	-1hour-0 hours
2	0.5 hours	± 5 min
3	2 hours	± 15 min
4	4 hours	± 30 min
5	8 hours	± 2 hours
6	24 hours	± 6 hours
7	48 hours	± 8 hours
8	72 hours	± 8 hours
9	96 hours (or time of discharge)	± 8 hours
10	Day 7-9 (or time of discharge)	
11	Day 14	± 2 days
12	Early Termination Day 28	± 3 days

Abbreviations: min = minutes

[a] Time post CPI-006 infusion and line flush except for pre-dose sample

APPENDIX 2
REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor 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 study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

- Participants must be informed that their participation is voluntary. Participants 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, US Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants 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 participant or the participant's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Sites will be allowed to use all processes approved by their IRB to ensure safety of staff and patients from Covid-19, while maintaining appropriate consent procedures for the duration of this study.

DATA PROTECTION

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant.
- The participant 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.

COMMITTEES STRUCTURE

The objectives of the iDMC are to evaluate interim clinical and safety data to protect participant welfare and to provide recommendations regarding study conduct. Details of iDMC responsibilities and procedures are specified in the iDMC charter.

DISSEMINATION OF CLINICAL STUDY DATA

Clinical Study Reports, periodic safety reports, and clinical study summary reports will be disclosed after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.

Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinTrials.gov and other publicly accessible sites.

Publication planning and other activities related to non-promotional, peer-reviewed publications will be conducted to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies should be through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party

DATA QUALITY ASSURANCE

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and

verifiable from source documents; that the safety and rights of participants 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.

- U.S. Food and Drug Administration (FDA) regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. No records may be transferred to another location or party without written notification to the Sponsor.

SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the CRF 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 study monitoring plan.

STUDY AND SITE CLOSURE

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

The investigator may initiate study-site 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 site 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 participants by the investigator
- Discontinuation of further study treatment development

PUBLICATION POLICY

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 3
CLINICAL LABORATORY TESTS

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.

Table 8 Protocol-Required Safety Laboratory Assessments

Chemistry	Hematology	Serum Quantitative Immunoglobulins	Inflammatory Biomarkers	Coagulation Testing
BUN (Blood Urea Nitrogen)	Platelet Count	IgA	C-reactive protein	PT
Potassium	RBC Count	IgG	Ferritin	aPTT
Creatinine	Hemoglobin	IgM		INR
Sodium	Hematocrit			D-dimer
Glucose	RBC (Red Blood Cell) indices: MCV MCH % Reticulocytes			Fibrinogen
Calcium				
Bilirubin (total & direct)				
Protein (total)				
LDH (Lactate Dehydrogenase)	WBC count (White Blood Cell) with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils			
AST				
ALT				

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell.

APPENDIX 4
ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, is accompanied by clinical symptoms, results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), results in a medical treatment (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
  - 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.
- For worsening of Covid-19 symptoms, the clinical event (s) that mark the worsening should be reported as AE or an SAE.
- If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event CRF Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Deaths that occur within 28 days after study treatment (CPI-006) should be reported as an SAE.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- "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 fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., 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 (e.g., hospitalization for signs/symptoms of the progression of disease under study). Hospitalization or ICU admissions due to Covid-19, worsening of Covid-19 in the 28 days during this study, or pulmonary conditions attributable to Covid-19 infection are considered efficacy-related endpoints. Therefore, Covid-19-related hospitalization or ICU admission is excluded from this definition.

A 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 participant 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 **Any adverse event that r causes prolonged hospitalization should be documented and reported as a serious adverse event (pe the definition of serious adverse event).** • For this study, the subjects will be hospitalized for Covid-19 treatment so initial hospitalization will not be considered as an SAE. Complications that occur during hospitalization are AEs/SAEs. If a complication prolongs hospitalization (or requires admission to ICU) or fulfills any other serious criteria, the event is serious. **An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:** • Hospitalization for respite care • Planned hospitalization required by the protocol (e.g., for the Covid-19 treatment).

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 (e.g., 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 participant or may require medical or surgical treatment to prevent 1 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 (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- 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. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF
- If vomiting results in severe dehydration, both events should be reported separately on the CRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the CRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF

All AEs should be recorded separately on the Adverse Event CRF if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient or participant evaluation timepoints. Such events should be recorded with each severity change on the Adverse Event CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported, with each subsequent change in severity recorded on the same AE CRF with the exception of a non-serious event becoming serious. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious.). A new AE should be recorded as serious in the CRF with the date the event became serious recorded as the start date and completing all data fields related to SAEs.

- A recurrent AE is one that resolves between patient or participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event CRF.

Assessment of Intensity

The guidelines outlined below will be used for assessing the severity of AEs. The severity/intensity of AEs and SAEs will be graded based upon the participant's symptoms according to the NCI CTCAE v5.

AEs that are not defined in the NCI CTCAE v5 should be evaluated for severity/intensity according to the following scale:

Table 9 Assessment of Severity of Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or treatment not indicated
2	Moderate; minimal, local, or non-invasive treatment indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living.[b,c] An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
4	Life-threatening consequences or urgent treatment indicated [d]
5	Death related to AE [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE per the definition of SAE in (see section above).

[d] Grade 4 and 5 events must be reported as SAEs per the definition of SAE in (see section above).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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 (IB) 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 Sponsor. 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 Sponsor.
- 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

- Treatment related AEs and SAEs should be followed up until resolution or until the AE is stable.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor 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 participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE Reporting to Corvus via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Corvus will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone or email.

SAE Reporting via Paper Report Forms

The primary mechanism for reporting an SAE to Sponsor will be through EDC. If EDC is down or not available, then the paper SAE report form can be used for SAE reporting.

Events That Occur Prior to the Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment (non-treatment emergent), **only SAEs caused by a protocol-mandated treatment** should be reported in EDC using the EDC SAE form. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event CRF and submit the report via the paper report form. All other non-treatment emergent AEs should be reported in the Medical History CRF.

Events That Occur after Study Treatment Initiation

- After initiation of study treatment, all AEs and SAEs will be reported for 28 days following stopping of study treatment and until participants complete the study. The site will enter the SAE data into the EDC SAE report form.

Adverse Events That Occur after the Adverse Event Reporting Period are described in the following section.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, then the site can report this information in EDC (see next section) or to the Sponsor's designee by telephone on the number listed in a section below.

If EDC is unavailable, then the paper Clinical Trial Serious Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators below. Please note that email is preferred over fax and phone.

Note: For Ex-US country-specific safety fax and phone numbers, refer to the study manual.

- 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 CRF pages within the designated reporting time frames.

APPENDIX 5
CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

WOMAN OF CHILDBEARING POTENTIAL (WOCBP)

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

1. Women in the following categories are not considered WOCBP
2. Premenarchal
    a. Premenopausal female with 1 of the following:
    b. Documented hysterectomy
    c. Documented bilateral salpingectomy
    d. Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    e. 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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    f. 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 PARTICIPANTS

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1] for six weeks after study treatment.

- 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 Table 1 of this appendix when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 6 weeks after study treatment.

Male participants 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 during the 28 days of study participation.

FEMALE PARTICIPANTS

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1.

Table 1 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 Contraceptive Methods That Are User Independent [a]

- Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b]
- IUD
- IUS
- Bilateral tubal occlusion

Vasectomized partner

A vasectomized partner is a highly effective contraception 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 defined as six weeks after receiving 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 participant.

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system; WOCBP = woman of childbearing potential

[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 participants 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, two highly effective methods of contraception should be utilized during the treatment period and for at least 6 weeks corresponding to time needed to eliminate study treatment after the last dose of study treatment.

PREGNANCY TESTING:

- WOCBP should only be included after a negative (urine or serum) pregnancy test at screening
- Additional pregnancy testing is required at end of study or at early termination (see Appendix 1 – Schedule of Activities)

COLLECTION OF PREGNANCY INFORMATION:

MALE PARTICIPANTS WITH PARTNERS WHO BECOME PREGNANT

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the

Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

FEMALE PARTICIPANTS WHO BECOME PREGNANT

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. 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 post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

APPENDIX 6
8-POINT ORDINAL SCALE FOR CLINICAL IMPROVEMENT

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID19 related or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices
7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
8. Death

APPENDIX 7
NEWS2 SCORING SYSTEM

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

National Early Warning Score (NEWS) 2

APPENDIX 8
EXAMPLE OF AN ASSESSMENT OF 14 COMMON COVID-19-RELATED SYMPTOMS: ITEMS AND RESPONSE OPTIONS

Example items *For items 1–10, sample item wording could be: "What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you **vomit (throw up)** in the last **24 hours**?**	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?**	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

APPENDIX 9
PROTOCOL AMENDMENT HISTORY

Table 10 Document History

Document History	Date of Issue
Version 001 (Original Protocol)	06-November-2020