CLINICAL STUDY PROTOCOL

A Phase 2/3, Randomized, Parallel-Group, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Hospitalized Patients with SARS-CoV-2 Infection

PROTOCOL NUMBER CT-P59 3.1

EudraCT Number:	2020-003401-60
Study Drug:	CT-P59 3.1
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Version and Date of Protocol:	Protocol Version 2.0, 04 September 2020

Protocol Approval

Study Title	A Phase 2/3, Randomized, Parallel-Group, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Hospitalized Patients with SARS-CoV-2 Infection
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Protocol accepted and approved by:

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Signature

07 Sep 20
Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled 'A Phase 2/3, Randomized, Parallel-Group, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Hospitalized Patients with SARS-CoV-2 Infection', and the accompanying current Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.0, 04 September 2020, the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice, Declaration of Helsinki (World Medical Association 2013), and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without Independent Ethics Committee (or Institutional Review Board) approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator Date

Printed Name of Principal Investigator:

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PROTOCOL SYNOPSIS

Protocol Number: CT-P59 3.1

Title: A Phase 2/3, Randomized, Parallel-Group, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Hospitalized Patients with SARS-CoV-2 Infection

Development Phase: Phase 2/3

Study Center(s): TBD

Dose and Route of Administration:

Test Investigational Product, Route of Administration:

- CT-P59 80 mg/kg by single intravenous (IV) administration over 90 minutes (± 15 minutes) with standard of care (SoC)

Reference Investigational Product, Route of Administration:

- Placebo 80 mg/kg by single IV administration over 90 minutes (± 15 minutes) with SoC

Study Objective(s):

The objective is to evaluate the efficacy and safety of CT-P59 in hospitalized patients with SARS-CoV-2 infection.

Primary Objectives

Part 1

- To assess that CT-P59 has the potential therapeutic efficacy relative to Placebo as determined by time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days

Part 2

- To demonstrate that CT-P59 has the clinical meaningful therapeutic efficacy relative to Placebo as determined by the time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days

Secondary Objectives

Part 1

- To evaluate overall safety of CT-P59

Part 2

- To evaluate the additional efficacy of CT-P59
- To evaluate overall safety of CT-P59, including immunogenicity and potential effects on the incidence of antibody-dependent enhancement (ADE)

Exploratory Objectives

Part 2

- To assess the pharmacokinetics (PK) of CT-P59 (optional, only for PK Cohort)
- To assess the viral efficacy and characterization of SARS-CoV-2 viral isolates
- To assess the serum antibodies against SARS-CoV-2

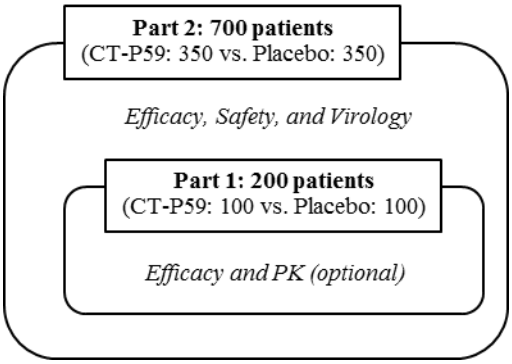
Number of Patients:

Approximately a total of 700 patients will be enrolled in this study. In Part 1, approximately 200 patients will be enrolled in a 1:1 ratio of CT-P59 or Placebo. In Part 2, approximately 500 subsequent patients will be randomly assigned in a 1:1 ratio to CT-P59 or placebo. In total, approximately 700 patients will be available for Part 2 analysis (including 100 patients from each CT-P59 or Placebo treatment group in Part 1).

Study Population:
Male or female patients, aged 18 years or older with SARS-CoV-2 infection, hospitalized, no more than 10 days prior to the study drug administration from the onset of symptom and no more than 4 days from the confirmation of SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) at local laboratory, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Study Design:
This is a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind, multicenter, international study with 2 parts to evaluate the efficacy and safety of CT-P59 in combination with SoC in hospitalized patients with SARS-CoV-2 infection.
Approximately a total of 700 hospitalized patients with SARS-CoV-2 infection will be enrolled in a 1:1 ratio to CT-P59 or Placebo (350 patients in each treatment group for Part 2, including the 100 patients from Part 1).
A PK sub-study will be performed on the patients who signed a separate informed consent to participate in a PK sub-study. Of the total number of patients to be enrolled, approximately 60 patients from Part 1 will be included in the PK Cohort (Figure S1).

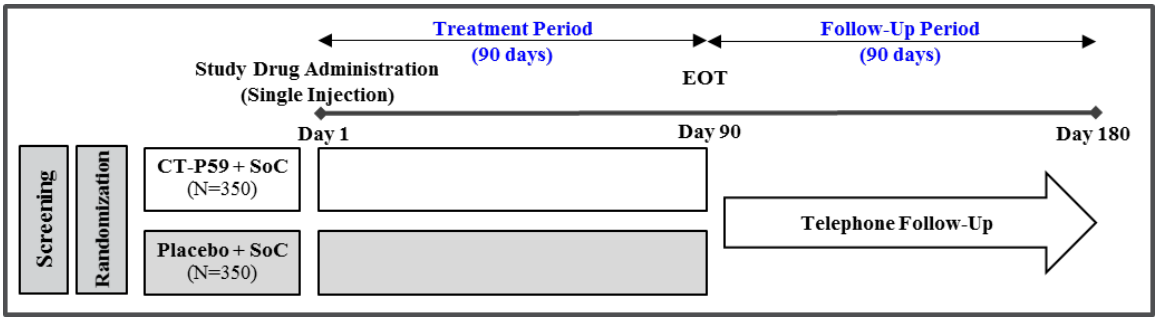
Figure S1. Schematic Diagram of Study Patients



Abbreviations: PK = pharmacokinetics.
Note: Patients who signed a separate informed consent for the PK assessment will be included in the PK Cohort.

This study will comprise 3 study periods including Screening Period, Treatment Period, and Follow-Up Period. An end-of-treatment (EOT) visit will occur on Day 90 (Figure S2).

Figure S2. Study Design Scheme



Abbreviations: EOT = end-of-treatment; SoC = Standard of Care.

The study continuation to Part 2 will be determined by Data and Safety Monitoring Board (DSMB) recommendation based on the evidence of potential safety issues and treatment benefits evaluated from the day 28 assessments of the last enrolled patient in Part 1 (approximately 200 patients). The additional patient enrollment for Part 2 will be paused during the DSMB review.

The study drug assignment will remain blinded to the investigators, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staff designated to prepare the study drug for administration and predefined unblinded teams in the sponsor and CRO), and patients until the final clinical study report is generated.

Inclusion Criteria:

Each patient must meet all of the following criteria to be randomized in this study:

1. Patient is male or female aged 18 years or older.
2. Patient has local laboratory confirmation of SARS-CoV-2 infection by RT-PCR from the upper or lower respiratory tract specimens no more than 4 days prior to the administration of the study drug.

   Note: *If there is available test result confirmed as SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 4 days prior to the administration of the study drug) and that result was from the RT-PCR by the upper or lower respiratory tract specimen, that test result can be allowed.*

   Note: *During the Screening Period, only one re-test for RT-PCR will be allowed if study drug can be administered no more than 10 days from onset of symptom based on re-test results.*
3. Onset of symptom no more than 10 days prior to the administration of the study drug.
4. Patient with conditions meeting the following criteria, and currently hospitalized (or will be hospitalized prior to the administration of the study drug):
   a) Oxygen saturation ≤ 94% on room air and/or PaO_2/FiO_2 ratio ≤ 300 mmHg, AND
   b) Requiring supplemental oxygen.
5. Patient with abnormal radiographic findings in lung suggestive of SARS-CoV-2 infection by investigator's discretion.
6. Patient's weight is of ≤ 99.9 kg.
7. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any study specific procedures.
8. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study (up to 6 months after the study drug administration) as specified in Section 6.2.2.7.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Patient who is requiring extracorporeal membrane oxygenation (ECMO), or invasive mechanical ventilation.
2. Patient had a history of and/or concurrent use of medications including any therapy of following(s):
   a) Drugs with possible anti-SARS-CoV-2 activity or immunomodulators including but not limited to remdesivir, chloroquine, hydroxychloroquine, dexamethasone (alternative corticosteroids to dexamethasone), tocilizumab, sarilumab, and other immunomodulatory agents and human immunodeficiency virus (HIV) protease inhibitors for therapeutic purpose of SARS-CoV-2 infection prior to the study drug administration.

      Note: *During the study, authorized drugs (or drugs approved for emergency use) against SARS-CoV-2 infection such as remdesivir or dexamethasone (alternative corticosteroids to dexamethasone), could be used by investigator's discretion considering the local practice where there is available supply.*
   b) Any SARS-CoV-2 human intravenous immunoglobulin (hIVIG), convalescent plasma from a person who recovered from SARS-CoV-2 infection or SARS-CoV-2 nMAb for the treatment of SARS-CoV-2 infection prior to the study drug administration.
   c) Any other investigational device or medical product including but not limited to any monoclonal antibody, fusion proteins or biologics for the treatment of SARS-CoV-2 infection prior to the study drug administration.
   d) Use of medications that are contraindicated with SoC.
   e) SARS-CoV-2 vaccine prior to the study drug administration.

3. Patient has known allergy or hypersensitivity reaction to any monoclonal antibody or to any components of study drug.
4. Patient has a history of and/or current disease or medical condition including any of following(s):
   a) Any active malignancy.
   b) Known severe liver disease (e.g., cirrhosis, or an Alanine Aminotransferase [ALT] level >5 × upper limit of normal [ULN], or an Aspartate Aminotransferase [AST] level >5 × the ULN).
   c) Renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis.
   d) Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment groups.
   e) Stroke or myocardial infarction, which is suspected to be related to SARS-CoV-2 infection after the onset of symptom.
   f) Documented current infection with HIV, hepatitis B or hepatitis C.
5. Patient who has received any other investigational device or medical product within 4 weeks prior to the study drug administration or 5 half-lives, whichever is longer.
6. Patient currently abuses alcohol or drugs.
7. Patient is not eligible for the study participation for whatever reason (including clinical laboratory results) in the opinion of the investigator, or shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limited the ability of the patient to comply with the protocol requirements in the opinion of the investigator, or unable to understand the protocol requirements, instructions and study related restrictions, the nature, scope and possible consequences of the clinical study, or is unable to give written informed consent or to comply fully with the protocol.
8. Anticipated transfer to another hospital which is not a study site.
9. Female patient who is currently pregnant or breastfeeding or planning to be pregnant or to breastfeed, or male patient is planning to father a child or donate sperms throughout the study (up to 6 months after the study drug administration).

Study Procedure:

Screening Period (Day -10 to Day 0)

No study procedures will be performed prior to informing the patient about the study and obtaining written informed consent. It is critical that patients receive study drug no more than 10 days from the onset of symptoms and 4 days from the confirmation of SARS-CoV-2 infection by RT-PCR at the local laboratory.

Screening will take place within 10 days before the study drug administration. Patients must have at least one positive result of SARS-CoV-2 infection by RT-PCR from the upper or lower respiratory tract specimens at local laboratory within 4 days prior to the study drug administration. It is recommended to collect nasopharyngeal specimen by a health professional. If not possible, other upper respiratory or lower respiratory specimen are acceptable alternatives.

During the Screening Period, only one re-test for RT-PCR will be allowed if study drug can be administered no more than 10 days from onset of symptom based on re-test results.

Treatment Period (Day 1 to Day 90)

On Day 1, approximately 700 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to one of two treatment groups to receive either a single dose of CT-P59 or Placebo. Patients in both treatment groups will be given optimal SoC.

Randomization will be stratified by region, disease severity (an 8-point ordinal scale 5 vs. 6) and age (≥ 60 years vs. < 60 years). The study drug will be administered on the randomization date (Day 1) and patient will be followed by Day 180.

Virology samples will be used for viral shedding based on reverse transcription-quantitative polymerase chain

reaction (RT-qPCR) and cell culture. The collected areas of specimen for SARS-CoV-2 should remain consistent for each patient receiving study drug. If Screening assessment and administration of the study drug are performed on the same day, nasopharyngeal swab samples will be collected respectively for local diagnostic test and central virology assessment.

All patients will be hospitalized up to Day 7. The extension of hospitalization period will be determined based on the following discharge criteria or by investigators' discretions:

- Resolution of fever without the use of fever-reducing medications for 24 hours, AND
- Improvement in clinical symptoms (e.g., cough, shortness of breath).

After discharge, the remaining visits will be conducted as out-patient and patients will be treated until EOT visit occurs on Day 90. If a patient withdraws prematurely after the study drug administration, the patient will be asked to return to the study site on the next scheduled visit for the EOT assessments.

Follow-Up Period (Up to Day 180)

For all survived patients including a patient who early terminated from the study, each telephone call follow-up will occur 2-weekly (±5 days) from 2 weeks after the EOT visit up to Day 180. During the Follow-Up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone call to capture the suspicious ADE occurrence.

Criteria for Evaluation:

Primary Endpoints

Efficacy

The following 8-point ordinal scale will be evaluated as primary endpoints;

1) Not hospitalized, no limitations of activities;
2) Not hospitalized, limitation of activities, home oxygen requirement, or both;
3) Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons);
4) Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (SARS-CoV-2 – related or other medical conditions);
5) Hospitalized, requiring any supplemental oxygen;
6) Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
7) Hospitalized, receiving invasive mechanical ventilation or ECMO
8) Death;

Primary endpoint:

- Time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days

Secondary Endpoints

Secondary efficacy and safety endpoints will be analyzed throughout the study.

Efficacy

- Proportion of recovered patients on Day 7, 14 and 28
- Proportion of intensive care unit transfer on Day 14 and 28
- Mortality rate on Day 14, 28 and 90
- Clinical status by the 8-point ordinal scale on Day 7, 14 and 28
- Time to improvement of at least 1 point from the status at baseline by 8-point ordinal scale up to Day 28
- Change from baseline of the 8-point ordinal scale on Day 7, 14 and 28
- Duration of hospitalization in survivors up to Day 28
- Number of free days of supplemental oxygen up to Day 28
- Proportion of new mechanical ventilation use on Day 14 and 28
- Change from baseline of National Early Warning Score (NEWS) on Day 7, 14 and 28

Safety

The safety endpoints will be assessed using the followings: AEs (including SAEs and AESI), potential effects on the incidence of ADE, immunogenicity, vital signs, hypersensitivity monitoring, ECG findings, SARS-CoV-2 infection related signs and symptoms, radiography (chest x-ray or chest CT), physical examination findings, clinical laboratory tests, pregnancy tests, and prior and concomitant medications.

Exploratory Endpoints

Exploratory PK (optional, only for PK Cohort) and virology endpoints will be analyzed throughout the study.

Pharmacokinetics (optional, only for PK Cohort)

- $AUC_{0\text{-last}}$: Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
- $AUC_{0\text{-inf}}$: Area under the concentration-time curve from time zero extrapolated to infinity
- C_{max}: Maximum concentration
- T_{max}: Time to C_{max}
- λ_z: Terminal elimination rate constant
- $T_{1/2}$: Terminal half-life
- CL: Total body clearance
- V_z: Apparent volume of distribution during terminal phase
- $\%AUC_{ext}$: Percent of $AUC_{0\text{-inf}}$ obtained by extrapolation

Virology

- Viral shedding in upper or lower respiratory tract based on RT-qPCR and cell culture
- Genotype and phenotype of SARS-CoV-2 viral isolates
- SARS-CoV-2 antibody test detecting serum antibodies against SARS-CoV-2

Sample Size Assumption:

For the primary efficacy endpoint, approximately 400 recovery events in hospitalized patients with SARS-CoV-2 infection are required for a power of 85% at a significance level of 5% (two-sided test) to detect a recovery rate ratio 1.35 up to Day 28.

Considering the overall recovery rate of 57%, a total 700 hospitalized patients (350 patients per treatment group) with SARS-CoV-2 infection will be enrolled in a 1:1 ratio to the CT-P59 or Placebo in this study. A reassessment of sample size after review of data up to Day 28 of the approximately 200^{th} patient will be considered by DSMB.

Statistical Methods:

Analysis Sets:

Intent-to-treat (ITT) Set: The ITT Set is defined as all randomly assigned patients to study drug.

Safety Set: The Safety Set is defined as all randomly assigned patients who receive a complete or partial dose of study drug.

Intent-to-treat infected (ITTI) Set: The ITTI Set is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-administration result (Day 1) of RT-qPCR or cell culture, who receive a complete dose of study drug.

Pharmacokinetic (PK) Set: The PK Set is defined as all randomly assigned patients who receive a complete dose of study drug and have at least one evaluable post treatment PK result.

Efficacy Analyses:

The primary efficacy endpoint, time to recovery up to Day 28, will be analyzed on the ITT Set presenting the p-value from a stratified log rank test, and stratified by region (United States vs. Asia Pacific vs. European Union vs. Other), disease severity based on a 8-point ordinal scale (5 vs. 6) and age (≥ 60 years vs. < 60 years) at the 2-sided significance level of 0.05. Additionally, receiving remdesivir and/or dexamethasone (alternative corticosteroids to dexamethasone) before achieving primary endpoint (Yes vs. No) will be considered as strata in stratified log rank test. The 25% percentile, 50% percentile (median), 75% percentile recovery time and 95% confidence interval (CI) for each treatment group will be presented using the Kaplan-Meier method. Hazard ratio and associated 95% CI will also be estimated using stratified cox proportional hazard model. The supportive analysis for primary endpoint will be performed in the ITTI Set. The sensitivity analysis of primary endpoint will be performed on the ITT Set using an unstratified log rank test.

For the primary efficacy endpoint, time to recovery up to Day 28, any patients that are lost to follow-up or discontinued/terminated early prior to an observed recovery and complete follow-up but do not experience recovery will be censored and time will be considered as 28 days. All deaths within Day 28 (and prior to recovery) will be censored and time will be considered as 28 days.

The results of secondary efficacy analyses will be presented using descriptive statistics or frequency tables. All secondary efficacy endpoints will be analyzed on both the ITT Set and ITTI Set.

Safety Analyses:

The safety evaluations will be performed during the study to measure the safety of CT-P59 or Placebo. The safety results including ADE and immunogenicity will be listed and summarized by treatment group. Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities. Adverse events will be graded for severity and the terminology of adverse events will be described according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All safety data will be listed and summarized by treatment group as appropriate. The primary population for this analysis will be the Safety Set.

Pharmacokinetic Analyses:

Pharmacokinetic parameters will be computed by non-compartmental methods using the Phoenix WinNonlin (Pharsight, St Louis, Missouri, USA). Pharmacokinetic parameters and PK concentration data will be presented in listings and summarized in tables by treatment groups. Pharmacokinetic parameters will include $AUC_{0–last}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, λ_z, $T_{1/2}$, CL, V_z and $\%AUC_{ext}$. The tables will display the following descriptive statistics: the number of observations (n), mean, standard deviation (SD), median, minimum, maximum, geometric mean and coefficient of variation. All PK analyses will be based on the PK Set.

Virology Analyses:

Viral efficacy (viral shedding in upper or lower respiratory tract based on RT-qPCR and cell culture), characterization of SARS-CoV-2 viral isolate (genotype and phenotype) and SARS-CoV-2 antibody test detecting serum antibodies against SARS-CoV-2 (e.g., IgM and IgG etc.) will be analyzed on the ITTI Set. Actual values and change from baseline for viral shedding, percentage of patients with positive/negative viral shedding, duration (in days) of viral shedding, and AUC of viral levels will be summarized by treatment groups at each scheduled visit using descriptive statistics or frequency tables. Mean viral load titer (log values) for each

scheduled time point will be plotted. Genotype, phenotype and SARS-CoV-2 antibody test results will be presented in data listing by treatment groups.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ADE	Antibody-dependent enhancement
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
CI	Confidence interval
CRO	Clinical research organization
CSR	Clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report from
EOS	End of the study participation
EOT	End-of-treatment
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hIVIG	human intravenous immunoglobulin
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IRB	Institutional review board
ITT	Intent-to-treat
ITTI	Intent-to-treat infected
IV	Intravenous

Abbreviation	Definition
IVRS	Interactive voice response system
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
RBD	Receptor binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RT-qPCR	Reverse transcription-quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoC	Standard of care
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization

1 Introduction

1.1 Background

Coronaviruses are single stranded ribonucleic acid (RNA) viruses, capable of causing life-threatening disease in humans and animals. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in China in December 2019. Most of the initial infections outside of China were travel associated (i.e., from people who had travelled from the infected regions of China to other countries), although person to person transmission in other countries was quickly established. The disease caused by the SARS-CoV-2 has been designated as COVID-19 (WHO COVID-19 outbreak, 2020).

Most people with SARS-CoV-2 infection develop only mild (40%) or moderate (40%) disease. However, approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury. Older age, smoking and underlying noncommunicable diseases, such as diabetes, hypertension, cardiac disease, chronic lung disease, and cancer have been reported as risk factors for severe disease and death.

Severe acute respiratory syndrome coronavirus 2 infection is also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, ischemic and hemorrhagic stroke, meningoencephalitis, impaired sense of smell or taste, anxiety, depression, and sleep problems. In many cases, neurological manifestations have been reported even without respiratory symptoms. Case reports of Guillain-Barré syndrome and meningoencephalitis among people with SARS-CoV-2 infection have also been reported. Clinical manifestations of SARS-CoV-2 infection are generally milder in children compared with adults. Relatively few cases of infants confirmed with SARS-CoV-2 infection have been reported. However, most recently a multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection in children and adolescents has been described (WHO Interim Guidance, 2020).

Coronavirus entry into host cells is an important determinant of viral infectivity and pathogenesis. It is also a major target for host immune surveillance and human intervention strategies. It has been established that SARS-CoV-2 binds via the angiotensin-converting enzyme (ACE) 2 receptor located on epithelial and endothelial cells which traverse multiple organs (Varga et al., 2020). SARS-CoV-2 infection is initiated by binding the SARS-CoV-2 spike (S) protein to ACE2 via the receptor binding domain (RBD) of the S protein, which mediates viral entry into the target cells. The virus is mutating, indicating that virulence and

transmission will shift over time, and showing diversity in critical surface protein. New evidence suggests there are 2 groups of SARS-CoV-2; L-type and S-type (Tang et al., 2020). S-type is the less aggressive (30%); the L-type is now the most prevalent version (70%) and is more aggressive. Additionally, individuals appear to be affected to different degree with varying symptoms and outcomes. These findings strongly support an urgent need for immediate comprehensive studies and robust validation of testing methods that combine genomic data, chart records and clinical symptoms, to help better understand the disease, enable risk assessment, triage and support public health resource planning.

1.2 CT-P59

CT-P59 is a human monoclonal antibody targeted against SARS-CoV-2 S protein as a treatment for SARS-CoV-2 infection, which is manufactured by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary mammalian cell line. The dosage form of CT-P59 is solution concentrate for dilution for administration in a single intravenous (IV) administration.

The main mechanism of action is blocking the binding between SARS-CoV-2 RBD and cellular receptor, ACE2, thus inhibiting their infection to host cells. Although it has known in many virus infections that antibodies can remove the virus-infected cells via antibody Fc-dependent function such as antibody-dependent cellular cytotoxicity, it’s unlikely that CT-P59 induces antibody Fc-dependent virus clearance, considering the life cycle of SARS-CoV-2 which is assembled inside cells and released via exocytosis. However, it is postulated that there are additional mechanisms of CT-P59 mediated virus clearance by opsonisation and complement activation (i.e., antibody-dependent, complement-dependent virolysis or antibody dependent phagocytosis).

1.2.1 Nonclinical Studies

The nonclinical program for CT-P59 has been designed to support clinical studies. Detailed information regarding the non-clinical pharmacology, pharmacokinetic (PK) and drug metabolism and toxicology of CT-P59 can be found in the investigator’s brochure (IB).

1.2.2 Clinical Studies

The clinical program to date consists of two Phase 1 studies.

Study CT-P59 1.1 is a randomized, double-blind, placebo-controlled, parallel group, single ascending dose, Phase 1 study to evaluate the safety, tolerability and PK of CT-P59 in healthy subjects. Thirty-two subjects in 4 cohorts are enrolled and each cohort consists of 8 subjects, 6 of whom received CT-P59 and 2 of whom received a Placebo. Detailed information regarding

the safety of CT-P59 in healthy subjects can be found in the IB.

Study CT-P59 1.2 is a randomized, double-blind, placebo-controlled, parallel group, single ascending dose, Phase 1, pilot study to evaluate the safety, tolerability and virology of CT-P59 in combination with standard of care (SoC), except potential antiviral drugs and/or immune-based therapy under evaluation for treatment of SARS-CoV-2 infection, in patients with mild symptoms of SARS-CoV-2 infection. Approximately 18 patients in 3 cohorts are planned for enrollment and each cohort will consist of 6 patients, 5 of whom will receive CT-P59 and 1 of whom will receive a Placebo. In each cohort, patients will be randomized in a 5:1 ratio to receive CT-P59 or Placebo. Study CT-P59 1.2 is ongoing.

1.3 Study Rationale

There are currently no approved monoclonal antibody therapies available to treat coronaviruses such as SARS-CoV-2, the causative agent of SARS-CoV-2 infection, and there is an urgent public health need for rapid development of such interventions. On 11 March 2020, WHO declared the SARS-CoV-2 infection outbreak a global pandemic as there are more than 118,000 cases in 114 countries, and 4,291 people have lost their lives. According to the WHO report, as of June 2020, about 6.28 million people were confirmed SARS-CoV-2 infection in 216 countries and death cases exceeded about 380,000 (WHO COVID-19 outbreak situation, 2020).

CT-P59 is currently being developed by CELLTRION, Inc. as a potential treatment for SARS-CoV-2 infection. The anticipated high affinity and targeted effect of CT-P59 is expected to enable antiviral activity. In the current study, the safety, tolerability, and therapeutic potential of CT-P59 will be evaluated.

1.3.1 Rationale for Study Population

The study population depends on the clinical data and recommendations from the regulatory authority but CELLTRION’s development program is focusing on evaluating efficacy and safety in hospitalized patients with SARS-CoV-2 infection. The expected patient population is adults only.

1.3.2 Rationale for Dose Selection

All the PK and efficacy results from the nonclinical and clinical studies including in vivo primary pharmacodynamics studies (in hamster, ferret and non-human primates), the toxicity and toxicokinetics results from the 2-weeks repeat-dose toxicity study (in cynomolgus monkey) as well as the maximum tolerated dose and the PK data from Study CT-P59 1.1 (in healthy volunteers) were taken into consideration. As all doses of Study CT-P59 1.1 were tolerable, the top dose of CT-P59 1.1, 80 mg/kg, was selected as administration dose for this study to

minimize any chances of less efficacy in patients with high risk.

1.4 Benefit and Risk Assessment

Despite the fact that numerous entities are under investigation, no potent and highly targeted antiviral options are available for treatment of coronaviruses such as SARS-CoV-2 at present.

CT-P59 may or may not improve clinical outcome of the participants in the current study. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agents under study as well as the natural history of the disease. While there may not be benefits for an individual patient, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global SARS-CoV-2 infection outbreak.

A global independent Data and Safety Monitoring Board (DSMB) will monitor safety data along the study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CT-P59 may be found in the current version of the IB.

The sponsor will immediately notify the investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, ICH Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) will meet the requirements of European Union – Good Manufacturing Practice.

The sponsor and Investigator may take appropriate urgent safety measures in order to protect the patients of a clinical study against any immediate hazard to their health or safety. If such measures are taken, the sponsor shall immediately give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

2 Study Objectives

The overall objective of this study is to evaluate the efficacy and safety of CT-P59 in hospitalized patients with SARS-CoV-2 infection. With this purpose, this study will be divided into 2 parts, each of which will assess its primary endpoint.

2.1 Primary Objectives

Part 1

- To assess that CT-P59 has the potential therapeutic efficacy relative to Placebo as determined by time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days

Part 2

- To demonstrate that CT-P59 has the clinical meaningful therapeutic efficacy relative to Placebo as determined by the time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days

2.2 Secondary Objectives

Part 1

- To evaluate overall safety of CT-P59

Part 2

- To evaluate the additional efficacy of CT-P59
- To evaluate overall safety of CT-P59, including immunogenicity and potential effects on the incidence of antibody-dependent enhancement (ADE)

2.3 Exploratory Objectives

Part 2

- To assess the PK of CT-P59 (optional, only for PK Cohort)
- To assess the viral efficacy and characterization of SARS-CoV-2 viral isolates
- To assess the serum antibodies against SARS-CoV-2

3 Investigational Plan

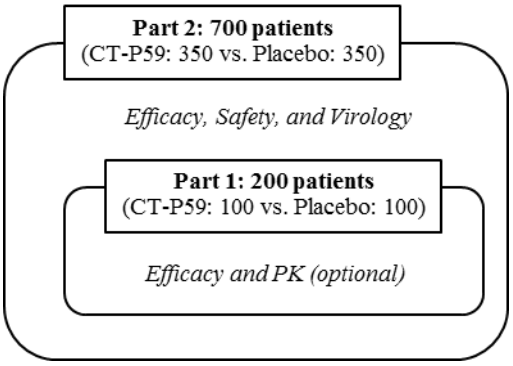
3.1 Study Design

This is a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind, multicenter, international study with 2 parts to evaluate the efficacy and safety of CT-P59 in combination with SoC in hospitalized patients with SARS-CoV-2 infection.

Approximately a total of 700 hospitalized patients with SARS-CoV-2 infection will be enrolled in a 1:1 ratio to CT-P59 or Placebo (350 patients in each treatment group for Part 2, including the 100 patients from Part 1). In Part 1, approximately 200 patients will be enrolled in a 1:1 ratio to CT-P59 or Placebo (approximately 100 patients each). In Part 2, approximately 500 subsequent patients will be randomly assigned in a 1:1 ratio to CT-P59 or Placebo (approximately 250 patients each). In total, approximately 700 patients will be available for Part 2 analysis (including 100 patients from each CT-P59 or Placebo treatment group in Part 1). Part 2 will include all patients in Part 1, and all patients in Part 1 will undergo all the assessment as Part 2. The study continuation to Part 2 will be determined by DSMB recommendation based on the evidence of potential safety issues and treatment benefits evaluated from the day 28 assessments of the last enrolled patient in Part 1 (approximately 200 patients). The additional patient enrollment for Part 2 will be paused during the DSMB review (Section 10.3.1).

A PK sub-study will be performed on the patients who signed a separate informed consent to participate in a PK sub-study. Of the total number of patients to be enrolled, approximately 60 patients from Part 1 will be included in the PK Cohort (Figure 1).

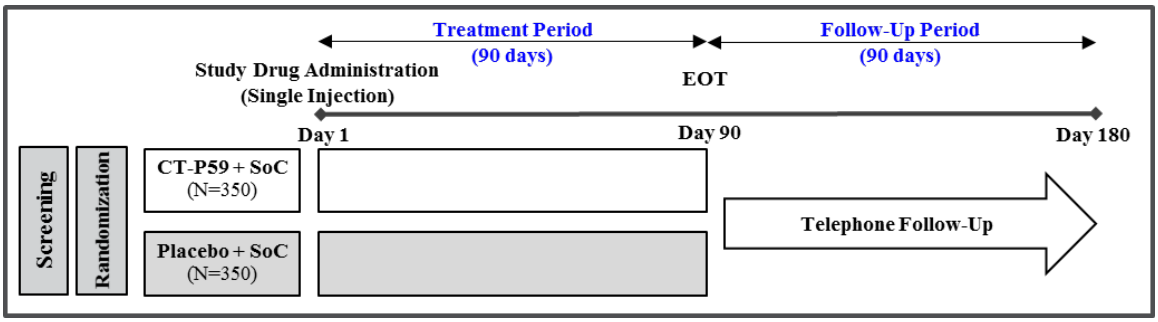
Figure 1 Schematic Diagram of Study Patients



Abbreviations: PK = pharmacokinetics.
Note: Patients who signed a separate informed consent for the PK assessment will be included in the PK Cohort.

This study will comprise 3 study periods including Screening Period, Treatment Period, and Follow-Up Period. An end-of-treatment (EOT) visit will occur on Day 90 (Figure 2).

Figure 2 Study Design Scheme



Abbreviations: EOT= end-of-treatment; SoC = Standard of Care.

3.1.1 Screening Period (Day -10 to Day 0)

No study procedures will be performed prior to informing the patient about the study and obtaining written informed consent. It is critical that patients receive study drug no more than 10 days from the onset of symptoms and 4 days from the confirmation of SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) at the local laboratory.

Screening will take place within 10 days before the study drug administration. Patients must have at least one positive result of SARS-CoV-2 infection by RT-PCR from the upper or lower respiratory tract specimens at local laboratory within 4 days prior to the study drug administration.

It is recommended to collect nasopharyngeal specimen by a health professional. If not possible, other upper respiratory or lower respiratory specimen are acceptable alternatives.

During the Screening Period, only one re-test for RT-PCR will be allowed if study drug can be administered no more than 10 days from onset of symptom based on re-test results.

3.1.2 Treatment Period (Day 1 to Day 90)

On Day 1, approximately 700 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to one of two treatment groups to receive either a single dose of CT-P59 or Placebo. Patients in both treatment groups will be given optimal SoC.

Randomization will be stratified by region, disease severity (an 8-point ordinal scale 5 vs. 6) and age (≥ 60 years vs. < 60 years). The study drug will be administered on the randomization date (Day 1) and patient will be followed by Day 180.

Virology samples will be used for viral shedding based on reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and cell culture. The collected areas of specimen for SARS-CoV-2 should remain consistent for each patient receiving study drug. If Screening assessment and administration of the study drug are performed on the same day, nasopharyngeal swab samples will be collected respectively for local diagnostic test and central virology assessment.

All patients will be hospitalized up to Day 7. The extension of hospitalization period will be determined based on the following discharge criteria or by investigators' discretions:

- Resolution of fever without the use of fever-reducing medications for 24 hours, AND
- Improvement in clinical symptoms (e.g., cough, shortness of breath).

After discharge, the remaining visits will be conducted as out-patient and patients will be treated until EOT visit occurs on Day 90. If a patient withdraws prematurely after the study drug administration, the patient will be asked to return to the study site on the next scheduled visit for the EOT assessments.

3.1.3 Follow-Up Period (Up to Day 180)

For all survived patients including a patient who early terminated from the study, each telephone call follow-up will occur 2-weekly (±5 days) from 2 weeks after the EOT visit up to Day 180. During the Follow-Up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone call to capture the suspicious ADE occurrence.

Patients will undergo the procedures at the time points specified in Table 1. If investigator considered ADE occurrence, all assessments specified in Table 2 will be conducted as unscheduled visit or, if required, all assessments can be done at any time, rather than waiting for the next scheduled visit.

4 Patient Selection and Withdrawal Criteria

It is expected that approximately 700 patients will be enrolled at approximately 60 study centers in 10 countries. Male or female patients, aged 18 years or older with SARS-CoV-2 infection, hospitalized, no more than 10 days prior to the study drug administration from the onset of symptom and no more than 4 days from the confirmation of SARS-CoV-2 infection by RT-PCR at local laboratory, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be randomized in this study:

1. Patient is male or female aged 18 years or older.
2. Patient has local laboratory confirmation of SARS-CoV-2 infection by RT- PCR from the upper or lower respiratory tract specimens no more than 4 days prior to the administration of the study drug.

   Note: *If there is available test result confirmed as SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 4 days prior to the administration of the study drug) and that result was from the RT-PCR by the upper or lower respiratory tract specimen, that test result can be allowed.*

   Note: *During the Screening Period, only one re-test for RT-PCR will be allowed if study drug can be administered no more than 10 days from onset of symptom based on re-test results.*
3. Onset of symptom no more than 10 days prior to the administration of the study drug.
4. Patient with conditions meeting the following criteria, and currently hospitalized (or will be hospitalized prior to the administration of the study drug):
   a. Oxygen saturation ≤ 94% on room air and/or PaO_2/FiO_2 ratio ≤ 300mmHg, AND
   b. Requiring supplemental oxygen.
5. Patient with abnormal radiographic findings in lung suggestive of SARS-CoV-2 infection by investigator’s discretion.
6. Patient's weight is of ≤ 99.9 kg.

7. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any study specific procedures.

8. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study (up to 6 months after the study drug administration) as specified in Section 6.2.2.7.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patient who is requiring extracorporeal membrane oxygenation (ECMO), or invasive mechanical ventilation.

2. Patient had a history of and/or concurrent use of medications including any therapy of following(s):

    a. Drugs with possible anti-SARS-CoV-2 activity or immunomodulators including but not limited to remdesivir, chloroquine, hydroxychloroquine, dexamethasone (alternative corticosteroids to dexamethasone), tocilizumab, sarilumab, and other immunomodulatory agents and human immunodeficiency virus (HIV) protease inhibitors for therapeutic purpose of SARS-CoV-2 infection prior to the study drug administration.

    Note: *During the study, authorized drugs (or drugs approved for emergency use) against SARS-CoV-2 infection such as remdesivir or dexamethasone (alternative corticosteroids to dexamethasone), could be used by investigator's discretion considering the local practice where there is available supply.*

    b. Any SARS-CoV-2 human intravenous immunoglobulin (hIVIG), convalescent plasma from a person who recovered from SARS-CoV-2 infection or SARS-CoV-2 nMAb for the treatment of SARS-CoV-2 infection prior to the study drug administration.

    c. Any other investigational device or medical product including but not limited to any monoclonal antibody, fusion proteins or biologics for the treatment of SARS-CoV-2 infection prior to the study drug administration.

    d. Use of medications that are contraindicated with SoC.

    e. SARS-CoV-2 vaccine prior to the study drug administration.

3. Patient has known allergy or hypersensitivity reaction to any monoclonal antibody or to any

components of study drug.

4. Patient has a history of and/or current disease or medical condition including any of following(s):
    a. Any active malignancy.
    b. Known severe liver disease (e.g., cirrhosis or an Alanine Aminotransferase [ALT] level >5 × upper limit of normal [ULN] or an Aspartate Aminotransferase [AST] level >5 × the ULN).
    c. Renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis.
    d. Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment groups.
    e. Stroke or myocardial infarction, which is suspected to be related to SARS-CoV-2 infection after the onset of symptom.
    f. Documented current infection with HIV, hepatitis B or hepatitis C.
5. Patient who has received any other investigational device or medical product within 4 weeks prior to the study drug administration or 5 half-lives, whichever is longer.
6. Patient currently abuses alcohol or drugs.
7. Patient is not eligible for the study participation for whatever reason (including clinical laboratory results) in the opinion of the investigator, or shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limited the ability of the patient to comply with the protocol requirements in the opinion of the investigator, or unable to understand the protocol requirements, instructions and study related restrictions, the nature, scope and possible consequences of the clinical study, or is unable to give written informed consent or to comply fully with the protocol.
8. Anticipated transfer to another hospital which is not a study site.
9. Female patient who is currently pregnant or breastfeeding or planning to be pregnant or to breastfeed, or male patient is planning to father a child or donate sperms throughout the study (up to 6 months after the study drug administration).

4.2 Withdrawal/Discontinuation of Patients from the Study

Patients are free to withdraw/discontinue from the study at any time for any reason. The investigator may also withdraw/discontinue the study at any time in the interest of patient safety. The primary reason for the study withdrawal/discontinuation must be recorded in the patient's medical record and in the electronic case report form (eCRF), with any comments (spontaneous or elicited) or complaints made by the patient.

As it is vital to obtain follow-up data on any patient withdrawn/discontinued because of an AE or serious AE (SAE) in every case, efforts must be made to undertake protocol-specified safety and follow-up procedures. For patients who early withdraw for any reason, all study procedures should be performed on the day of withdrawal (or the day after withdrawal) and all attempts should be made to complete all EOT assessments (patient will be asked to return to the study site on the next scheduled visit). For patients who discontinued during the Follow-Up Period, the reason of discontinuation will be recorded eCRF.

Reason for study withdrawal/discontinuation include the following:

- Withdrawal of consent
- Lost to follow-up
- Protocol deviation
- Adverse event
- Death
- Investigator's decision
- Study termination

If necessary, the investigator may discuss with sponsor or its designee any patient's reason for withdrawal/discontinuation. The sponsor may be contacted if clarification is required on a case-by-case basis. All patients who are withdrawn/discontinued from the study will retain their patient number.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and withdraw/discontinue before the study completion will not be replaced. Patients who are screen failed, for any reason, can be rescreened only once. Rescreened patient will be assigned with new patient identification number.

4.3 Premature Termination of the Study

Reason for premature termination of this study may include a failing to meet the requirements of regulatory authority, change in opinion of the independent ethics committee (IEC)/ institutional review board (IRB), unexpected or significant safety risk, or at the discretion of sponsor. The DSMB will thoroughly review and evaluate the efficacy (for Part 1) and safety data of study patients, and provide recommendations regarding the acceptability of continuing the study based on the efficacy (for Part 1) and safety monitoring. For the review of all available data from Part 1, the study will be temporarily paused and will be progressed to Part 2 if there are evidence of a potential treatment benefit and no safety concerns may suggest risk to the patients. Further details are specified in Section 10.3.1.

The sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is terminated prematurely by the sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the IRB or IEC, where applicable, of any premature termination or suspension of the study.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Group

Randomization will be performed using an interactive voice response system (IVRS) or interactive web response system (IWRS). Unblinded biostatisticians will generate the randomization schedule for IVRS or IWRS, which will link sequential patient randomization numbers to treatment codes. The randomization numbers will be blocked, and within each block the pre-specified ratio of patients will be allocated to each treatment group. The block size will not be revealed.

The randomization will be stratified as followings:

- Region
- Disease severity based on an 8-point ordinal scale (5 vs. 6)
- Age (≥ 60 years vs. < 60 years)

5.2 Identity of CT-P59

CT-P59 is a monoclonal antibody which is being developed by the Sponsor as a potential treatment for SARS-CoV-2 infection.

CT-P59 is supplied as a sterile, preservative-free solution of SARS-CoV-2 RBD binding monoclonal antibody in a 20 mL single use vial for IV administration. CT-P59 is a clear to opalescent, colorless to pale yellow solution for injection, with a pH of 6.0 and 960 mg of SARS-CoV-2 RBD binding monoclonal antibody in 16 mL for IV administration. One vial (16 mL) delivers 960 mg SARS-CoV-2 RBD binding monoclonal antibody, 13.12 mg of L-histidine, 15.84 mg of L-histidine monohydrochloride monohydrate, 8.0 mg of polysorbate 80, 505.584 mg of L-Arginine monohydrochloride, and water for injection. The container closure system includes type I borosilicate glass vial, Fluroetec Film coated rubber stopper and flip-off type aluminum cap.

5.3 Identity of Placebo

Placebo contains the same ingredient as the CT-P59 formulation listed in Section 5.2, excluding SARS-CoV-2 RBD binding monoclonal antibody. Each Placebo vial contains 13.12 mg of L-histidine, 15.84 mg of L-histidine monohydrochloride monohydrate, 8.0 mg of polysorbate 80, 505.584 mg of L-Arginine monohydrochloride, and water for injection in 16 mL. The pH of the placebo solution is 6.0. The container closure system includes type I borosilicate glass vial, Fluroetec Film coated rubber stopper and flip-off type aluminum cap.

5.4 Treatment Administered

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned to one of 2 treatment groups, CT-P59 or Placebo, according to randomization scheme. On day 1, the CT-P59 or Placebo will be administered as an IV administration over 90 minutes (±15 minutes) with SoC.

Patients will receive study drug as follows:

- Treatment Group 1: CT-P59 80 mg/kg
- Treatment Group 2: Placebo 80 mg/kg

A 250 mL administration solution of 0.9% weight/volume sodium chloride will be used for patient administration. The bag will be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions will be inspected visually for particulates and discoloration prior to administration and administration will not be performed if any particulates and discoloration are found. The detailed method about mixing the solution will be described in the pharmacy manual.

When calculating total volume of study drug to be administered, the body weight of each patient measured on the administration of study drug date (Day 1) will be used. Placebo will be administered as in the same volume as the active dose used for CT-P59.

5.5 Management of Clinical Supplies

5.5.1 Study Drug Package, Labelling, and Storage

The appropriate number of study drug will be allocated to each patient via IVRS or IWRS system.

A label will be attached to the outside of each patient kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Patient number/site number
- Contents and quantity
- Lot number
- Randomization code/kit number

- Investigator’s name
- Route of administration
- Direction for use
- Storage instructions
- Caution statement (for clinical trial use only)
- Sponsor’s contact name and address
- Expiry date

Study drug (CT-P59 or Placebo) in a vial should be stored in a refrigerator between 2°C and 8°C and not frozen. It should be kept in its original outer packaging to protect it from light and it should not be shaken.

5.5.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. If case an on-site monitoring visit cannot be made because of SARS-CoV-2 pandemic situation, the sponsor and contract research organization (CRO) will be discussed with clinical investigator. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

The investigator agrees not to supply the study drug to any person other than sub-investigators, designated staffs, and the patients participating in the study. Study drug may not be relabeled or reassigned for use by other patients unless approved by the sponsor.

The investigator will return or destroy all study drugs according to the pharmacy manual. The investigator will destroy empty or partially used vials in a blinded manner as well as its cartons after reconstitution per site standard operating procedure (SOP), and keep tear-off labels for accountability. This authorization may also be granted to destroy used vials immediately after administering to patients. The list of destroyed vials must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with the sponsor. Details on study drugs accountability and destruction will be followed according to the pharmacy manual.

5.6 Blinding

This study will be double-blind, and will remain blinded to the investigator, all designated study

staff (with the exception of the unblinded study pharmacists or unblinded staff designated to prepare the study drug for administration and predefined unblinded teams in the Sponsor and CRO), and patients until the final clinical study report (CSR) is generated.

5.6.1 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should only be broken if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management or regulatory requirement (e.g., for SAE, death or report the clinical activity). In such cases, the investigator may, in emergency, determine the identity of the study drug by using the IVRS or IWRS.

The date, time and reason for the unblinding must be documented in the source documents and the appropriate field of the eCRF. The medical monitor will be informed as soon as possible. All unblinding events will be reported to the medical monitor and the sponsor. Any patients for whom the blind is broken may continue in the study at the investigator's discretion.

The study will be unblinded to the predefined unblinded teams of sponsor and/or CRO after completion of the day 28 assessments of the last enrolled patient in Part 2. The overall randomization code will be broken only for reporting purposes after completion of the day 28 assessments of the last enrolled patient in Part 2. However, the study drug assignment will remain blinded to the investigators, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staff designated to prepare the study drug for administration and predefined unblinded teams in the sponsor and CRO), and patients until the final CSR is generated.

The DSMB and the predefined statistician(s) who provides the safety or interim analyses for the DSMB will be unblinded upon the request from DSMB members during closed session.

5.7 Treatment Compliance

Patient compliance will be determined based on drug accountability as well as source documents. The date and time of the study drug administration will be documented and every effort will be made to encourage the patients' compliance with the study visits.

5.8 Prior and Concomitant Therapy

Any medical product, such as prescribed drug (including SoC) or over-the-counter drug, including herbal and other non-traditional remedies, is considered as a concomitant medication. Prior and concomitant medication will be recorded for the 30 days prior to the patient signs the ICF (inclusive of the applicable periods for prohibited medication as defined in Section 4.1.2) until the EOT. Use of SoC will also be properly recorded. Concomitant medication is permitted

if indicated by the investigator for treatment of AE.

5.9 Prohibited Therapy

The following medications and treatments are prohibited during the study. Patients who have received or plan to receive these prohibited medications or treatment will not be enrolled in the study (see Section 4.1.2 for exclusion criteria).

- Any agents with actual or possible anti-SARS-CoV-2 activity or immunomodulators for the therapeutic purpose of SARS-CoV-2 infection

  Note: *Authorized drugs (or drugs approved for emergency use) against SARS-CoV-2 infection such as remdesivir or dexamethasone (alternative corticosteroids to dexamethasone), could be used by investigator's discretion considering the local practice where there is available supply.*

- Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from SARS-CoV-2 infection or SARS-CoV-2 nMAb
- Any other investigational device or medical product including but not limited to any monoclonal antibody, fusion proteins or biologics for the treatment of SARS-CoV-2 infection
- Medications that are contraindicated with SoC that could not be replaced or stopped during the trial period

6 Study Assessments and Procedures

Before performing any study procedures, all potential patients will be informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, before signing and dating the ICF. The investigator will respond to any questions raised by the patient. The investigator will also sign the ICF.

Patients will undergo the procedures at the time points specified in Table 1. If investigator considered ADE occurrence, all assessments specified in Table 2 will be conducted as unscheduled visit or, if required, all assessments can be done at any time, rather than waiting for the next scheduled visit (Table 1).

6.1 Efficacy Assessments

6.1.1 Ordinal Scale

The investigator will assess the patients' clinical status using 8-point ordinal scale (Beigel et al., 2020; Appendix 12.2) once daily (at approximately 24-hour intervals) during the hospitalized period. For outpatients, subsequent assessment will be performed at the specified time points (Table 1 and Table 2). This ordinal outcome included 8 well-defined mutually exclusive categories, each which assesses further progression of disease, as well as recovery from SARS-CoV-2 infection, as follows:

1) Not hospitalized, no limitations of activities;
2) Not hospitalized, limitation of activities, home oxygen requirement, or both;
3) Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons);
4) Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (SARS-CoV-2 – related or other medical conditions);
5) Hospitalized, requiring any supplemental oxygen;
6) Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
7) Hospitalized, receiving invasive mechanical ventilation or ECMO;
8) Death

The worst clinical status (i.e., the highest ordinal scale) of the day will be recorded for each assessment.

6.1.2 Intensive care unit transfer

The information of intensive care unit transfer during the study (from signing of ICF to end of study participation [EOS]) will be recorded in the eCRF and source documents. Information to be collected includes the transfer and discharge date for the intensive care unit.

6.1.3 Hospitalization

The information of hospitalization during the study (from signing of ICF to EOS) will be recorded in the eCRF and source documents. Information to be collected includes the start and end date of hospitalization.

6.1.4 Requirement of supplemental oxygen

The information of supplemental oxygen during the study (from signing of ICF to EOS) will be recorded in the eCRF and source documents. Information to be collected includes the start and end date of supplemental oxygen.

6.1.5 Mechanical ventilation use

The information of mechanical ventilation use during the study (from signing of ICF to EOS) will be recorded in the eCRF and source documents. Information to be collected includes type of mechanical ventilation and the start and end date of mechanical ventilation use.

6.1.6 National Early Warning Score (NEWS)

The information of National Early Warning Score (NEWS) (Appendix 12.3) assessed at the time points specified in the schedule of assessments (Table 1 and Table 2) will be recorded in the eCRF and source documents.

6.2 Safety Assessments

Safety assessments include monitoring of AEs (including SAEs and adverse events of special interest [AESI: infusion related reactions including hypersensitivity and anaphylactic reactions]), potential effects on the incidence of ADE, immunogenicity including anti-drug antibodies and neutralizing antibodies, vital signs, hypersensitivity monitoring, 12-lead ECG, SARS-CoV-2 infection related signs and symptoms, radiography (chest x-ray or chest computed tomography [CT]), physical examination, clinical laboratory tests, pregnancy tests, and prior and concomitant medications.

6.2.1 Adverse Events

6.2.1.1 Definition of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. An AE is defined as any untoward medical occurrence in a patient during the study which does not necessarily have a causal relationship with the study drug. Patients will be instructed to contact the investigator at any time after the ICF was signed if any symptoms develop. Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent AE (TEAE).

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Treatment due to an AE will be recorded.

A TEAE is any untoward medical occurrence in a patient after administration of a study drug, which does not necessarily have to have a causal relationship with this the study drug. A TEAE can therefore be any unfavorable and unintended sign (including laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Abnormal results of diagnostic procedures including laboratory test abnormalities are considered as AEs if they fulfill the following criteria:

- Result in discontinuation from the study drug
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are clinically significant as evaluated by the investigator

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.2.1.1.1 Adverse Events of Special Interest

Infusion related reactions (hypersensitivity/anaphylactic reactions) is considered as AESI because TEAE related to infusion related reactions (hypersensitivity/anaphylactic reactions) is typical in monoclonal antibody therapy, and will be reported using the same process as for AEs.

6.2.1.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening (refers to an AE in which the patient is at immediate risk of death at the time of event). It does not refer to an event which may have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening, result in death, or require hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. These should also be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered as SAEs. Any admission (even if < 24 hours) to a healthcare facility meets these criteria. Admission also include transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)

- Social admission (e.g., patient has no place to sleep)
- Purely for convenience (e.g., for easier performance of study assessments)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient

6.2.1.1.3 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., IB) for an unapproved investigational product.

6.2.1.1.4 Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all suspected Unexpected Serious Adverse Reactions against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the sponsor will assess the expectedness of these events using the applicable reference documents (e.g., IB).

Reporting requirements will also be based on the investigator’s assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.2.1.2 Eliciting and Documenting Adverse Events

All AEs will be reported by the investigator via eCRF from the date patients signs the ICF until EOT visit, regardless of the relationship to the study drug. Where an adverse drug reaction (ADR) (i.e., related to study drug) is ongoing at the EOT visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure.

At every study visit, patient will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF and source documents. Information to be collected includes drug treatment, action taken with study drug, event term, date/time of onset and end date, investigator-specified assessment of severity and relationship to study drug, seriousness of AE, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illness, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported from the date patients signs the ICF until EOT visit.

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE. The investigator’s assessment of an AE’s relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Section 6.2.1.6 and Section 6.2.1.7, respectively.

All AEs (and SAEs) should be reported until the EOT visit regardless of the relationship of the study drug. After the EOT visit, serious adverse drug reactions will be reported to the sponsor or its designee.

6.2.1.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.2.1.1.2) must be reported to PPD PVG within 24 hours from the time study center staff first learn about the event and during normal business hours. The following contact information is to be used for SAE reporting:

Medical Affairs/Pharmacovigilance
PPD PVG
EMEA/APAC SAE Hotline: +44 1223 374240
EMEA/APAC SAE Fax line: +44 1223 374102
NA back-up SAE Hotline (IDMC): +1 800 201 8725
NA back-up SAE Fax line (IDMC): +1 888 488 9697
LA SAE Hotline: +55 114 504 4801
LA SAE Fax line: +55 11 3958 0983
SAE Email: emeaasiasafetycentral.sm@ppdi.com

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax it to PPD PVG within 24 hours of awareness of the event. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or sub-investigator. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the patient to be stable.

The sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

The sponsor or its designee is responsible for reporting unexpected fatal or life-threatening Suspected Unexpected Serious Adverse Reaction (expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The sponsor or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

6.2.1.5 Follow-up of Adverse Events

Where an adverse drug reaction (ADR) (e.g., related to study drug) is ongoing at the EOT visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure.

6.2.1.6 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE Version 5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[1]

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an AE upgrades in severity or changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in severity, it should not be reported as a new AE. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.1.7 Assessments of Causality

As discussed in Section 6.2.1.3, the investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, e.g., the events follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease states, or concurrent medication reaction) do not appear to explain the event.

6.2.2 Other Safety Assessments

6.2.2.1 Immunogenicity Assessments

The immunogenicity of CT-P59 will be assessed by anti-drug antibody and neutralizing antibody test in validated immunoassay. Blood samples for immunogenicity assessments will be collected prior to dosing at the time points specified in the schedule of assessments (Table 1). If the blood sample is unable to be analyzed or is missing, extra blood samples collected for PK assessment at the same time point can be used for immunogenicity assessment. Additional serum samples for immunogenicity testing may be collected when immune-related AEs occur.

Analysis will be performed at the central laboratory.

6.2.2.2 Hypersensitivity Monitoring

Hypersensitivity will be assessed at the time points specified in the schedule of assessments (Table 1).

Additional vital sign measurements including blood pressure, heart and respiratory rates, and body temperature will be evaluated for possible hypersensitivity reactions.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed if a patient experiences cardiac symptoms.

For patients who experience or develop life threatening treatment-related hypersensitivity reactions, study drug must be stopped immediately.

Details will be recorded in both the source documents and the eCRF.

6.2.2.3 Vital Signs, Weight, and Height

Vital signs, weight and height measurements will be performed at the time points specified in the schedule of assessments (Table 1 and Table 2). Vital signs (including blood pressure, heart and respiratory rates, body temperature and SpO_2) will be assessed before the study drug administration and be measured after 5 minutes of rest. SpO_2 will be measured while breathing normal room air (If not possible, PaO_2/FiO_2 ratio can be measured as alternatives). Height will be assessed at Screening only as a baseline measurement. All other measurements will be documented at each study center visit. Details will be recorded in both the eCRFs and source documents.

Additional vital sign measurements will also be monitored before and after the study drug administration as part of the hypersensitivity monitoring (Section 6.2.2.2).

6.2.2.4 Electrocardiogram

All scheduled 12-lead ECGs will be performed after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of assessments (Table 1 and Table 2) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The investigator will then report the event in the eCRF and source documents. Regardless of 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion.

In case of hypersensitivity, any type of ECG can be performed (Section 6.2.2.2).

6.2.2.5 Physical Examination

Physical examination will be performed before study drug administration at the time points specified in the schedule of assessments (Table 1).

Information about the physical examination will be recorded by the investigator or designee in the eCRF and source documents. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded in the eCRF and source documents.

6.2.2.6 Hepatitis B, Hepatitis C, and Human Immunodeficiency Viruses-1 and -2

Documented infection with hepatitis B, hepatitis C or HIV data available before signing the ICF can be used for the Screening assessment for eligibility confirmation and only patients confirmed negative and patients with unknown status of infection will be eligible and enrolled in the study

Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody, hepatitis C virus (HCV) RNA, and HIV-1 and -2 tests will be performed in all patients at the central laboratory.

6.2.2.7 Pregnancy

Pregnancy test (serum or urine, where applicable) will be conducted for female patients with childbearing potential at the time points specified in the schedule of assessments (Table 1). Only patients who are confirmed as nonpregnant can be enrolled in the study.

Pregnancy test samples will be analyzed at the local laboratory.

In an event of unexpected pregnancy throughout the study (up to 6 months after the study drug administration), patients will be counselled to inform the investigator. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to the sponsor and PPD within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Even if the pregnancy is confirmed with a pregnancy test, female patients will not be withdrawn from the study and will be followed up. Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to the sponsor and PPD within 24 hours.

Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.2.1.4).

To prevent pregnancy, a highly effective method of birth control should be used correctly and consistently from inform consent date to 6 months after the study drug administration in patients and their partner of childbearing potential. A highly effective method of birth control may be defined as those which result in a low failure rate (e.g., <1% per year, when used consistently and correctly). Examples of acceptable forms of highly effective contraception for females include followings:

- Sexual abstinence,
- Simultaneous use of hormonal contraceptives starting at least 4 weeks before the study drug administration and must agree to use the same hormonal contraceptive throughout the study and condom for the male partner,
- Simultaneous use of intra-uterine contraceptive device placed at least 4 weeks before the study drug administration and condom for male partner,
- A sterilized male partner (vasectomized at least 6 months before the study drug administration)

Examples of acceptable forms of highly effective contraception for male patients include;

- Sexual abstinence
- Simultaneous use of a male condom and hormonal contraceptives use or intra-uterine contraceptive device at least 4 weeks before the study drug administration for the female partner

Examples of non-acceptable methods of contraception include solo use of a barrier method (including use of diaphragm, cervical cap or condom), periodic abstinence, the withdrawal method, or use of spermicide.

6.2.2.8 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments including clinical chemistry, hematology, and urinalysis will be collected at the time points specified in the schedule of event (Table 1 and Table 2). To determine eligibility, clinical laboratory testing will be performed at the local laboratory at Screening. All clinical laboratory test for all visits will also be analyzed at the central laboratory (except erythrocyte sedimentation rate).

Clinical chemistry: Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ-glutamyl transferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-myocardial band isoenzyme, troponin (I or T, [only one applicable]), albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP

Hematology: Red blood cells, erythrocyte sedimentation rate, total white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit

Urinalysis: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination of white blood cell count, red blood cell count, and bacteria

Coagulation: Prothrombin International Normalized Ratio, activated partial thromboplastin time, D-dimer

6.2.2.9 Radiography

Radiography (chest x-ray or chest CT) will be performed at the scheduled time points specified in the schedule of assessments (Table 1) and when the investigator considers it is clinically necessary (e.g., abnormal findings of SpO_2).

6.2.2.10 SARS-CoV-2 Infection Related Signs and Symptoms

The Investigator or designee will perform a respiratory signs and symptoms assessment (which could include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and assessment for potential complications of SARS-CoV-2 infection at the scheduled time points specified in the schedule of assessments (Table 1 and Table 2).

6.2.2.11 SARS-CoV-2 Infection Symptom Checklist

If patients discharge before Day 28, any signs and symptoms of SARS-Cov-2 infection will be captured on the patient diary for SARS-CoV-2 Infection Symptom Checklist (Appendix 12.4). Patients will complete the checklist once daily (at approximately 24-hour intervals) up to Day 28 (Table 1). Patients will complete the checklist during the suspicious ADE Follow-Up period as well (Table 2). Any signs and symptoms of SARS-CoV-2 infection captured on SARS-CoV-2 Infection Symptom Checklist will not be reported as AEs.

SARS-CoV-2 Infection Symptom Checklist consists of 7 symptoms and the intensity of patient's self-aware for each SARS-CoV-2 infection symptom. The 7 symptoms of SARS-CoV-2 infection are feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache. Scores for SARS-CoV-2 infection symptom are absent (0), mild (1), moderate (2), and severe (3), defined as below:

- Mild: no interference with normal daily activity
- Moderate: interference with normal daily activity
- Severe: prevents normal daily activity

The worst severity (i.e., the highest severity) of symptoms of the day will be recorded for each assessment. A full SARS-CoV-2 Infection Symptom Checklist is described in Appendix 12.4.

6.2.2.12 Potential Effects of the Incidence of Antibody-dependent Enhancement

Occurrence of ADE of SARS-CoV-2 infection may advocate cautious development of SARS-CoV-2 antibody in human, and provide new ways of investigation to understand the pathogenesis of SARS.

Patients with suspicious ADE occurrence is defined as following:

- If patient has excessive progression of symptoms regarded as related to viral infection (e.g., excessive infiltration of inflammatory cells in the lung), OR
- If patient has other SARS-CoV-2 infection related signs and symptoms which are judged as possible manifestations of ADE according to the medical opinion of the investigator

If a patient meets any of the criteria for suspicious ADE, additional evaluations will be performed as specified in Table 2 during the Treatment Period, EOT, and Follow-Up period. Those patients will need to record the Patients diary for SARS-CoV-2 Infection Symptom Checklist for 7 days from the day of suspicious ADE occurrence. If symptoms have not resolved or have worsened up to Day 7 after the day of suspicious ADE occurrence, same procedure will repeat until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

6.3 Virology Assessments

The information of virology during the study (from signing of ICF to EOT) will be recorded in the eCRF and source documents. Viral shedding (RT-qPCR and cell culture), genotyping and phenotyping of SARS-CoV-2 isolates will be performed using the biologic samples. Test for detecting serum antibodies against SARS-CoV-2 (e.g., IgG and IgM etc.) will be performed using the blood samples if the test kit supply is available. Samples for viral shedding, genotyping and phenotyping will be secured for analysis and backup samples will be retained.

Samples for virology assessments will be collected at the time points specified in the schedule of assessment (Table 1 and Table 2). Among collected samples, genotyping and phenotyping will be performed on the samples including but not limited to the ones with suspected resistance.

6.4 Pharmacokinetic Assessments (Optional)

Blood samples for analysis of study drug concentration in the serum will only be obtained from patients who signed a separate ICF for the PK assessment, at the time points specified in the schedule of events (Table 1). For the patients, the total number of blood samples for analysis of study drug concentration will be 10 blood samples per patient.

Actual sampling times for each patient will be recorded in the patient’s eCRF and individual source documents. See Section 6.5.1 and Section 7.6.4.1 for further information on PK blood sampling and the PK endpoints.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual. Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.1 Pharmacokinetic Blood Sampling

Pharmacokinetic samples will be collected for analysis at the time points specified in the schedule of assessments (Table 1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Table 1) or when immune-related AEs occur. All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.3 Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing), pregnancy test and/or SARS-CoV-2 specific antibody will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Table 1).

6.5.4 Virology Sampling

Virology samples will be collected for analysis at the time points specified in the schedule of assessments (Table 1 and Table 2). All samples should be collected as close as possible to the scheduled time point. For central laboratory, the actual sampling date and time will be recorded in both the eCRF and source documents. For SARS-CoV-2 antibody test, the actual sampling date will be recorded in both the eCRF and source documents.

6.6 Labelling, Storage, and Transportation of Samples

6.6.1 Sample Labelling

Each sample tube will be clearly labelled with the following information: study number, study center number, patient number, tube identification and the scheduled sampling time by day (and hour, when necessary).

6.6.2 Sample Storage and Shipment

During the study, blood samples for PK, immunogenicity, and safety analyses and virology samples will be collected. Blood samples for PK and immunogenicity and virology samples will be transferred to the central laboratories.

Additionally, back-up sample for PK, immunogenicity and virology should be retained at the central laboratory as a backup for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK and immunogenicity is not required, the sample will be stored at the sponsor or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by the sponsor to destroy the sample. Additional tests can be conducted at the sponsor or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual. Virology samples will be secured at the central laboratory for analysis and backup samples will be retained. The samples can be destroyed by a specific authorization of the sponsor.

7 Statistical Analysis Plan

The statistical methods for this study will be described in a detailed Statistical Analysis Plan (SAP).

Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the CSR.

7.1 Primary Endpoints

The 8-point ordinal scale will be evaluated as primary endpoint (Section 6.1.1);

- Time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2 or 3 on the 8-point ordinal scale for 7 days.

7.2 Secondary Endpoints

7.2.1 Efficacy Endpoints

Secondary efficacy and safety endpoints will be analyzed throughout the study.

The following parameters for the study drug will be determined as secondary endpoints:

- Proportion of recovered patients on Day 7, 14 and 28
- Proportion of intensive care unit transfer on Day 14 and 28
- Mortality rate on Day 14, 28 and 90
- Clinical status by the 8-point ordinal scale on Day 7, 14 and 28
- Time to improvement of at least 1 point from the status at baseline by 8-point ordinal scale up to Day 28
- Change from baseline of the 8-point ordinal scale on Day 7, 14 and 28
- Duration of hospitalization in survivors up to Day 28
- Number of free days of supplemental oxygen up to Day 28
- Proportion of new mechanical ventilation use on Day 14 and 28
- Change from baseline of National Early Warning Score (NEWS) on Day 7, 14 and 28

7.2.2 Safety Endpoints

The safety endpoints will be assessed using the followings: AEs (including SAEs and AESI),

potential effects on the incidence of ADE, immunogenicity, vital signs, hypersensitivity monitoring, ECG findings, SARS-CoV-2 infection related signs and symptoms, radiography (chest x-ray or chest CT), physical examination findings, clinical laboratory tests, pregnancy tests, and prior and concomitant medications.

7.2.3 Exploratory Endpoints

Exploratory PK (optional, only for PK Cohort) and virology endpoints will be analyzed throughout the study.

7.2.3.1 Pharmacokinetic Endpoints

The following PK parameters for the study will be determined as exploratory PK endpoints for PK Cohort only:

- $AUC_{0\text{-last}}$: Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
- $AUC_{0\text{-inf}}$: Area under the concentration-time curve from time zero extrapolated to infinity
- C_{max}: Maximum concentration
- T_{max}: Time to C_{max}
- λ_z: Terminal elimination rate constant
- $T_{1/2}$: Terminal half-life
- CL: Total body clearance
- V_z: Apparent volume of distribution during terminal phase
- $\%AUC_{ext}$: Percent of $AUC_{0\text{-inf}}$ obtained by extrapolation

7.2.3.2 Virology Endpoints

- Viral shedding in upper or lower respiratory tract based on RT-qPCR and cell culture
- Genotype and phenotype of SARS-CoV-2 viral isolates
- SARS-CoV-2 antibody test detecting serum antibodies against SARS-CoV-2

7.3 Sample Size Calculation

For the primary efficacy endpoint, approximately 400 recovery events in hospitalized patients with SARS-CoV-2 infection are required for a power of 85% at a significance level of 5% (two-

sided test) to detect a recovery rate ratio 1.35 up to Day 28 based on Schoenfeld D., 1981.

Considering the overall recovery rate of 57%, a total 700 hospitalized patients (350 patients per treatment group) with SARS-CoV-2 infection will be enrolled in a 1:1 ratio to the CT-P59 or Placebo in this study. A reassessment of sample size after review of data up to Day 28 of the approximately 200th patient will be considered by DSMB.

7.4 Analysis Set

The following analysis sets will be used in the statistical analyses.

Intent-to-treat (ITT) Set: The ITT Set is defined as all randomly assigned patients to study drug.

Safety Set: The Safety Set is defined as all randomly assigned patients who receive a complete or partial dose of study drug.

Intent-to-treat infected (ITTI) Set: The ITTI Set is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-administration result (Day 1) of RT-qPCR or cell culture, who receive a complete dose of study drug.

Pharmacokinetic Set: The PK Set is defined as all randomly assigned patients who receive a complete dose of study drug and have at least one evaluable post treatment PK result.

7.5 Description of Subgroups to be Analyzed

Subgroup analysis could be implemented to reflect medical, regulatory, regional or ethnic consideration, and important stratification variables.

7.6 Statistical Analysis Methodology

7.6.1 General Consideration

Statistical analyses will be conducted using SAS software version 9.4 or later (SAS Institute Inc., Cary, North Carolina, United States of America [USA]).

Continuous variables will be summarized using descriptive statistics including the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

Data for each Part will be independently analyzed and presented, unless otherwise specified.

Pharmacokinetic parameters will be computed by noncompartmental methods using the appropriate validated software WinNonlin (Pharsight, St Louis, Missouri).

7.6.2 Efficacy Analyses

The primary efficacy endpoint, time to recovery up to Day 28, will be analyzed on the ITT Set presenting the p-value from a stratified log rank test, and stratified by region (United States vs. Asia Pacific vs. European Union vs. Other), disease severity based on a 8-point ordinal scale (5 vs. 6) and age (≥ 60 years vs. < 60 years) at the 2-sided significance level of 0.05. Additionally, receiving remdesivir and/or dexamethasone (alternative corticosteroids to dexamethasone) before achieving primary endpoint (Yes vs. No) will be considered as strata in stratified log rank test. The 25% percentile, 50% percentile (median), 75% percentile recovery time and 95% confidence interval (CI) for each treatment group will be presented using the Kaplan-Meier method. Hazard ratio and associated 95% CI will also be estimated using stratified cox proportional hazard model. The supportive analysis for primary endpoint will be performed in the ITTI Set. The sensitivity analysis of primary endpoint will be performed on the ITT Set using an unstratified log rank test.

For the primary efficacy endpoint, time to recovery up to Day 28, any patients that are lost to follow-up or discontinued/terminated early prior to an observed recovery and complete follow-up but do not experience recovery will be censored and time will be considered as 28 days. All deaths within Day 28 (and prior to recovery) will be censored and time will be considered as 28 days.

The secondary efficacy endpoints will be treated as follows;

- Proportion of recovered patients on Day 7, 14 and 28
- Proportion of intensive care unit transfer on Day 14 and 28
- Mortality rate on Day 14, 28 and 90
- Clinical status by the 8-point ordinal scale on Day 7, 14 and 28
- Time to improvement of at least 1 point from the status at baseline by 8-point ordinal scale up to Day 28
- Change from baseline of the 8-point ordinal scale on Day 7, 14 and 28
- Duration of hospitalization in survivors up to Day 28
- Number of free days of supplemental oxygen up to Day 28
- Proportion of new mechanical ventilation use on Day 14 and 28
- Change from baseline of NEWS on Day 7, 14 and 28

The results of secondary efficacy analyses will be presented using descriptive statistics or frequency tables. All secondary efficacy endpoints will be analyzed on both the ITT Set and

ITTI Set.

All efficacy data will be listed and summarized by treatment, where appropriate.

7.6.3 Safety Analyses

The safety evaluations detained in Section 6.2 will be performed during the study to measure the safety of study drug. Further details will be presented in the SAP as appropriate. The safety analyses will be performed using the Safety Set. The safety results including ADE and immunogenicity will be listed and summarized by treatment group. The results of other safety analyses will be presented using descriptive statistics or shift tables, as appropriate. Terminology and severity grading of AEs will be recorded according to the CTCAE Version 5.0. Adverse events will be coded to system organ class and preferred term according to the MedDRA. Serious adverse events and AESIs will be summarized separately. Prior and concomitant medications will be coded to drug class and preferred term using the WHO drug dictionary.

7.6.3.1 Other Safety Analyses

Demographics (e.g., age, sex, and race etc.), baseline and background characteristics will be summarized. Qualitative data (e.g., medical history) will be summarized in contingency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

7.6.4 Exploratory Analysis

7.6.4.1 Pharmacokinetic Analyses

All PK analyses will be conducted in the PK Set. The PK parameters of CT-P59 will be analyzed using noncompartmental methods based on the actual sampling time points. All parameters will be calculated using Phoenix WinNonlin (Pharsight, St Louis, Missouri, USA).

Pharmacokinetic parameters of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $\lambda_{z,}$ $T_{1/2}$, CL, V_z and $\%AUC_{ext}$ will be presented in data listings and summarized at each scheduled visit using descriptive statistics.

Serum concentration data will be presented in data listings and summarized at each scheduled visit using descriptive statistics.

7.6.4.2 Virology Analysis

Viral efficacy (viral shedding in upper or lower respiratory tract based on RT-qPCR and cell culture) and characterization of SARS-CoV-2 viral isolate (genotype and phenotype) and SARS-CoV-2 antibody test detecting serum antibodies against SARS-CoV-2 (e.g., IgM and IgG etc.) will be analyzed on the ITTI Set. Actual values and change from baseline for viral shedding, percentage of patients with positive/negative viral shedding and SARS-CoV-2 antibody, duration (in days) of viral shedding, and AUC of viral levels will be summarized by treatment groups at each scheduled visit using descriptive statistics or frequency tables. Mean viral load titer (log values) for each scheduled time point will be plotted. Genotype, phenotype and SARS-CoV-2 antibody test results will be presented in data listing by treatment groups.

7.7 Interim Analysis

The analysis of Part 1 at Day 28 will be considered as an interim analysis for futility and safety. The DSMB will review interim data based on pre-specified guidelines in the DSMB charter.

7.8 Data Quality Assurance

Step to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff prior to the study, periodic monitoring visits by the sponsor or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRFs will be reviewed for accuracy and completeness by the monitor during on-site monitoring visits; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from the sponsor or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should immediately notify the sponsor or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

7.8.1 Data Management

It is the intent of this study to acquire study data via electronic format. As part of the

responsibilities assumed by participating in the study, the principal investigator or sub investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain source documentation (e.g., laboratory reports), to enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. For identification of source data, all data to be recorded on the eCRF must reflect to corresponding source documents. Indication for prior medication and concomitant medication drugs or therapies recorded directly on the eCRF is to be considered source data.

The eCRFs are accessed through the appropriate system, which allows for on-site data entry and data management. The electronic data capture system will be validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11.

Study center users can read from and write to the sponsor’s database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon account and password that allow for record traceability. Thus, the system, and subsequently any investigative reviews can identify coordinators, investigators and individuals who have entered or modified records. A quality review of the data will be performed by the study site with additional reviews by the clinical monitor through source data verification.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonized tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the data approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing risk to patients.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient or legal guardian understands the implications of participating in the study, the patient or legal guardian will be asked to give consent to participate in the study by signing the ICF. When legal guardian is not possible to present in the site, considering the pandemic situation of COVID-19, electronic form of ICF can be used.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The Patient’s right to withdraw from the clinical study at any time without giving reason and without jeopardizing the patient’s further course of medical treatment
- The existence of patient insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or sub-investigator and the patient’s legal representatives (according to the local regulations) before the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator’s study file. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IRB/IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRFs, that informed consent has been obtained.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject changed based on industry and government SOP, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendment.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities or the IRB/IEC.

The investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor its designee is financially responsible for further testing or treatment or any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Before beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulation by providing the following essential documents, including but not limited to:

- Independent review board/IEC approval

- Original investigator-signed investigator agreement page of the protocol
- Curriculum vitae for the principal investigator and each sub-investigator. Current licensure must be noted in the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and sub-investigators at the start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- Independent review board/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center.

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Reporting Requirements

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.2.1.4. In addition, the principal investigator or sub-investigator agrees to submit annual report to his or her IRB/IEC as appropriate.

9.7 Investigator’s Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide IRB/IEC with a summary of the study’s outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Record Retention

All correspondence (e.g., with sponsor, IRB/IEC, or Clinical Research Associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRFs, and drug inventory sheets pertaining to the study must kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the sponsor.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors based on SOPs of the sponsor, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data publication thereof will not be unduly withheld.

10 Study Management

10.1 Sponsor

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10.2 Vendor Contact

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SAE Email: emeaasiasafetycentral.sm@ppdi.com

10.3 Monitoring

10.3.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. Further details of operational procedures will be provided in the independent DSMB charter.

Further progression to Part 2 will be temporarily paused and the DSMB make a decision on continuation of the study in accordance with pre-specified guidelines. If it is revealed that any clinical findings which may indicate potential safety issue and no therapeutic benefit to the patients, the study will be terminated. A reassessment of sample size after review of data up to Day 28 of the approximately 200th patient will be considered by DSMB. If it is decided to continue to Part 2, the supporting data will be submitted to the regulatory authorities.

10.3.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

Due to actual scenario through this Pandemic COVID-19, the access to any site participating in this study could be restricted due to public health order or even due to site internal action plan against COVID-19. These restrictions could impact on attending to onsite interim monitoring visits. In order to avoid this situation, the source data verification could be performed remotely by the clinical research associates in case the local regulatory allows the remote source document verification. In case where a monitoring visit cannot be made because of SARS-CoV-2 pandemic situation, the monitor will discuss with the sponsor, CRO, and the investigator for further plan.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and SOPs.

10.3.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor or its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.4 Management of Protocol Amendments and Deviations

10.4.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Substantial amendments to the protocol must be submitted in writing to the applicable investigator's IRB/IEC or regulatory authority for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from the sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

10.4.2 Protocol Deviation

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or investigator that results in a significant and additional risk to the patient's right, safety and well-being. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.5 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date of final database lock with no further database change for the final CSR.

10.6 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of CSRs.

The sponsor plans to prepare 2 CSRs for reporting purpose, as the follows:

- Day 28 of last enrolled patient in Part 2
- Completion of the study

If additional CSRs are required for regulatory or academic purposes, CSRs will be generated after the first database lock and unblinding process.

11 Reference List

Beigel J. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med, 2020 May, doi: 10.1056/NEJMoa2007764

Schoenfeld D. The Asymptotic Properties of Nonparametric Tests for Comparing Survival Distributions. Biometrika, 1981 Apr, 68(1), 316-319

Tang X, Wu C, Li X, et al. On the origin and continuing evolution of SARS-CoV-2. National Science Review, 2020 Mar, doi: 10.1093/nsr/nwaa036.

Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet, 2020;395(10234):1417-1418. doi:10.1016/S0140-6736(20)30937-5

World Health Organization (WHO). Coronavirus disease (COVID-19 outbreak situation). Accessed June 1, 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

World Health Organization | Coronavirus disease (COVID-19 outbreak). Accessed June 1, 2020. Available from: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/novel-coronavirus-2019-ncov

World Health Organization. Clinical management of COVID-19: Interim Guidance, May 27, 2020. Available from: https://apps.who.int/iris/handle/10665/332196

12 Appendices

12.1 Appendix: Schedule of Assessments

Table 1 Schedule of Assessments

	Screening [1]	**Treatment Period**								**EOT** [2]	**Follow-Up Period** [3]
Study day (Visit windows)	**-10 to 0**	**1**	**2**	**3**	**5**	**7**	**14 (±1)**	**28 (±3)**	**56 (±5)**	**90 (±5)**	**2-weekly up to 180 (±5)**
Hospitalization Period [4]		**X**					**X (as required)**				
Informed Consent	X										
Demographic and medical history	X										
Inclusion/exclusion criteria	X	X [5]									
Weight, BMI and height [6]	X	X [5]								X	
Physical examination	X									X	
Hepatitis B, C and HIV-1 and -2 [7]	X										
Pregnancy test (serum or urine, where applicable) [8]	X									X	
Clinical laboratory analyses [9]	X	X [5]	X	X		X	X	X	X	X	
Vital Signs [10]	X	X [5]	X	X	X	X	X	X	X	X	
12-lead ECG	X	X [5]				X	X			X	
Radiography [11]	X					X	X	X	X	X	
Randomization		**X** [5]									
Administration of CT-P59 or Placebo [12]		**X**									
Standard of care	X (as required)										
Blood sampling for PK (central, only PK Cohort) [13]		X	X	X		X	X	X	X	X	
Blood sampling for immunogenicity (central)		X [5]				X	X	X	X	X	
Blood sampling for SARS-CoV-2 antibody test		X [5]				X	X	X	X	X	
Monitoring for immediate hypersensitivity [14]		X									
Collection of virology sample [15]											
• SARS-CoV-2 infection by RT-PCR [16]	X										
• Viral shedding (RT-qPCR and Cell culture), genotyping and phenotyping of SARS-CoV-2 viral		X [5]	X	X	X	X	X	X		(X) [17]	

Study day (Visit windows)	Screening [1]	Treatment Period								EOT [2]	Follow-Up Period [3]
	-10 to 0	1	2	3	5	7	14 (±1)	28 (±3)	56 (±5)	90 (±5)	2-weekly up to 180 (±5)
Hospitalization Period [4]		X					X (as required)				
isolates (central)											
SARS-CoV-2 infection related signs & symptoms assessment [18]	X	X [5]	X	X	X	X	X	X	X	X	X
SARS-CoV-2 Infection Symptom Checklist [19]							(X)				
8-point ordinal scale [20]	X	X [5]	X	X	X	X	X	X	X	X	
NEWS [21]	X	X [5]	X	X	X	X	X	X	(X)	(X)	
Additional assessment (intensive care unit transfer, hospitalization, use of supplemental oxygen, mechanical ventilation use)	X (as required)										
Prior and concomitant medication [22]	X										
Adverse events [23]	X										

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; CRP=c-reactive protein; CT=computerized tomography; ECG=electrocardiogram; ESR= Erythrocyte sedimentation rate; EOT=End-of-treatment; HIV=Human immunodeficiency virus; ICF=informed consent form; NEWS= National Early Warning Score; pH=potential of Hydrogen; PK=pharmacokinetic; RT-qPCR=reverse transcription-quantitative polymerase chain reaction; RT-PCR=reverse-transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=peripheral capillary oxygen saturation.

Note: If required, additional assessments can be performed as unscheduled visit by investigator's discretion during the hospitalization period. All laboratory assessments will be centrally performed during the treatment period.

1. If Screening visit date and the administration of study drug date (Day 1) are same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the date before randomization.
2. End-of-treatment visit assessments will be performed on Day 90. If a patient withdraws prematurely after the study drug administration, the patient will be asked to return to the study site on the next scheduled visit for the EOT assessments.
3. For all survived patients including a patient who early terminated from the study, each telephone call follow-up will occur bi-weekly from 2 weeks (± 5 days) after the EOT visit up to Day 180. During the Follow-Up Period, SARS-CoV-2 infection related signs and symptoms will be assessed by telephone call to capture the suspicious ADE occurrence.
4. For this study, patients are to be hospitalized up to Day 7. The extension of hospitalization period will be determined based on discharge criteria or by investigators' discretions.
5. These assessments should be performed prior to the study drug administration.
6. Measurement of height will be performed once at Screening. When calculating total volume of study drug to be administered, the body weight of each patient measured on the administration of study drug date (Day 1) will be used.
7. Documented infection with hepatitis B, hepatitis C or HIV data available before signing the ICF can be used for the Screening assessment for eligibility confirmation and only patients confirmed negative and patients with unknown status of infection will be eligible and enrolled in the study. Hepatitis B, hepatitis C antibody, and HIV analysis will be performed at the central laboratory.
8. For female patients of child-bearing potential only. Female patients of childbearing potential with a negative pregnancy test results can be enrolled.
9. Clinical laboratory testing (clinical chemistry, hematology, urinalysis and coagulation) will be performed.

Clinical	Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ-glutamyl transferase, blood urea nitrogen, creatinine, creatine kinase,

chemistry	creatine kinase-myocardial band isoenzyme, troponin (I or T, only one applicable), albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP
Hematology	Red blood cells, ESR, total white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination of white blood cell count, red blood cell count, and bacteria
Coagulation	Prothrombin International Normalized Ratio, activated partial thromboplastin time, D-dimer

10. Assessments will be measured after 5 minutes of rest. If measuring of SpO_2 is not possible, PaO_2/FiO_2 ratio can be measured as alternatives. The region of body temperature measurement should remain consistent for each patient during the study.
11. Additional radiography (chest x-ray or chest CT) can be performed when the Investigator considers it is clinically necessary (e.g., abnormal findings of SpO_2).
12. Treatment with study drug must occur no more than 10 days after the onset of symptoms and 4 days after the local laboratory confirmation of SARS-CoV-2 infection by RT-PCR from the upper or lower respiratory tract specimens.
13. A PK sub-study will be performed on the patients who signed informed consent to participate in a PK sub-study. PK blood sampling at:
    - Day 1: pre-infusion (predose within the day), at the end of infusion (within 15 minutes after the end of study drug infusion), and 1 hour (within 15 minutes) after the end of the study drug infusion.
    - Day 2: 24 hours (±1 hours) after the start of the study drug infusion
    - Day 3: 48 hours (±1 hours) after the start of the study drug infusion
    - Day 7: 144 hours (±4 hours) after the start of the study drug infusion
    - Day 14: 312 hours (±1 day) after the start of the study drug infusion
    - Day 28 (±3 days), Day 56 (±5 days), and Day 90 (±5 days)/EOT visit
14. Hypersensitivity monitoring will be performed at Day 1 pre-infusion (predose within the day), 15 minutes (±5 minutes), 30 minutes (±5 minutes), 60 minutes (±5 minutes), 90 minutes (±5 minutes)/end of infusion, 2 hours (±15 minutes), 3 hours (±15 minutes) and 4 hours (±15 minutes) after the start of the study drug infusion
    Vital signs including blood pressure, heart and respiratory rates and body temperature will be evaluated for possible hypersensitivity reactions. Any type of ECG will be performed if a patient experiences cardiac symptom. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (inhalational therapy, oxygen and artificial ventilator) must be available.
15. When collecting the respiratory tract specimens, swabbing will be performed by trained site personnel. The collected areas of specimen should remain consistent for each patient during the study.
16. If there is available test result confirmed as SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 4 days prior to the administration of the study drug) and that result was from the RT-PCR by the upper or lower respiratory tract specimen, that test result can be allowed. During the Screening Period, only one re-test for RT-PCR will be allowed if study drug can be administered no more than 10 days from onset of symptom based on re-test results.
17. If the RT-qPCR result on Day 28 show positive of SARS-CoV-2 infection, additional viral shedding will be conducted on Day 90.
18. The Investigator or designee will perform a respiratory signs and symptoms assessment (which should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and assessment for potential complications of SARS-CoV-2 infection.
19. If patients discharge before Day 28, any signs and symptoms of SARS-Cov-2 infection will be captured on the patient diary for SARS-CoV-2 Infection Symptom Checklist. Patients will complete the checklist once daily (at approximately 24-hour intervals) up to Day 28.
20. The investigator will assess the patients' clinical status using 8-point ordinal scale once daily (at approximately 24-hour intervals) during the hospitalized period. For outpatients, subsequent assessment will be performed at the specified time points. The worst clinical status (i.e., the highest ordinal scale) of the day will be recorded for each assessment.
21. Assessment will be performed while hospitalized only. But for baseline and Days 7, 14 and 28, assessments will be performed regardless of hospitalization.
22. Use of all prior and concomitant medications, from 30 days prior to the administration of the study drug (Day 1) until the EOT visit, will be recorded.
23. Adverse events will be assessed from the date the patient signs the ICF until the EOT visit. After the EOT visit, serious adverse drug reactions will be reported to the sponsor or its designee.

Table 2 Schedule of Assessments for Patients with Suspicious ADE Occurrence

Evaluation	Suspicious ADE Assessment				
	Day of occurrence [1]	Day 2	Day 3	Day 5	Day 7 [2]
Collection of virology sample					
• RT-PCR (local) [3]			X		
• Viral shedding (RT-qPCR and Cell culture), genotyping and phenotyping of SARS-CoV-2 viral isolates (central)	X	X	X	X	X
8-point ordinal scale [4]			X		
NEWS [5]			X		
SARS-CoV-2 infection related signs & symptoms assessment [6]	X	X	X	X	X
SARS-CoV-2 Infection Symptom Checklist [7]			X		
Vital sign [8]	X	X	X	X	X
12-lead ECG [9]	X		X		X
Troponin test (I or T, only one applicable) [10]	X		X		X

Abbreviations: ADE=antibody-dependent enhancement; NEWS= National Early Warning Score; RT-qPCR=reverse transcription-quantitative polymerase chain reaction; RT-PCR=reverse-transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2= peripheral capillary oxygen saturation.

Note: For suspicious ADE assessment, patients can be hospitalized based on the investigator's decision. If required, additional assessments can be performed by investigator's discretion during the hospitalization period. Otherwise, the assessment will be done by out-patient visit.

1. The day of suspicious ADE occurrence.
   - If patient has excessive progression of symptoms regarded as related to viral infection (e.g., excessive infiltration of inflammatory cells in the lung), OR
   - If patient has other SARS-CoV-2 infection related signs and symptoms which are judged as possible manifestations of ADE according to the medical opinion of the investigator
2. If symptoms have not resolved or have worsened up to Day 7 after day of ADE occurrence, same procedure will repeat until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).
3. If required, RT-PCR (local) can be performed at any time by investigator's discretion.
4. The investigator will assess the patients' 8-point ordinal scale from the day of suspicious ADE occurrence. (Daily, if possible)
5. Assessment will be performed while hospitalized only.
6. The Investigator or designee will perform a respiratory signs and symptoms assessment (which should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and assessment for potential complications of SARS-CoV-2 infection.
7. Patients will complete the checklist once daily from the day of suspicious ADE occurrence (at approximately 24-hour intervals).
8. Assessments will be measured after 5 minutes of rest. If measuring of SpO_2 is not possible, PaO_2/FiO_2 ratio can be measured as alternatives. The region of body temperature measurement should remain consistent for each patient during the study.
9. All scheduled 12-lead ECGs must be performed after the patient has rested quietly for at least 5 minutes. Regardless of the 12-lead ECG result, further cardiological evaluation can be performed at the Investigator's discretion.
10. If required, clinical laboratory testing (including but not limited to troponin test) at the local laboratory can be performed at any time by investigator's discretion.

12.2 Appendix: 8-point ordinal scale

The worst clinical status (i.e., the highest ordinal scale) of the day will be recorded.

1	**Not hospitalized, no limitations of activities**	
2	**Not hospitalized, limitation of activities, home oxygen requirement, or both**	
3	**Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)**	
4	**Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (SARS-CoV-2 – related or other medical conditions)**	
5	**Hospitalized, requiring any supplemental oxygen**	
6	**Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices**	
7	**Hospitalized, receiving invasive mechanical ventilation or ECMO**	
8	**Death**	

12.3 Appendix: National Early Warning Score (NEWS)

Criteria	Point Value
Respiratory Rate (breaths per minute)	
≤ 8	+ 3
9 – 11	+ 1
12 – 20	0
21 – 24	+ 2
≥ 25	+ 3
Oxygen Saturation (%)	
≤ 91	+ 3
92 – 93	+ 2
94 – 95	+ 1
≥ 96	0
Any Supplemental Oxygen	
Yes	+ 2
No	0
Temperature in °C	
≤ 35.0	+ 3
35.1 – 36.0	+ 1
36.1 – 38.0	0
38.1 – 39.0	+ 1
≥ 39.1	+ 2
Systolic Blood Pressure	
≤ 90	+ 3
91 – 100	+ 2
101 – 110	+ 1
111 – 219	0
≥ 220	+ 3
Heart Rate (beats per minute)	
≤ 40	+ 3
41 – 50	+ 1
51 – 90	0
91 – 110	+ 1
111 – 130	+ 2
≥ 131	+ 3
AVPU	
A	0
V, P, or U	+ 3

Abbreviations: A = alert; P = pain; U = unresponsive; V= voice.

12.4 Appendix: SARS-CoV-2 Infection Symptom Checklist

Please read the below question and check one box that describes your symptoms of the following SARS-CoV-2 infection symptoms.

		Absent (0)	Mild (1)	Moderate (2)	Severe (3)
1	**Feeling feverish**				
2	**Cough**				
3	**Shortness of breath or difficulty breathing**				
4	**Sore throat**				
5	**Body pain or muscle pain**				
6	**Fatigue**				
7	**Headache**				

Mild: no interference with normal daily activity
Moderate: interferes with normal daily activity
Severe: prevents normal daily activity