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 Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

PROTOCOL NUMBER CT-P59 3.2

EudraCT Number:	2020-003369-20
Test Formulation:	CT-P59
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Version and Date of Protocol:	Protocol Version 2.1, 07 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 Outpatients with SARS-CoV-2 Infection
Protocol Number	CT-P59 3.2
Protocol Date	Protocol Version 2.1, 07 September 2020

Protocol accepted and approved by:

Head of Clinical Planning Department

Sung Hyun Kim
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Sung Hyun Kim
Signature

07 Sep 2020
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 Outpatients 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 2.1, dated 07 September 2020, the International Council for Harmonisation harmonised 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 3.2

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 Outpatients with SARS-CoV-2 Infection

Development Phase: Phase 2/3

Study Center(s): Approximately 91 study centers in 16 countries in Part 1 and Part 2

Dose and Route of Administration:

Test Investigational Product:
Part 1
- CT-P59 80 mg/kg by single intravenous (IV) infusion over 90 minutes (±15 minutes) with Standard of Care (SoC)
- CT-P59 40 mg/kg by single IV infusion over 90 minutes (±15 minutes) with SoC

Part 2*
- CT-P59 80 mg/kg (**OR** 40 mg/kg) by single IV infusion over 90 minutes (±15 minutes) with SoC

*_**Note:** The actual dose of Part 2 will be determined based on the results from the Part 1_

Reference Investigational Product:
Part 1
- Placebo matching in volume of CT-P59 80 mg/kg by single IV infusion over 90 minutes (±15 minutes) with SoC

Part 2*
- Placebo matching in volume of CT-P59 80 mg/kg (**OR** 40 mg/kg) by single IV infusion over 90 minutes (±15 minutes) with SoC

*_**Note:** The actual dose of Part 2 will be determined based on the results from the Part 1_

Study Objective(s): The objective is to evaluate the efficacy, safety, pharmacokinetics (PK) and virology of CT-P59 in outpatients with mild to moderate symptoms of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, not requiring supplemental oxygen therapy.

Primary Objectives (Part 1)
- To assess the potential therapeutic efficacy of CT-P59 as determined by proportion of patient with negative conversion in nasopharyngeal swab specimen based on reverse transcription-quantitative polymerase chain reaction (RT-qPCR) or cell culture at each visit up to Day 14 **OR**
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 **OR**
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 **OR**
- To assess the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Primary Objective (Part 2)
- To demonstrate the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Secondary Objectives (Part 1 and 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)

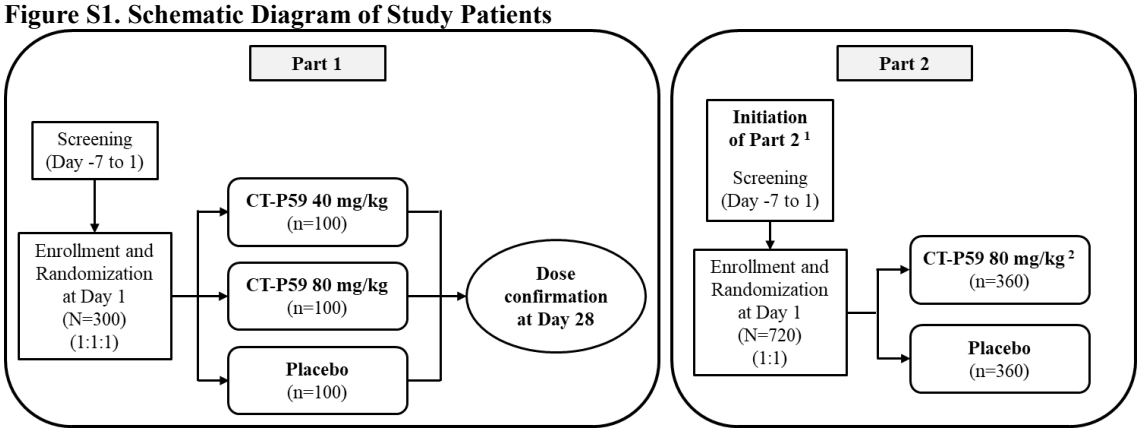
Exploratory Objectives (Part 1 and Part 2)
- To assess the PK of CT-P59 (only for Part 1)
- To assess the viral efficacy and genotype and phenotype of SARS-CoV-2 viral isolates
- To assess the serology of SARS-CoV-2 antibody

Number of Patients: Approximately, a total of 1020 patients will be enrolled in this study.

- **Part 1 (N=300):** Approximately 300 patients will be randomly assigned in a 1:1:1 ratio to receive CT-P59 80 mg/kg, 40 mg/kg or placebo.
- **Part 2 (N=720):** Approximately 720 patients will be randomly assigned in a 1:1 ratio to receive CT-P59 80 mg/kg (or 40 mg/kg) or placebo. The actual dose of Part 2 will be determined based on the results from Part 1.

The number of patients included in each part of the study is shown in Figure S1.

Figure S1. Schematic Diagram of Study Patients



1. Part 2 will be initiated based upon the independent data and safety monitoring board (DSMB)'s review of all available data after all patients have reached Day 28 in Part 1.
2. The actual dose of Part 2 will be decided based on the results from Part 1.

Study Population: Male or female outpatients, aged 18 or above with SARS-CoV-2 infection (confirmed locally by a sponsor-supplied rapid SARS-CoV-2 diagnostic test or reverse transcription polymerase chain reaction (RT-PCR) at Screening, or having a previous RT-PCR result [within 72 hours prior to the study drug administration] confirming SARS-CoV-2 infection even if before signing the informed consent form [ICF]) will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria. 'Outpatient' in this study includes patients visiting the study center, and patients confined in the study center or quarantine at home due to local regulation or at discretion of the investigator.

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

1. Adult male or female patient, aged 18 or above.
2. Patient diagnosed with SARS-CoV-2 infection at Screening by using the sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR.
   Note: *If patient had a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.*
   Note: *During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.*
3. Patient with conditions meeting all of the following criteria:
   a. Oxygen saturation >94% on room air.
   b. Not requiring supplemental oxygen.
   Note: *Patient with clinical signs of pneumonia but no signs of severe pneumonia at the investigator's discretion is eligible for this study.*
4. Patient whose onset of symptom is no more than 7 days prior to the study drug administration. Onset time of symptom is defined as the time when the patient experienced the presence of at least one SARS-CoV-2 infection associated symptom.
5. Patient who has one or more of the following (but not limited to) SARS-CoV-2 infection associated symptoms within 7 days prior to the study drug administration:
   a. Feeling feverish
   b. Cough

c. Shortness of breath or difficulty breathing
d. Sore throat
e. Body pain or muscle pain
f. Fatigue
g. Headache
h. Chills
i. Nasal obstruction or congestion
j. Loss of taste or smell
k. Nausea or vomiting
l. Diarrhea

6. Patient who has one or more of the following SARS-CoV-2 infection associated symptoms present within 48 hours prior to the study drug administration:
   a. Feeling feverish
   b. Cough
   c. Shortness of breath or difficulty breathing
   d. Sore throat
   e. Body pain or muscle pain
   f. Fatigue
   g. Headache
7. Patient with a body weight of ≤99.9 kg.
8. Patient (or legal guardian, if applicable) who is 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 prior to participation in the study.
9. For both male and female patients, the patient and his or her partner of childbearing potential who agree to use a highly effective or medically acceptable methods of contraception during the course of the study and for 6 months following discontinuation of study drug as specified below:
   - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation
   - Intrauterine devices
   - True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence of the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.
   - Condom in addition to use spermicide, hormonal contraceptive or barrier method in female; for male patient with his female partner of childbearing potential only. Spermicide condom (condoms coated with spermicide) use alone is not allowed.

   Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any highly effective or medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

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

1. Patient with current serious condition meeting one of the following criteria:
   a. Previously or currently hospitalized or requires hospitalization for treatment of serious SARS-CoV-2 related conditions.
   b. Respiratory distress with respiratory rate ≥30 breaths/min.
   c. Requires supplemental oxygen.
   d. Experience shock.
   e. Complicated with other organs failure, and intensive care unit monitoring treatment is needed by investigator's discretion.
2. Patient who has received or has a plan to receive any of following prohibited medications or treatments:
   a. Drugs with actual or possible antiviral drugs and/or possible anti-SARS-CoV-2 activity including but not limited to remdesivir, chloroquine, hydroxychloroquine (unless used chronically for autoimmune diseases), dexamethasone, and other immunomodulatory agents and human immunodeficiency virus protease inhibitors for therapeutic purpose of SARS-CoV-2 infection prior to study drug administration.
      Note: *During the study, rescue therapies using the current available SoC treatment including*

but not limited to antiviral or immunomodulatory therapies are allowed in the event of progression of SARS-CoV-2 infection or in other situations the investigator confirms necessary based on the patient's clinical disease status. Where treatments become SoC for the populations outlined in this study, the new SoC treatment will be added on to all of the treatment groups during the study. For SoC with a similar mechanism of action as the investigational agent (CT-P59), modifications to study design may be considered for Part 2 of this study.

b. Any SARS-CoV-2 human intravenous immunoglobulin, convalescent plasma for the treatment of SARS-CoV-2 infection prior to study drug administration.
c. Any other investigational device or medical product including but not limited to any monoclonal antibody (tocilizumab, sarilumab, etc.), 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 who has known allergy or hypersensitivity reaction to any monoclonal antibody or to any components of study drug.
4. Patient who has a current or history of any of the following infections:
   a. Any active infection other than SARS-CoV-2 requiring systemic treatment.
   b. Documented current infection with human immunodeficiency virus, hepatitis B or hepatitis C.
   c. Severe infection, in the investigator's opinion, within 30 days prior to the administration of study drug that required parenteral antibiotic use or hospitalization.
5. Patient who has a medical condition including one or more of the following at Screening:
   a. Any uncontrolled clinically significant respiratory disease in the investigator's opinion (e.g., chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, asthma).
   b. Abnormal liver function values including but not limited to the aspartate transaminase, alanine transaminase or alkaline phosphatase $\geq 5 \times$ upper limit normal.
   c. Renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis.
   d. History or presence of congestive heart failure with symptoms consistent with New York Heart Association Class III or IV functional status within 6 months prior to the study drug administration.
   e. Presence of clinically significant abnormality on a 12-lead electrocardiogram at Screening that, at the investigator's clinical judgment, may compromise the safety of the patient or affect the outcome of the study.
   f. Uncontrolled diabetes mellitus or hypertension, at the discretion of investigator.
   g. Any active malignancy.
   h. Currently immunocompromised, whether due to underlying medical condition (e.g., malignancy, transplantation) or medical therapy (e.g., medications, chemotherapy, radiation).
   i. Any co-morbidity requiring surgery within <7 days prior to the study drug administration, or that is considered life threatening within 30 days prior to study drug administration.
   j. Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage)
   k. Patient shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate health information, consent, or limit the ability of the patient to comply with the protocol requirements in the opinion of the investigator.
   l. 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 arms.
6. Anticipated transfer to another hospital which is not a study site.
7. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 12 months prior to the study drug administration.
8. 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.
9. Patient who is not likely to complete the study for whatever reason other than criteria listed above in the opinion of the investigator.
10. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.
11. 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 Design:

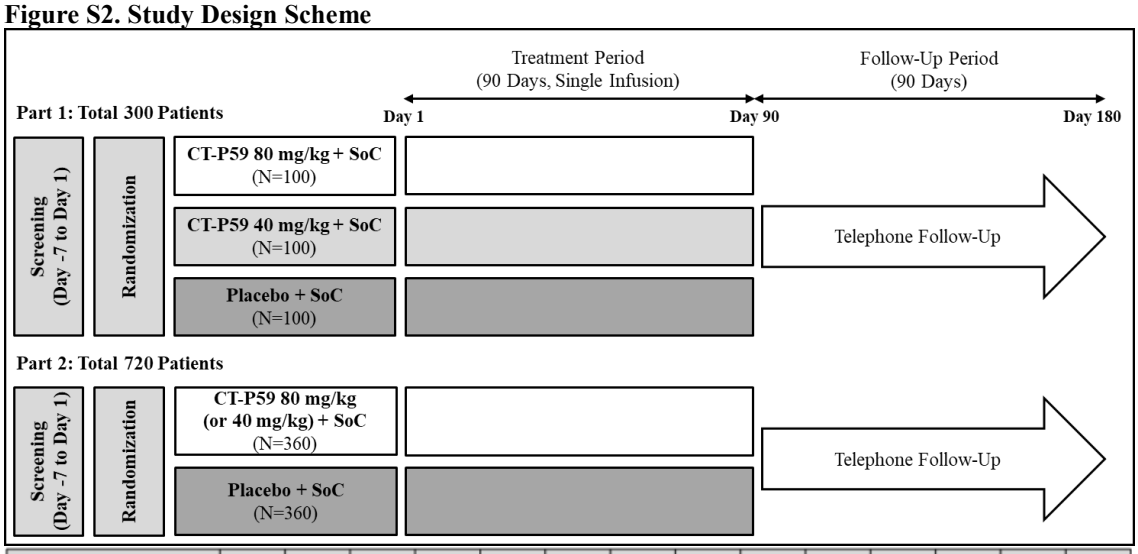
This is a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study with 2 parts to evaluate the efficacy, safety, PK and virology of CT-P59 in combination with SoC (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs) in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy.

Approximately, a total of 1020 patients will be enrolled in this study. In Part 1, approximately 300 patients will be randomly assigned in a 1:1:1 ratio of CT-P59 80 mg/kg, 40 mg/kg or placebo. In Part 2, approximately 720 patients will be randomly assigned in a 1:1 ratio to CT-P59 80 mg/kg (or 40 mg/kg), or placebo. The actual dose of Part 2 will be determined based on the result from Part 1. Same study procedures will be conducted for both Part 1 and Part 2, unless otherwise specified.

The study will be unblinded to the predefined unblinded teams of sponsor and contract research organization for reporting purposes after completion of the Day 28 assessments of the last enrolled patient in Part 1 and Part 2, respectively. However, the treatment 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 infusion), and patients until the final clinical study report is generated (Section 9.8).

The study will comprise of 3 study periods (including Screening, Treatment Period and Follow-up Period). An End-of-Treatment (EOT) visit will occur on Day 90 and the total study duration is planned as 180 days for each patient. The overview of the study is presented in Figure S2.

Figure S2. Study Design Scheme



Day	1	2	3	4	5	6	7	10	14	21	28	56	90	180
Administration of Study Drug	●													
Viral Shedding (RT-qPCR and Cell culture)	●	●	●	●	●	●	●	●	●	●	●			
Patient Diary						●								
SARS-CoV-2 infection related signs and symptoms assessment							●							
Pharmacokinetics (only for Part 1)	●	●	●		●		●	●	●		●	●	●	
Safety							●							

Note: The actual dose of Part 2 will be determined based on the results from the Part 1.
Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoC = standard of care; RT-qPCR = reverse transcription quantitative polymerase chain reaction.

Study Procedure:

Screening Period (Day -7 to Day 1)

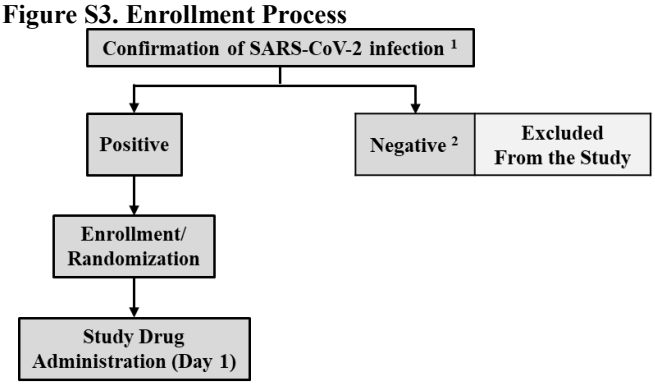
No study procedures will be performed prior to informing the patient about the study and obtaining written ICF. It is critical that patients receive study drug no more than 7 days from the onset of symptoms.

Screening evaluations will be completed prior to the randomization on Day 1. Outpatients with mild to moderate symptoms of SARS-CoV-2 infection not requiring supplemental oxygen therapy will be eligible for enrollment. Patients must have a local confirmation of SARS-CoV-2 infection by positive test result from a sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR. If the patient had a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.

If Screening visit date and the date of study drug administration (Day 1) are the same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the same day before randomization.

During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result. The enrollment process is presented in Figure S3.

Figure S3. Enrollment Process



1. Must be locally done by a sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR. If the patient has a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.
2. During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.

Abbreviation: RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Treatment Period (Day 1 to prior to End-of-Treatment Visit)

In the Treatment Period, the patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized on Day 1. If it is concluded that the patients are not eligible in Day 1 assessments before randomization, the patients will be considered as screening failure even if he/she was eligible based on assessments results performed during Screening Period.

In Part 1, approximately 300 patients will be randomly assigned in a 1:1:1 ratio (100 patients, respectively) to receive either a single dose of CT-P59 80 mg/kg, 40 mg/kg or placebo on Day 1. In Part 2, approximately 720 patients will be randomly assigned in a 1:1 ratio (360 patients, respectively) to receive either a single dose of CT-P59 80 mg/kg (or 40 mg/kg), or placebo on Day 1. All patients will be given optimal SoC (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs).

Randomization will be stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus), region and participation in PK sub-study (Yes vs. No) in Part 1, and by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic

respiratory disease, hypertension, and diabetes mellitus) and region in Part 2, respectively. In Part 1, a PK sub-study will be performed on the patients who signed informed consent to participate in a PK sub-study. Of the total number of 300 patients from Part 1, approximately 90 patients (30 patients per CT-P59 treatment groups and placebo group) will be included in the subgroup (PK) cohort, and PK samples from the patients in this cohort will be collected according to the schedule of assessments.

All enrolled patients in the study will complete the study visits during the treatment period either by visiting the study center, confinement in the study center, or home visiting services by health care professionals, whichever applicable according to the local regulation or at discretion of investigator.

Patients will comply with all appropriate visits and assessments. Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about AEs and concomitant medications and will be monitored for the disease status. Patients will undergo the procedures at the time points specified in Table 11-1 and Table 11-2.

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 (From End-of-Treatment Visit to Day 180)

For all patients including patients who withdraw prematurely after the study drug administration, each telephone call follow-up will occur biweekly from 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 calls to capture the suspicious ADE occurrence.

Study Endpoint:

Primary Endpoints

Efficacy for Part 1:

- Proportion of patient with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit up to Day 14 **OR**
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 **OR**
- Time to clinical recovery up to Day 14 **OR**
- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Clinical recovery is defined as all symptoms on the SARS-CoV-2 Infection Symptom Checklist being recorded as ‘absent’ or ‘mild’ in intensity for at least 24 hours. To meet the clinical recovery, symptoms ‘severe’ or ‘moderate’ in intensity at baseline should be changed to ‘mild’ or ‘absent’, or symptoms ‘mild’ in intensity at baseline should be changed to ‘absent’, after the study drug administration. If a symptom ‘absent’ in intensity at baseline becomes ‘severe’, ‘moderate’, or ‘mild’ during the study, this should be changed back to ‘absent’ for at least 24 hours. Symptoms of SARS-CoV-2 Infection Symptom Checklist are defined as feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pains or muscle pain, fatigue, and headache.

Efficacy for Part 2:

- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28.

Secondary Endpoints

Efficacy for Part 1 and Part 2

The following secondary efficacy endpoints will be assessed up to Day 14 and up to Day 28:

- Proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection
- Proportion of patients with intensive care unit transfer due to SARS-CoV-2 infection
- Proportion of patients with all-cause mortality
- Time to clinical recovery

- Duration of fever defined as the last day in the patient diary on which the temperature >38 ℃ (100.4 °F) is recorded, or a potentially antipyretic drug (acetaminophen or ibuprofen) is taken
- Proportion of patients with hospital admission due to SARS-CoV-2 infection
- Proportion of mechanical ventilation due to SARS-CoV-2 infection
- Proportion of patients requiring additional prescription medication due to SARS-CoV-2 infection
- Proportion of patient with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture

Additional prescription medication is defined as increase in dose or addition of any medication due to SARS-CoV-2 infection after the study drug administration on Day 1.

Safety for Part 1 and Part 2

Safety assessments will occur throughout the study. The following safety parameters are determined as secondary safety endpoints:

- Adverse events (AEs, including serious adverse events [SAEs])
- Adverse events of special interest (Infusion related reactions [hypersensitivity/ anaphylactic reactions])
- Potential effects on the incidence of ADE
- Immunogenicity
- Vital sign measurements (blood pressure, heart rate, respiratory rate, saturation peripheral oxygen and body temperature), weight and BMI
- Hypersensitivity monitoring
- 12-lead electrocardiogram
- Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) infection related signs and symptoms
- Radiography (chest x-ray or chest computed tomography)
- Physical examination findings
- Clinical laboratory analyses (clinical chemistry, hematology and urinalysis)
- Pregnancy testing (serum)
- Prior and concomitant medications

Exploratory Endpoints

Pharmacokinetics for PK sub-study of Part 1

For patients who sign an ICF to participate in the PK sub-study, a blood samples for evaluation of PK parameters will be collected throughout the study.

- $AUC_{0\text{-}last}$: Area under the concentration-time curve from time zero to the last quantifiable concentration
- $AUC_{0\text{-}inf}$: Area under the concentration-time curve from time zero to infinity
- C_{max}: Maximum serum 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: Volume of distribution during the elimination phase
- $\%AUC_{ext}$: Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation

Virology for Part 1 and Part 2

- Viral shedding in nasopharyngeal swab specimen based on RT-qPCR and cell culture
- Genotype and phenotype of SARS-CoV-2 viral isolates
- Viral serology for SARS-CoV-2 antibody

Sample Size Assumption:

The objective of efficacy analyses in Part 1 is a preliminary assessment of potential activity of CT-P59 80 mg/kg or CT-P59 40 mg/kg compared to placebo. A total sample size of 300 patients with SARS-CoV-2 infection will be randomly assigned in a 1:1:1 ratio of CT-P59 80 mg/kg, 40 mg/kg or placebo. With 100 patients per group, in the range of 30% to 90% of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture in the group, the half of the width of 95% confidence interval (CI) of the point estimate of the percentage would be no more than ±9.8%. Table S1 shows the half of the width based on various percentage of patients with negative conversion in a group.

Table S1. Half of the Width of 95% CI for Various Percentage of Patients with Negative Conversion

Number of patients in a group	Percentage of patients with negative conversion (%)	Half-width 95% CI (two-sided)
100	30	9.0
100	40	9.6
100	50	9.8
100	60	9.6
100	70	9.0
100	80	7.8
100	90	5.9

Abbreviations: CI = confidence interval

In addition, 100 patients per group would provide reasonable power to detect a 20% absolute difference in percentage of patients with negative conversion for a range of percentages with negative conversion in the placebo group. The power was calculated for the comparison of two proportions using a fisher's exact test, with one-sided type I error rate of 5%. Table S2 shows the power of over 86% is achieved regardless of the percentage of patients with negative conversion in the placebo group.

Table S2. Power to Detect a 20% Absolute Difference for Various Percentage of Patients with Negative Conversion

Number of placebo group	Number of experimental group[1]	Percentage of negative conversion in placebo group (%)	Percentage of negative conversion in experimental group[1] (%)	Power (%)
100	100	30	50	86.6
100	100	40	60	86.0
100	100	50	70	86.6
100	100	60	80	91.0
100	100	70	90	96.7

[1] The number of patients in CT-P59 80 mg/kg or CT-P59 40 mg/kg.

For Part 2, to demonstrate the efficacy of CT-P59 80 mg/kg (or 40 mg/kg) compared to placebo by proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28, a total of 720 (360 patients per group) patients will provide over 85% power to detect 8% reduction at a significance level of 5% (2-sided test) assuming placebo rate of 16%. A reassessment of sample size accounting for the actual placebo rate and effect size will be made using the results from Part 1.

Statistical Methods:

Analysis Sets:

Intent-to-treat (ITT) Set: The ITT Set is defined as all randomly assigned patients to 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-infusion result (Day 1) of RT-qPCR or cell culture, who receive a complete dose of study drug.

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

Pharmacokinetic (PK) Set (Part 1 only): The PK Set is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of RT-qPCR or cell culture and signed informed consent to participate in the PK sub-study, who receive a complete dose of study drug and have at least one evaluable post-treatment PK result.

Efficacy Analyses:

Primary (Part 1): The primary efficacy endpoints for Part 1 will be analyzed on the ITTI set. Time to event analyses will be analyzed using Kaplan-Meier analysis presenting 95% CI of median. The others will be summarized using frequency tables with 95% CI.

Primary (Part 2): The primary efficacy endpoint for Part 2 will be analyzed on the ITT set using the p-value from logistic regression model with stratification factors as covariates at the 2-sided significance level of 5%. For sensitivity analysis, Fisher's exact test will be conducted on ITT set. Also, supportive analysis will be performed on ITTI set.

Secondary (Part 1 and Part 2): The secondary efficacy endpoints will be analyzed on both ITTI and ITT set. Time to event analyses will be analyzed using Kaplan-Meier analysis. The others will be summarized using descriptive statistics or frequency tables.

Safety Analyses:

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 according to the Common Terminology Criteria for Adverse Events Version 5.0. Prior and concomitant medications will be coded to drug class and preferred term according to the World Health Organization Drug Dictionary. All safety data will be listed and summarized by treatment groups as appropriate in the safety population.

Pharmacokinetic Analyses (Part 1 only):

Pharmacokinetic parameters will be computed by non-compartmental methods using appropriate validated software such as Phoenix WinNonlin (Pharsight, St Louis, Missouri, USA). The PK parameters and concentrations at each time point will be presented in listings and summarized in tables. The summary tables will display the following descriptive statistics: the number of observations, mean, median, standard deviation, minimum, maximum, geometric mean, and the coefficient of variation. The PK parameters and concentrations will be summarized in the PK population.

Virology Analyses:

Virology Assessments 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 serology results will be presented in data listing by treatment groups.

List of Abbreviations

Abbreviation	Definition
ABV	Alcohol by volume
ACE	Angiotensin-converting enzyme
ADE	Antibody-dependent enhancement
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End-of-Treatment
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IgG1	Human immunoglobulin G1
IRB	Institutional review board
ITT	Intent-to-treat
ITTI	Intent-to-treat infected
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
PK	Pharmacokinetics
RBD	Receptor binding domain
RT-PCR	Reverse transcription polymerase chain reaction
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

SoC	Standard of care
SOP	Standard operating procedure
SpO_2	Saturation peripheral oxygen
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1 Introduction

1.1 Background

Coronaviruses are single stranded ribonucleic acid 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 the People's Republic of China (hereafter "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 SARS-CoV-2 has been designated as coronavirus disease 2019, known as COVID-19 (World Health Organization, 03 June 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 (Word Health Organization Guidelines, 2014).

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 2 (ACE2) receptor located on epithelial and endothelial cells which traverse multiple organs (Varga et al. 2020)

SARS-CoV-2 infection is initiated by binding of the SARS-CoV-2 spike protein to ACE2 via the receptor binding domain (RBD) of the spike 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 strains 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 spike protein as a treatment for SARS-CoV-2 infection, which is manufactured by recombinant deoxyribonucleic acid 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) infusion.

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 been 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 is 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 opsonization 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 nonclinical 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. Approximately 32 subjects in 4 cohorts are planned for enrollment and each cohort will consist of 8 subjects, 6 of whom will receive CT-P59 and 2 of whom will receive a placebo. Detailed information regarding the safety of CT-P59 in healthy volunteers 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. Study CT-P59 1.2 is ongoing.

1.3 Study Rationale

There are currently no approved monoclonal antibody therapy available to treat coronaviruses such as SARS-CoV-2 and there is an urgent public health need for rapid development of such interventions. On 11 March 2020, World Health Organization (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 (World Health Organization, 05 January 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 outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy. The expected patient population is adults only. 'Outpatient' in this study includes patients visiting the study center, and patients confined in the study center or quarantine at home due to local regulation or at discretion of the investigator.

1.3.2 Rationale for Dose Selection

The PK profile of CT-P59 is expected to be similar to that of CT-P27, which is an anti-influenza antibody drug to treat influenza under development by CELLTRION, Inc. CT-P27 drug product is a combination of the two human immunoglobulin G1 (IgG1) monoclonal antibodies. This is due to the structural similarity between the CT-P27 monoclonal antibodies and the CT-P59 monoclonal antibody, in that CT-P59 shares an identical human IgG1 Fc region backbone with the two monoclonal antibodies of CT-P27.

In the 2-week repeat dose non-human primate toxicity study of CT-P27, which included safety pharmacology endpoints (e.g., clinical observations, body temperature, respiratory rate, heart rate, blood pressure, and electrocardiogram [ECG]) and full histopathology, there were no treatment-related adverse effects at IV doses up to 320 mg/kg. The main finding was a minimal to mild inflammatory response at the catheter insertion sites; however, the effects were fully reversible and not considered adverse. Applying a safety factor of 10, it is expected that a dose of up to 32 mg/kg could be supported as posing a very low risk of inducing adverse effects in human as well.

In the Study CT-P59 1.1, the first dose was 10 mg/kg via IV administration. Based on the non-human primate repeat dose toxicity study of CT-P27 with a No-observed-adverse-effect level (NOAEL) of 320 mg/kg, which was the highest dose tested and did not cause any adverse effects, and applying a safety factor of 10, it was expected that a dose of up to 32 mg/kg could be supported as posing a very low risk of inducing adverse effects in this study as well. However, to maximize the safety, a lower dose of 10 mg/kg was adapted as starting dose in Study CT-P59 1.1.

The proposed top dose of 80 mg/kg in Study CT-P59 1.1 is expected to ensure 2.8 times of margin of exposure based on the CT-P27 studies results (area under the concentration-time curve results of NOAEL dose in nonclinical study and expected area under the concentration-time curve value of 80 mg/kg in clinical study with healthy volunteers).

In this study, the actual dose will be determined based on the results from the Study CT-P59 1.1. If all doses of Study CT-P59 1.1 are tolerable, the proposed 40 mg/kg or 80 mg/kg will be administered in Part 1 to minimize any chances of less efficacy. The actual dose of Part 2 will be determined based on the results from the Part 1. It is suggested that clinical benefit is not necessarily dose dependent in a linear relationship especially for molecularly targeted agents. Such that, in a comprehensive basis, the overall efficacy and safety profile of Part 1 will be considered for selecting the therapeutic appropriate dose of Part 2.

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 principal investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (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

2.1 Primary Objective (Part 1)

- To assess the potential therapeutic efficacy of CT-P59 as determined by proportion of patient with negative conversion in nasopharyngeal swab specimen based on reverse transcription quantitative polymerase chain reaction (RT-qPCR) or cell culture at each visit up to Day 14 **OR**
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 **OR**
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 **OR**
- To assess the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

2.2 Primary Objective (Part 2)

- To demonstrate the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

2.3 Secondary Objectives (Part 1 and 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)

2.4 Exploratory Objectives (Part 1 and Part 2)

- To assess the PK of CT-P59 (only for Part 1)
- To assess the viral efficacy and genotype and phenotype of SARS-CoV-2 viral isolates
- To assess the serology of SARS-CoV-2 antibody

3 Investigational Plan

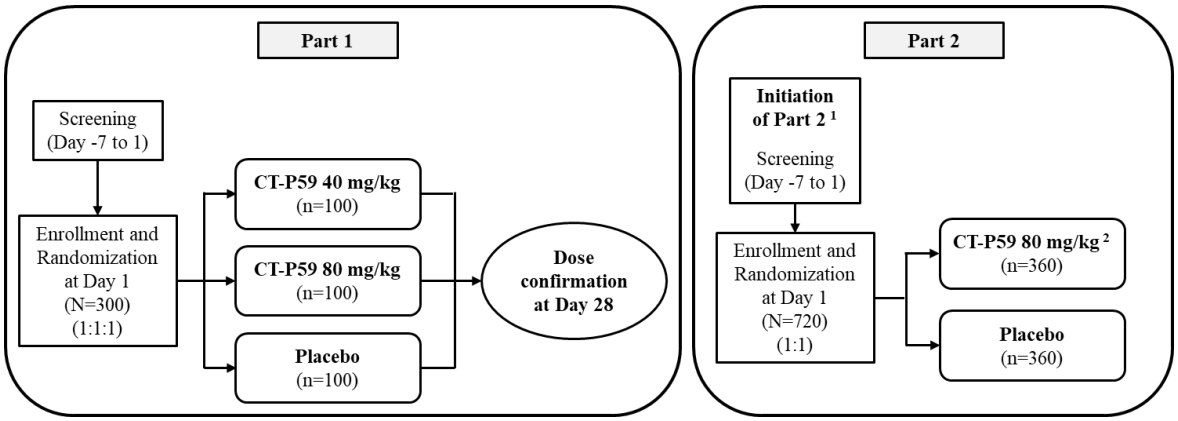
3.1 Study Design

This is a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study with 2 parts to evaluate the efficacy, safety, PK and virology of CT-P59 in combination with SoC (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs) in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy.

Approximately a total of 1020 patients will be enrolled in this study. In Part 1, approximately 300 patients will be randomly assigned in a 1:1:1 ratio of CT-P59 80 mg/kg, 40 mg/kg or placebo. In Part 2, approximately 720 patients will be randomly assigned in a 1:1 ratio to CT-P59 80 mg/kg (or 40 mg/kg), or placebo. The actual dose of Part 2 will be determined based on the result from Part 1. Part 2 will be initiated based upon the DSMB's review of all available data after all patients have reached Day 28 in Part 1.Same study procedures will be conducted for both Part 1 and Part 2, unless otherwise specified. The number of patients included in each part of the study is shown in Figure 3-1.

The study will be unblinded to the predefined unblinded teams of sponsor and Contract Research Organization (CRO) for reporting purposes after completion of the Day 28 assessments of the last enrolled patient in Part 1 and Part 2, respectively. However, the treatment 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 infusion), and patients until the final clinical study report (CSR) is generated (Section 9.8).

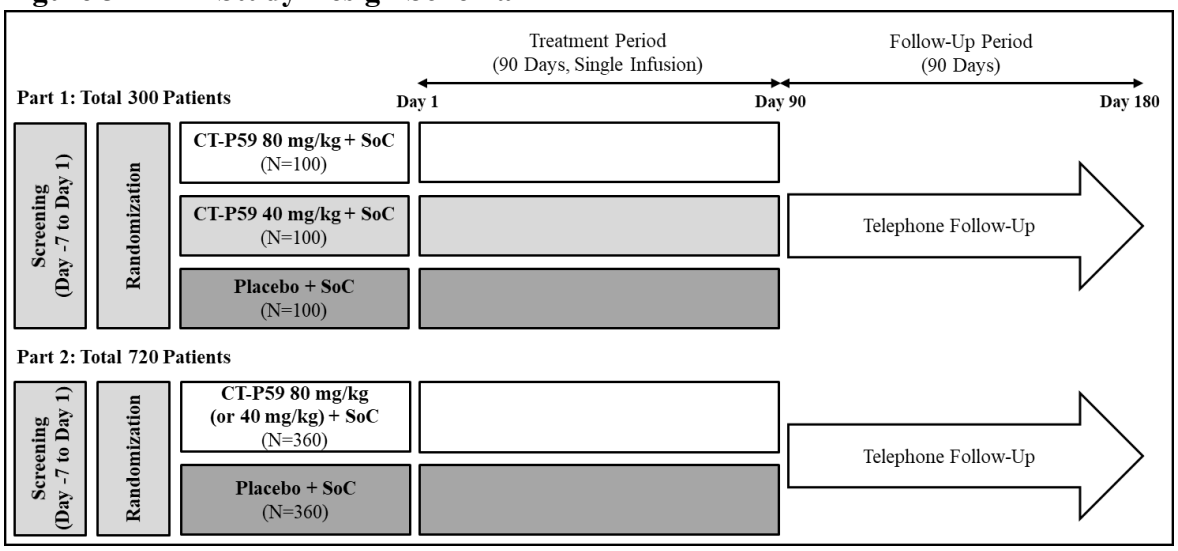
Figure 3-1 Schematic Diagram of Study Patients



1. Part 2 will be initiated based upon the independent data and safety monitoring board (DSMB)'s review of all available data after all patients have reached Day 28 in Part 1.
2. The actual dose of Part 2 will be decided based on the results from Part 1.

The study will comprise of 3 study periods (including Screening, Treatment Period and Follow-up Period). An end-of-treatment (EOT) visit will occur on Day 90 and the total study duration is planned as 180 days for each patient. The overview of each part is presented in Figure 3-2.

Figure 3-2 Study Design Schema



Day	1	2	3	4	5	6	7	10	14	21	28	56	90	180
Administration of Study Drug	●													
Viral Shedding (RT-qPCR and Cell culture)	●	●	●	●	●	●	●	●	●	●	●			
Patient Diary						●								
SARS-CoV-2 infection related signs and symptoms assessment							●							
Pharmacokinetics (only for Part 1)	●	●	●		●		●	●	●		●	●	●	
Safety							●							

Note: The actual dose of Part 2 will be determined based on the result from Part 1.
Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoC = standard of care; RT-qPCR = reverse transcription quantitative polymerase chain reaction.

3.1.1 Screening Period (Day -7 to Day 1)

No study procedures will be performed prior to informing the patient about the study and obtaining written informed consent form (ICF). It is critical that patients receive study drug no more than 7 days from the onset of symptoms.

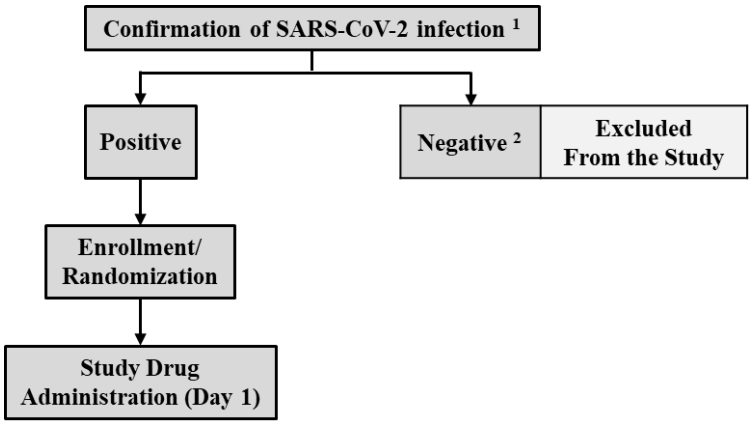
Screening evaluations will be completed prior to the randomization on Day 1. Outpatients with mild to moderate symptoms of SARS-CoV-2 infection not requiring supplemental oxygen therapy will be eligible for enrollment. Patients must have a local confirmation of SARS-CoV-2 infection by positive test result from a sponsor-supplied rapid SARS-CoV-2

diagnostic test or reverse transcription polymerase chain reaction (RT-PCR). If the patient has a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.

If Screening visit date and the date of study drug administration (Day 1) are the same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the same day before randomization.

During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result. The enrollment process is presented in Figure 3-3.

Figure 3-3 Enrollment Process



1. Must be locally done by a sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR. If the patient has a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.
2. During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.

Abbreviation: RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

3.1.2 Treatment Period (Day 1 to prior to End-of-Treatment Visit)

In the Treatment Period, the patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized on Day 1. If it is concluded that the patients are not eligible in Day 1 assessments before randomization, the patients will be considered as screening failure even if he/she was eligible based on assessments results performed during Screening Period.

In Part 1, approximately 300 patients will be randomly assigned in a 1:1:1 ratio (100

patients, respectively) to receive either a single dose of CT-P59 80 mg/kg, 40 mg/kg, or placebo on Day 1. In Part 2, approximately 720 patients will be randomly assigned in a 1:1 ratio (360 patients, respectively) to receive either a single dose of CT-P59 80 mg/kg (or 40 mg/kg), or placebo on Day 1. All patients will be given optimal SoC (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs).

Randomization will be stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus), region and participation in PK sub-study (Yes vs. No) in Part 1, and by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus) and region in Part 2, respectively. In Part 1, a PK sub-study will be performed on the patients who signed informed consent to participate in a PK sub-study. Of the total number of 300 patients from Part 1, approximately 90 patients (30 patients per CT-P59 treatment groups and placebo group) will be included in the subgroup (PK) cohort, and PK samples from the patients in this cohort will be collected according to the schedule of assessments.

All enrolled patients in the study will complete the study visits during the treatment period either by visiting the study center, confinement in the study center, or home visiting services by health care professionals, whichever applicable according to the local regulation or at discretion of investigator.

Patients will comply with all appropriate visits and assessments. Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about AEs and concomitant medications and will be monitored for the disease status. Patients will undergo the procedures at the time points specified in Table 11-1 and Table 11-2.

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 (From End-of-Treatment Visit to Day 180)

For all patients including patients who withdraw prematurely after the study drug administration, each telephone call follow-up will occur biweekly from 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 calls to capture the suspicious ADE occurrence.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 1020 patients will be enrolled at approximately 91 study centers in 16 countries in Part 1 and Part 2. Male or female outpatients, aged 18 or above with SARS-CoV-2 infection (confirmed locally by a sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR at Screening, or having a previous RT-PCR result [within 72 hours prior to the study drug administration] confirming SARS-CoV-2 infection even if before signing the ICF) will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria. 'Outpatient' in this study includes patients visiting the study center, and patients confined in the study center or quarantine at home due to local regulation or at discretion of the investigator.

4.1.1 Inclusion Criteria

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

1. Adult male or female patient, aged 18 or above.

2. Patient is diagnosed with SARS-CoV-2 infection at Screening by using the sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR.

   ***Note**: If the patient had a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.*
   ***Note**: During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.*

3. Patient with conditions meeting all of the following criteria:

   a. Oxygen saturation >94% on room air.
   b. Not requiring supplemental oxygen.

   ***Note:** Patient with clinical signs of pneumonia but no signs of severe pneumonia at the investigator's discretion is eligible for this study.*

4. Patient whose onset of symptom is no more than 7 days prior to the study drug administration. Onset time of symptom is defined as the time when the patient experienced the presence of at least one SARS-CoV-2 infection associated symptom.

5. Patient has one or more of the following (but not limited to) SARS-CoV-2 infection associated symptoms within 7 days prior to the study drug administration:

    a. Feeling feverish
    b. Cough
    c. Shortness of breath or difficulty breathing
    d. Sore throat
    e. Body pain or muscle pain
    f. Fatigue
    g. Headache
    h. Chills
    i. Nasal obstruction or congestion
    j. Loss of taste or smell
    k. Nausea or vomiting
    l. Diarrhea

6. Patient has one or more of the following SARS-CoV-2 infection associated symptoms present within 48 hours prior to the study drug administration:

    a. Feeling feverish
    b. Cough
    c. Shortness of breath or difficulty breathing
    d. Sore throat
    e. Body pain or muscle pain
    f. Fatigue
    g. Headache

7. Patient with a body weight of ≤99.9 kg.

8. Patient (or legal guardian, if applicable) who is 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 ICF prior to participation in the study.

9. For both male and female patients, the patient and his or her partner of childbearing potential who agree to use a highly effective or medically acceptable methods of contraception during the course of the study and for 6 months following discontinuation of study drug as specified below:

    - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation

- Intrauterine devices
- True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence of the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.
- Condom in addition to use spermicide, hormonal contraceptive or barrier method in female; for male patient with his female partner of childbearing potential only. Spermicide condom (condoms coated with spermicide) use alone is not allowed.

Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any highly effective or medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

4.1.2 Exclusion Criteria

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

1. Patient with current serious condition meeting one of the following criteria:

    a. Previously or currently hospitalized or requires hospitalization for treatment of serious SARS-CoV-2 related conditions.
    b. Respiratory distress with respiratory rate ≥30 breaths/min.
    c. Requires supplemental oxygen.
    d. Experience shock.
    e. Complicated with other organs failure, and intensive care unit monitoring treatment is needed by investigator’s discretion.

2. Patient who has received or has a plan to receive any of following prohibited medications or treatments:

    a. Drugs with actual or possible antiviral drugs and/or possible anti-SARS-CoV-2 activity including but not limited to remdesivir, chloroquine, hydroxychloroquine (unless used chronically for autoimmune diseases), dexamethasone, and other immunomodulatory agents and human immunodeficiency virus (HIV) protease inhibitors for therapeutic purpose of SARS-CoV-2 infection prior to study drug administration.

Note: *During the study, rescue therapies using the current available SoC treatment including but not limited to antiviral or immunomodulatory therapies are allowed in the event of progression of SARS-CoV-2 infection or in other situations the investigator confirms necessary based on the patient's clinical disease status. Where treatments become SoC for the populations outlined in this study, the new SoC treatment will be added on to all of the treatment groups during the study. For SoC with a similar mechanism of action as the investigational agent (CT-P59), modifications to study design may be considered for Part 2 of this study.*

b. Any SARS-CoV-2 human intravenous immunoglobulin, convalescent plasma for the treatment of SARS-CoV-2 infection prior to study drug administration.
c. Any other investigational device or medical product including but not limited to any monoclonal antibody (tocilizumab, sarilumab, etc.), 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 who has a current or history of any of the following infections:

a. Any active infection other than SARS-CoV-2 requiring systemic treatment.
b. Documented current infection with HIV, hepatitis B or hepatitis C.
c. Severe infection, in the investigator's opinion, within 30 days prior to the administration of study drug that required parenteral antibiotic use or hospitalization.

5. Patient who has a medical condition including one or more of the following at Screening:

a. Any uncontrolled clinically significant respiratory disease in the investigator's opinion (e.g., chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, asthma).
b. Abnormal liver function values including but not limited to the aspartate transaminase, alanine transaminase or alkaline phosphatase ≥5 × upper limit normal.
c. Renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal

dialysis.

d. History or presence of congestive heart failure with symptoms consistent with New York Heart Association Class III or IV functional status within 6 months prior to the study drug administration.
e. Presence of clinically significant abnormality on a 12-lead ECG at Screening that, at the investigator's clinical judgment, may compromise the safety of the patient or affect the outcome of the study.
f. Uncontrolled diabetes mellitus or hypertension, at the discretion of investigator.
g. Any active malignancy.
h. Currently immunocompromised, whether due to underlying medical condition (e.g., malignancy, transplantation) or medical therapy (e.g., medications, chemotherapy, radiation).
i. Any co-morbidity requiring surgery within <7 days prior to the study drug administration, or that is considered life threatening within 30 days prior to study drug administration.
j. Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage)
k. Patient shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate health information, consent, or limit the ability of the patient to comply with the protocol requirements in the opinion of the investigator.
l. 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 arms.

6. Anticipated transfer to another hospital which is not a study site.

7. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 12 months prior to the study drug administration.

8. 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.

9. Patient is not likely to complete the study for whatever reason other than criteria listed above in the opinion of the investigator.

10. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

11. Female patient 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 from the study at any time for any reason. The investigator may also withdraw the patients at any time in the interest of patient safety. The primary reason for withdrawal from the study must be recorded in the patient's medical record and in the electronic case report form (eCRF).

When possible, the sponsor should be notified of the withdrawal of a patient from the study. 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 at planned time points of EOT visit. For patients who discontinued of Follow-up period, the reason of discontinuation will be recorded eCRF. Any comments (spontaneous or elicited) or complaints made by the patient, together with the reason for withdrawal from the study, and the date of cessation of study drug must be recorded in the eCRF and source documents. As it is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE) in every case, efforts must be made to undertake protocol-specified safety and follow-up procedures.

The reasons for withdrawal are as following:

- Withdrawal of consent
- Lost to follow-up
- Adverse event that would compromise his or her safety if he or she continues to participate in the study
- Death
- Investigator's decision

The status of patients who fail to complete final assessments will be documented in the eCRF. If necessary, the investigator may discuss with sponsor or its designee any patient's reason for withdrawal. The sponsor may be contacted if clarification is required on a case-by-case basis. All withdrawn patients will retain their patient number with the reason for withdrawal from the study.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and 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 discontinuation 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. An independent DSMB will thoroughly review and evaluate the safety data of study patients, and provide recommendations regarding the acceptability of continuing the study based on safety monitoring (Section 9.4).

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 IEC or IRB of any premature termination or suspension of the study, where applicable.

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:

- Age (≥60 years vs. <60 years)
- Region
- Baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus)
- Participation in PK sub-study (Yes vs. No): only for Part 1

5.2 Treatment Administered

When calculating total volume of study drug to be administered, the body weight of each patient measured on Day 1 will be used.

In Part 1, CT-P59 80 mg/kg, 40 mg/kg, and placebo matching in volume of CT-P59 80 mg/kg will be administered as an IV infusion over 90 minutes (±15 minutes).

In Part 2, based on the result from Part 1, CT-P59 80 mg/kg (or 40 mg/kg) and placebo matching in volume of CT-P59 (80 mg/kg or 40 mg/kg) will be administered as an IV infusion over 90 minutes (±15 minutes).

All patients in both Part 1 and Part 2 will be given optimal SoC. Optimal SoC can include rehydration therapy, antipyretics or antitussives prescribed by the investigator's discretion. Potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs are not allowed during the study, unless specified in Section 5.7. The routine use of antibiotics is not recommended, but antibiotics may be used if bacterial infections are present or suspected. The type of antibiotic will be selected based on the patient's clinical disease status and symptoms with discretion of investigator.

A 250 mL infusion solution of 0.9% weight/volume sodium chloride will be used for patient infusion. 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.

5.2.1 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 infusion. 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 intravenous infusion. 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.

5.2.2 Identity of Placebo

Placebo contains the same ingredient as the CT-P59 formulation listed in Section 5.2.1, 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, and 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.

5.2.3 Dose Modification

No dose modifications or dose omissions are permitted for CT-P59 or placebo.

5.3 Management of Clinical Supplies

5.3.1 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.

5.3.2 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 on-site monitoring visit cannot be made because of the SARS-CoV-2 pandemic situation, the sponsor and CRO will discuss with the 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 in study drugs accountability and destruction will be followed according to the pharmacy manual.

5.4 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 staffs designated to prepare the study drug for infusion and predefined unblinded teams in the sponsor and CRO), and patients until the final CSR is generated.

5.4.1 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should be broken only 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 from Part 1). In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure.

The date, time and reason for the unblinding must be documented in the source document and appropriate field of the eCRF, and the medical monitor will be informed as soon as possible. All unblinding events will be recorded and reported to the medial monitor and the sponsor. Any patients for whom the blind is broken may continue in the study at the investigator’s discretion. Suspected unexpected serious adverse reactions (SUSAR), which are subject to expedited reporting, should be unblinded before submission to the regulatory

authorities if required.

The DSMB and the statistician(s) who provide the safety analyses for the DSMB will also be unblinded upon request from DSMB members during closed session.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Day 28 of the last enrolled patient in Part 1, and up to Day 28 of the last enrolled patient in Part 2. The unblinded personnel will be predefined and documented before performing the analyses.

5.5 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.

5.6 Prior and Concomitant Therapy

Use of all prior and concomitant medications for the treatment of SARS-CoV-2 infection, from the diagnosis of disease until the EOT visit, will be recorded in both the source documents and the eCRF.

Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 1) or from when the ICF is signed, whichever is earlier, will be recorded until the EOT visit. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in both the source documents and the eCRF.

5.7 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).

- Drugs with actual or possible antiviral drugs and/or possible anti-SARS-CoV-2 activity including but not limited to remdesivir, chloroquine, hydroxychloroquine (unless used chronically for autoimmune diseases),

dexamethasone, and other immunomodulatory agents and HIV protease inhibitors for therapeutic purpose of SARS-CoV-2 infection

- Any SARS-CoV-2 human intravenous immunoglobulin, convalescent plasma for the treatment of SARS-CoV-2 infection
- Any other investigational device or medical product including but not limited to any monoclonal antibody (tocilizumab, sarilumab, etc.), fusion proteins or biologics for the treatment of SARS-CoV-2 infection
- Medications that are contraindicated with SoC
- SARS-CoV-2 vaccine

However, rescue therapies using the current available SoC treatment including but not limited to antiviral or immunomodulatory therapies are allowed in the event of progression of SARS-CoV-2 infection or in other situations the investigator confirms necessary based on the patient's clinical disease status. Where treatments become SoC for the populations outlined in this study, the new SoC treatment will be added on to all of the treatment groups during the study. For SoC with a similar mechanism of action as the investigational agent (CT-P59), modifications to study design may be considered for Part 2 of this study.

5.8 Restriction (Only for Patients in PK Sub-study)

The investigator, or delegated clinical staff member, will check if patient who participates in the PK sub-study in Part 1 is complying with these restraints during the study.

5.8.1 Dietary and Fluid Restrictions

Alcohol: Alcohol containing products (including alcohol, alcohol-containing foods, medications, or beverages) must be avoided from 48 hours before the study drug administration and up to Day 7, and 24 hours before any study visit. Patients must abstain from alcohol-containing products for 24 hours prior to each PK sampling time point. Patient will not exceed an alcohol consumption of 14 units per week until the end of the study period. One standard unit is equal to approximately 285 mL of full strength beer (4.8% alcohol by volume [ABV]), 30 mL of spirits (40% ABV), or 100 mL of wine (13.5% ABV).

Caffeine: Patients will not be permitted to drink caffeine or xanthine-containing products (e.g., coffee, black tea, cola, etc., or use caffeine or xanthine-containing products) for 24 hours prior to the study drug administration and up to Day 7. Patients must abstain from caffeine or

xanthine-containing products for 24 hours prior to each PK sampling time point.

Nicotine: Patients will be permitted to smoke less than 10 cigarettes or equivalent per day until the end of the study period, but will not be allowed to smoke at least up to Day 7.

Meals: Patients must abstain from all food and drink (except water) at least 8 hours prior to the study drug administration. Water is permitted until 1 hour prior to the study drug administration and may be consumed without restriction beginning 1 hour after the study drug administration. If the patient is confined in the study center at the discretion of the investigator, no outside food or drink is permitted at the study center; all meals will be provided by the study center.

5.8.2 Other Restrictions

Activity: Strenuous activity (e.g., heavy lifting, weight training, calisthenics, and aerobics) is prohibited from 72 hours prior to the study administration until Day 7. After Day 7, mild physical activity can be resumed, but strenuous physical activity is prohibited 72 hours prior to each study visit.

Hygiene: Patients should follow the country/local guideline for SARS-CoV-2 infection prevention.

Medications: Restrictions on medication during the study is described in Section 5.7.

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.

Patient will undergo the procedures at the time points specified in Table 11-1 and Table 11-2. If investigator suspects the ADE occurrence, all assessments can be done at any time, rather than waiting for the next scheduled visit.

6.1 Efficacy Assessments

6.1.1 Patient Diary

Patient diary consists of SARS-CoV-2 Infection Symptom Checklist, and body temperature. Patient diary will be issued to all patients at Screening and patients will be required to record the diary daily from Day 1 until Day 28, and after Day 28 if applicable (Section 6.1.1.1) after patients got instructed on how to appropriately complete the patient diary. The patient diary will be recorded once at Screening. On the date of study drug administration (Day 1), the patient diary will be recorded twice; before and after the study drug administration. If Screening visit date and the date of study drug administration are the same, patient diary will be also recorded twice; before and after the study drug administration. From Day 2, the patient diary will be recorded twice a day at approximately 12-hour intervals in the morning (between 6 and 10 AM, approximately) and in the evening (between 6 and 10 PM, approximately).

Study site staff will instruct the patients on the use of the diary. Patients will be told to bring their completed diary each time they return to the study site. The study site staff will review the entries in the diary at each study visit. If the patient is not compliant in regard to filling out the diary (omissions, discrepancies, or other difficulties), instructions on how to use the diary may be repeated. The study site staff should encourage the patient to complete the diary and remind the patient of the importance of following study procedures while at home.

All information obtained from the diary will be entered to the eCRF. These results will be used in the assessment of primary and secondary efficacy endpoints.

After Day 28, additional recording of the diary will be required if following conditions are met:

- For patient who achieves the clinical recovery on Day 28, the patient will record the diary until Day 29 to confirm whether the patient’s condition is maintained at least 24 hours.
- For patient who shows deterioration (at the discretion of the investigator) or is still not recovered, the patient will record the diary until the achievement of clinical recovery.
- For patient with suspicious ADE occurrence, the patient will record the diary for 7 days from the day of suspicious ADE occurrence (specified in Table 11-2). If suspicious ADE has not resolved or has worsened during the 7 days, same procedure of recording patient diary for 7 days will be repeated from the

beginning until the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

However, if patient's condition is not available to record the patient diary at the discretion of investigator (e.g. sedation state for mechanical ventilator therapy), recording can be discontinued. Recording will be resumed when the patient's condition becomes available to record the patient diary.

6.1.1.1 SARS-CoV-2 Infection Symptom Checklist

Signs and symptoms of SARS-CoV-2 infection throughout the study (including the Screening Period, up to Day 28, and after Day 28 if applicable [see Section 6.1.1]), will be captured on the patient diary for SARS-CoV-2 Infection Symptom Checklist and the symptoms recorded on this 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

A full SARS-CoV-2 Infection Symptom Checklist is described in Section 11.2.

Clinical recovery is defined as all symptoms on the SARS-CoV-2 Infection Symptom Checklist being recorded as 'absent' or 'mild' in intensity for at least 24 hours. To meet the clinical recovery, symptoms 'moderate' or 'severe' in intensity at baseline should be changed to 'mild' or 'absent', or symptoms 'mild' in intensity at baseline should be changed to 'absent', after the study drug administration. If a symptom 'absent' in intensity at baseline becomes 'severe', 'moderate', or 'mild' during the study, this should be changed back to 'absent' for at least 24 hours.

6.1.1.2 Body Temperature

Body temperature for the patient diary will be collected for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection in the SARS-CoV-2 Infection Symptom Checklist at Screening, or the patients who record feeling feverish in the SARS-CoV-2 Infection Symptom Checklist at any time throughout the study.

The body temperature will be self-measured by the patients, twice a day (at approximately 12-hour intervals; in the morning [between 6 and 10 AM, approximately] and in the evening [between 6 and 10 PM, approximately]) from the first day on which the patient records feeling feverish until the day of subsidence of a fever (subsides to ≤38.0 °C), except Screening visit. The body temperature will be recorded once at Screening. The sponsor will supply a tympanic thermometer to the patients along with guideline for use of it.

6.1.2 Disease Status Monitoring

Disease status including requirement of supplemental oxygen, intensive care unit transfer, mechanical ventilation use, hospitalization and additional prescription medication due to SARS-CoV-2 infection will be monitored during the study period (from signing of ICF to EOT).

6.1.2.1 Requirement of Supplemental Oxygen

The information of supplemental oxygen due to SARS-CoV-2 infection during the study (from signing of ICF to EOT) will be recorded in the eCRF and source documents. Information to be collected includes the start and end date of supplemental oxygen.

6.1.2.2 Intensive Care Unit Transfer

The information of intensive care unit transfer due to SARS-CoV-2 infection during the study (from signing of ICF to EOT) will be recorded in the eCRF and source documents. Information to be collected includes the transfer and discharge date for the intensive care unit.

6.1.2.3 Mechanical Ventilation Use

The information of mechanical ventilation use due to SARS-CoV-2 infection during the study (from signing of ICF to EOT) will be recorded in the eCRF and source documents. Information to be collected includes the start and end date of mechanical ventilation use.

6.1.2.4 Hospitalization

For patients who are participating the study and are not confined in the study center due to local regulation or at discretion of the investigator, the information of hospitalization due to SARS-CoV-2 infection during the study (from signing of ICF to EOT) for medical treatments (e.g. supplemental oxygen therapy) or for monitoring purposes in a hospitalized setting (≥24 hours of acute care, in a hospital or similar acute care facility) will be

recorded in the eCRF and source documents. Information to be collected includes the start and end date of hospitalization due to SARS-CoV-2 infection.

6.1.2.5 Additional Prescription Medication

Additional prescription medication is defined as increase in dose or addition of any medication due to SARS-CoV-2 infection after the study drug administration on Day 1.

The information of additional prescription medication due to SARS-CoV-2 infection after the study drug administration (Day 1) will be recorded in the eCRF and source documents.

6.2 Safety Assessments

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 any patient during the study which does not necessarily have to 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 (Section 6.2.1.3). Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or worsening of the underlying disease or of other pre-existing conditions will be reported. In addition, changes in vital signs, physical examination, and laboratory tests will be recorded as (S)AE(s) in the eCRF if they are judged clinically significant by the investigator.

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

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 associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact
- 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. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

6.2.1.1.1 Adverse Events of Special Interest

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

All AEs related to infusion related reactions (hypersensitivity/anaphylactic reactions) include but are not limited to the following: bronchospasm, larynx irritation, throat irritation, hypotonia (collapse), syncope, incontinence, dizziness, vascular headache, generalized urticaria, rash, itch, flushing, swollen lips, swollen tongue, uvula swelling, angioedema, abdominal crampy pains, nausea, vomiting, hypotension, hypertension, tachycardia, bradycardia, palpitation, arthralgia, myalgia, and pyrexia (fever).

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 was 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 or result in death or 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 includes 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 (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 Events

The sponsor will promptly evaluate all SUSARs 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 the last assessment date or 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's self-reporting of AEs (Section 6.2.3), 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 (from signing of ICF to EOT) will be recorded on the AE page in the eCRF and source documents. Information to be collected includes drug treatment, dosage, 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. All AEs will be followed up to adequate resolution.

Adverse events will be graded for severity according to 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 which is present during Screening 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.

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 CRO within 24 hours from the time the investigator or designee 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**
NA back-up SAE Hotline (IDMC):	**+1 800 201 8725**
LA SAE Hotline:	**+55 114 504 4801**
EMEA/APAC SAE Fax line:	**+44 1223 374102**
NA back-up SAE Fax line (IDMC):	**+1 888 488 9697**
LA SAE Fax line:	**+55 11 3958 0983**
SAE E-mail:	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 email the form to CRO (emeaasiasafetycentral.sm@ppdi.com) or fax it to CRO within 24 hours of awareness of the event. The remote data capture system should be updated as

soon as it is available. 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), ICH guidelines, and/or local regulatory requirements.

The sponsor or its designee is responsible for reporting fatal or life-threatening SUSAR (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 IRBs/IECs by a written safety report within 15 calendar days of notification.

6.2.1.5 Follow-up of Patients Reporting Adverse Events

Where an 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 (Section 6.2.1.2).

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 Medical History and Demographic

Medical history and demographic information (age, sex, ethnicity, and race) will be recorded on both the source documents and eCRF.

6.2.3 Patient's Self-Reporting of Adverse Events and Concomitant Medications

Patients will be advised to contact the investigator at any time after the study drug administration on Day 1 if any severe symptoms develop and the investigator will determine whether the patient should be referred to a specialist. All AEs and concomitant medications reported by the patient will be recorded on the appropriate pages in the eCRF.

6.2.4 Immunogenicity Assessments

The immunogenicity of CT-P59 will be assessed by ADA and NAb test in validated immunoassay. Blood samples for immunogenicity assessments will be collected at the time points specified in the schedule of assessments (Table 11-1). 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 the immunogenicity assessment. Additional immunogenicity test will be performed if a patient experiences any immune-related AEs after the study drug administration.

Analysis will be performed at the central laboratory.

6.2.5 Hypersensitivity Monitoring

Hypersensitivity monitoring will be performed at the following time points, as specified in the schedule of assessments (Table 11-1).

- Prior to the beginning of study drug administration on Day 1 (within 30 minutes)

- Thirty minutes (±15 minutes), and 60 minutes (±15 minutes) after the start of the study drug administration
- Fifteen minutes after the end of the study drug administration (+15 minutes)
- Two hours (±15 minutes), and 4 hours (±15 minutes) after the start of the study drug administration

Additional vital signs measurements including systolic and diastolic blood pressure, heart rate, respiratory rate, 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.

6.2.6 Urine Drug Test

A urine drug test will be performed at Screening for the patients included in the PK sub-study in Part 1. The screen for drug abuse includes methamphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates. The urine drug test can be repeated once at the discretion of the investigator. Patients with positive results at Screening will not be eligible for the study if the patient is on drug abuse at the discretion of the investigator.

6.2.7 Vital Signs, Weight, Height, and Body Mass Index

Vital signs, weight, height measurements, and BMI will be performed at the time points specified in the schedule of assessments (Table 11-1). Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, saturation peripheral oxygen [SpO_2] and body temperature) will be measured after the patient has rested quietly for at least 5 minutes. SpO_2 will be measured while breathing normal room air. Body temperature will be measured using tympanic thermometer throughout the study (from signing of ICF to EOT). Height and BMI will be assessed at Screening only as a baseline measurement. 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 6.2.5).

6.2.8 Electrocardiogram

A 12-lead ECG will be performed at the time points specified in the schedule of assessments (Table 11-1) and if the patient experienced cardiac symptoms during the study drug administration. All scheduled 12-lead ECGs will be performed after the patient has rested quietly for at least 5 minutes. 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 6.2.5).

6.2.9 Physical Examination

Physical examination will be performed at the time points specified in the schedule of assessments (Table 11-1). The physical examination includes an assessment of general appearance and a review of systems.

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.

6.2.10 Hepatitis B and C and Human Immunodeficiency Virus-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 virus antibody, hepatitis C virus ribonucleic acid, and HIV-1 and -2 tests will be performed in all patients at the time points specified in the schedule of assessments (Table 11-1).

Hepatitis B, hepatitis C antibody, and HIV analysis will be performed at the central laboratory.

6.2.11 Pregnancy

Serum pregnancy test will be performed for female patients with childbearing potential and conducted at the time points specified in the schedule of assessments (Table 11-1). However, if serum pregnancy test is not available at the study site, urine pregnancy test can be performed. Only female patients of childbearing potential with a negative pregnancy test results can be enrolled.

The serum pregnancy test samples will be analyzed at the local laboratory.

In an event of unexpected pregnancy with 6 months after the study drug administration, the 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 CRO within 24 hours of the study center's knowledge of the likelihood of pregnancy while confirmation is pending. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to the sponsor and CRO within 24 hours of the pregnancy being detected.

Pregnant patients or the pregnant partners of male patients will be followed up until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed up for 1 year after the birth, when provided consent is obtained.

In female patients or female partners of patients, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs. 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).

6.2.12 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of event (Table 11-1).

The following clinical laboratory analyses will be performed.

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 (local), 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

To determine eligibility, clinical laboratory testing will be performed at the local laboratory at Screening. All clinical laboratory test for all visit will also be analyzed at the central laboratory.

6.2.13 Radiography

Radiography (chest x-ray or chest computed tomography [CT]) will be performed at Screening following the schedule of assessments (Table 11-1) and when the investigator considers it is clinically necessary (e.g., abnormal values of SpO_2).

6.2.14 SARS-CoV-2 Infection Related Signs and Symptoms

During Screening, Treatment Period, and EOT visit, the investigator or designee will perform a respiratory signs and symptoms assessment at the scheduled time points specified in the schedule of assessment (Table 11-1). SARS-CoV-2 infection related signs and symptoms should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs and the assessment for potential complications of SARS-CoV-2 infection throughout the study. During the Follow-up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone calls.

6.2.15 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 will be monitored for symptoms and levels of viral shedding suggestive of suspicious ADE throughout the study.

Patients will be considered to possibly have ADE if they meet any of the following criteria:

- 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 11-2 during the Treatment Period, EOT, and Follow-up periods. The patients will need to record the patient 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 until 7 days after the day of suspicious ADE occurrence, same procedure will be repeated from the beginning until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

6.3 Pharmacokinetic Assessments

For the patients signed informed consent to participate in a PK sub-study in Part 1, blood samples for the study drug will be collected at the specific time points (Table 6-1).

Table 6-1 Blood Sampling Time Points for PK Assessment for Part 1

Day	Time point	Window
Day 1	Pre-dose	Pre-dose within the day
	End of infusion	+ 15 minutes
	1 hour after end of infusion	
Day 2	24 hours after start of infusion	± 2 hours
Day 3	48 hours after start of infusion	
Day 5	96 hours after start of infusion	± 4 hours
Day 7	144 hours after start of infusion	
Day 10	216 hours after start of infusion	
Day 14	312 hours after start of infusion	± 1 day
Day 28	648 hours after start of infusion	± 3 days
Day 56	1,320 hours after start of infusion	± 5 days
Day 90 (or EOT visit)	2,136 hours after start of infusion	

Abbreviation: EOT = End-of-treatment; PK = pharmacokinetic

All samples should be collected as close as possible to the scheduled time point. If the PK blood sample is unable to be analyzed or is missing, extra blood samples collected for immunogenicity assessment at the same time point can be used for PK assessment. Assay of serum concentrations of CT-P59 will be done at a central laboratory. Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. See Section 6.5.3 for further information on sample collection for PK analysis.

Exposure-response analyses can be conducted including the patients who signed informed consent to participate in the PK sub-study of Part 1, if it is required from a regulatory or medical perspective.

6.4 Virology and Serology Assessments

Viral shedding based on RT-qPCR and cell culture, genotyping and phenotyping of SARS-CoV-2 isolates will be performed using the nasopharyngeal swab samples for all patients. Samples will be secured at the central laboratory for analysis and backup samples will be retained. Viral serology for SARS-CoV-2 antibody test with assays detecting serum antibodies against SARS-CoV-2 will also be performed locally using the serum samples (if the assay is available). The sample for virology and serology assessments will be collected for analysis at the time points specified in Table 11-1.

Details of biologic sampling time points and acceptable tolerance windows for virology assessments are described in Table 6-2.

Table 6-2 Nasopharyngeal Swap Sampling Time Points for Virology Assessment

Day	Time point	Window
Day 1	Pre-dose	Pre-dose within the day
Day 2	24 hours after start of infusion	± 4 hours
Day 3	48 hours after start of infusion	
Day 4	72 hours after start of infusion	
Day 5	96 hours after start of infusion	
Day 6	120 hours after start of infusion	
Day 7	144 hours after start of infusion	
Day 10	216 hours after start of infusion	
Day 14	312 hours after start of infusion	± 1 day
Day 21	480 hours after start of infusion	
Day 28	648 hours after start of infusion	± 3 days

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 Safety Blood Sampling

Blood samples for routine safety monitoring (clinical laboratory test including clinical chemistry and hematology test), and serum pregnancy test will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Table 11-1). All samples should be collected as close as possible to the scheduled time point, and the actual sampling date must be recorded in both the source documents and the eCRF.

6.5.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Table 11-1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date will be recorded in both the eCRF and source documents.

6.5.3 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each patient (only patients who participate in the PK sub-study of Part 1) at the time point specified in Table 6-1. 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.

6.5.4 Virology Sampling

Virology (for viral shedding and genotype and phenotype of SARS-CoV-2 viral isolates) and serology samples (for SARS-CoV-2 specific antibody) will be collected for analysis at the time points specified in Table 6-2 and Table 11-1. 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.

6.6 Labelling, Storage, and Transportation of Samples

6.6.1 Sample Labelling

Each sample tube will be clearly labelled with the following information: study number, patient number, tube identification and the scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples for PK, immunogenicity, virology and safety analyses will be collected.

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and backup samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the backup samples.

Additionally, backup samples for PK and immunogenicity 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 follow the laboratory manual. Virology samples will be secured at the central laboratory for analysis and backup samples will be retained. Additional tests can be conducted for virology samples with suspected resistance. The samples can be destroyed by a specific authorization of the sponsor.

7 Statistical Analysis Plan

The statistical analysis will be performed using Statistical Analysis System (SAS) software Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA). 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.

Randomization will be stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus), region and participation in PK sub-study (Yes vs. No) in Part 1, and by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, and diabetes mellitus) and region in Part 2, respectively.

Final determination of the major protocol deviations that can affect the data analysis will be made at the blinded data review meeting held in accordance with ICH Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E9.

7.1 Primary Efficacy Endpoints

For Part 1, the primary endpoints are defined as:

- Proportion of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit up to Day 14 **OR**
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 **OR**
- Time to clinical recovery up to Day 14 **OR**
- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Clinical recovery is defined as all symptoms on the SARS-CoV-2 Infection Symptom Checklist being recorded as ‘absent’ or ‘mild’ in intensity for at least 24 hours. To meet the clinical recovery, symptoms ‘moderate’ or ‘severe’ in intensity at baseline should be changed to ‘mild’ or ‘absent’, or symptoms ‘mild’ in intensity at baseline should be changed to ‘absent’, after the study drug administration. If a symptom ‘absent’ in intensity at baseline becomes ‘severe’, ‘moderate’, or ‘mild’ during the study, this should be changed back to ‘absent’ for at least 24 hours. Symptoms of SARS-CoV-2 Infection

Symptom Checklist are defined as feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache.

For Part 2, the primary endpoint is defined as:

- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28.

7.2 Secondary Endpoints

The following secondary endpoints will be analyzed for both Part 1 and Part 2 throughout the study.

7.2.1 Efficacy

The following secondary efficacy endpoints will be assessed up to Day 14 and up to Day 28.

- Proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection
- Proportion of patients with intensive care unit transfer due to SARS-CoV-2 infection
- Proportion of patients with all-cause mortality
- Time to clinical recovery
- Duration of fever defined as the last day in the patient diary on which the temperature >38 ℃ (100.4 °F) is recorded, or a potentially antipyretic drug (acetaminophen or ibuprofen) is taken
- Proportion of patients with hospital admission due to SARS-CoV-2 infection
- Proportion of mechanical ventilation due to SARS-CoV-2 infection
- Proportion of patients requiring additional prescription medication due to SARS-CoV-2 infection
- Proportion of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture

Additional prescription medication is defined as increase in dose or addition of any medication due to SARS-CoV-2 infection after the study drug administration on Day 1.

7.2.2 Safety

Safety assessments will occur throughout the study.

The following safety parameters are determined as secondary safety endpoints:

- Adverse events (including SAEs)
- Adverse events of special interests (infusion related reactions [hypersensitivity /anaphylactic reactions])
- Potential effects on the incidence of ADE
- Immunogenicity
- Vital sign measurements (systolic and diastolic blood pressure, heart rate, respiratory rate, SpO_2 and body temperature), weight and BMI
- Hypersensitivity monitoring
- 12-lead ECG
- Severe Acute Respiratory Syndrome Coronavirus 2 infection related signs and symptoms
- Radiography (chest x-ray or chest CT)
- Physical examination findings
- Clinical laboratory analyses (clinical chemistry, hematology and urinalysis)
- Pregnancy testing (serum)
- Prior and concomitant medications

7.3 Exploratory Endpoints

7.3.1 Pharmacokinetics

- Area under the concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$)
- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-inf}}$)
- Maximum serum concentration (C_{max})
- Time to C_{max} (T_{max})
- Terminal half-life ($t_{1/2}$)
- Percentage of AUC0-inf obtained by extrapolation ($\%AUC_{ext}$)
- Terminal elimination rate constant (λ_z)
- Total body clearance (CL)
- Volume of distribution during the elimination phase (V_z)

7.3.2 Virology

- Viral shedding in nasopharyngeal swab specimen based on RT-qPCR and cell culture
- Genotyping and phenotyping of SARS-CoV-2 viral isolates
- Viral serology for SARS-CoV-2 antibody

7.4 Sample Size Calculation

The objective of efficacy analyses in Part 1 is a preliminary assessment of potential activity of CT-P59 80 mg/kg or CT-P59 40 mg/kg compared to placebo. A total sample size of 300 patients with SARS-CoV-2 infection will be randomly assigned in a 1:1:1 ratio of CT-P59 80 mg/kg, 40 mg/kg or placebo. With 100 patients per group, in the range of 30% to 90% of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture in the group, the half of the width of 95% confidence interval (CI) of the point estimate of the percentage would be no more than ±9.8%. Table 7-1 shows the half of the width based on various percentage of patients with negative conversion in a group.

Table 7-1 Half of the Width of 95% CI for Various Percentage of Patients with Negative Conversion

Number of patients in a group	Percentage of patients with negative conversion (%)	Half-width 95% CI (two-sided)
100	30	9.0
100	40	9.6
100	50	9.8
100	60	9.6
100	70	9.0
100	80	7.8
100	90	5.9

Abbreviations: CI = confidence interval

In addition, 100 patients per group would provide reasonable power to detect a 20% absolute difference in percentage of patients with negative conversion for a range of percentages with negative conversion in the group. The power was calculated for the comparison of two proportions using a fisher's exact test, with one-sided type I error rate of 5%. Table 7-2 shows the power of over 86% is achieved regardless of the percentage of patients with negative conversion in the placebo group.

Table 7-2 Power to Detect a 20% Absolute Difference for Various Percentage of Patients with Negative Conversion

No. of placebo group	No. of experimental group[1]	Percentage of negative conversion in placebo group (%)	Percentage of negative conversion in experimental group[1] (%)	Power (%)
100	100	30	50	86.6
100	100	40	60	86.0
100	100	50	70	86.6
100	100	60	80	91.0
100	100	70	90	96.7

[1] The number of patient in experimental group implies CT-P59 80 mg/kg or CT-P59 40 mg/kg.

For Part 2, to demonstrate the efficacy of CT-P59 80 mg/kg (or 40 mg/kg) compared to placebo by proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28, a total of 720 patients (360 patients per group) will provide over 85% power to detect 8% reduction at a significance level of 5% (2-sided test) assuming placebo rate of 16%. A reassessment of sample size accounting for the actual placebo rate and effect size will be made using the results from Part 1.

7.5 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.

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

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

Pharmacokinetic (PK) Set (Part 1 only): The PK Set is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result of RT-qPCR or cell culture and signed informed consent to participate in a PK sub-study, who receive a complete dose of study drug and have at least one evaluable post-treatment PK result.

7.6 Description of Subgroups to be Analyzed

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

7.7 Statistical Analysis Methodology

7.7.1 General Consideration

Continuous variables will be summarized by reporting using descriptive statistics: the number of observations, mean, standard deviation, 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.

7.7.2 Study Population

7.7.2.1 Disposition of Patients

The number and percentage of patients entering and completing the clinical study will be presented by each treatment arm.

The number of patients who enroll in the study and the number and percentage of patients who complete the study will be presented. Frequency and percentage of patients who is withdrawn or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.7.3 Efficacy Analysis

7.7.3.1 Primary Efficacy Analysis

The primary analyses of Part 1 are as below:

- Proportion of patient with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit up to Day 14 **OR**
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 **OR**
- Time to clinical recovery up to Day 14 **OR**
- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Time to clinical recovery will be assessed by the patient diary for SARS-CoV-2 Infection Symptom Checklist. The checklist consists of 7 symptoms (feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache) and the intensity of patient's self-aware for each SARS-CoV-2 infection symptom. Scores for SARS-CoV-2 infection symptom are absent (0), mild (1), moderate (2), and severe (3). Time to clinical recovery analysis defined as the first day on which the

patient satisfies the following:

- Patient who records as ‘absent’ or ‘mild’ in intensity for all symptoms on the SARS-CoV-2 Infection Symptom Checklist for at least 24 hours.

The primary analysis of Part 2 is as below:

- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28.

For Part 1, the primary endpoints will be analyzed on the ITTI set. Time to event analyses will be analyzed using Kaplan-Meier analysis presenting 95% CI of median. The others will be summarized using frequency tables with 95% CI.

The primary efficacy endpoint of Part 2 will be analyzed on the ITT set using the p-value from logistic regression model with stratification factors as covariates at the 2-sided significance level of 5%. For sensitivity analysis, Fisher’s exact test will be conducted on ITT set. Also, supportive analysis will be performed on ITTI set.

7.7.3.2 Secondary Efficacy Analysis for both Part 1 and Part 2

The secondary efficacy endpoints will be assessed up to Day 14 and up to Day 28 and analyzed on both ITTI and ITT sets. Time to event analyses will be analyzed using Kaplan-Meier analysis. The others will be summarized using descriptive statistics or frequency tables.

7.7.3.2.1 Clinical Recovery

Time to clinical recovery will be summarized by each treatment group.

Time to clinical recovery, defined as the first day on which the patient records as ‘absent’ or ‘mild’ in intensity for all symptoms on the SARS-CoV-2 Infection Symptom Checklist for at least 24 hours, will be analyzed using Kaplan-Meier analysis.

7.7.3.2.2 Intensive Care Unit Transfer

The proportion of patients transferring to intensive care unit due to SARS-CoV-2 infection will be separately summarized by each treatment group.

7.7.3.2.3 Mortality Rate

The proportion of patient with all-cause mortality will be separately summarized by each

treatment group.

7.7.3.2.4 Requirement of Supplemental Oxygen

The proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection will be separately summarized by each treatment group.

7.7.3.2.5 Hospitalization

The proportion of patients with hospital admission due to worsening of signs and symptoms related to SARS-CoV-2 infection for patients who are participating the study and are not confined in the study center due to local regulation or at discretion of the investigator will be summarized by each treatment group.

7.7.3.2.6 Additional Prescription Medication

The proportion of patients requiring additional prescription medication due to SARS-CoV-2 infection will be summarized by each treatment group.

7.7.3.2.7 Mechanical Ventilation Use

The proportion of patients with new mechanical ventilations use due to SARS-CoV-2 infection will be summarized by each treatment group.

7.7.3.2.8 Body Temperature

Duration of fever (>38 ℃ [100.4 ℉]) will be summarized by each treatment group. Duration of fever is defined as the last day in the patient diary on which the body temperature of >38.0 ℃ (100.4 ℉) is recorded, or a potentially antipyretic drug (acetaminophen or ibuprofen) is taken.

7.7.3.2.9 Viral Shedding on RT-qPCR and Cell Culture

As the efficacy endpoints, percentage of patients with negative conversion, and time to negative conversion will be summarized by each treatment group using descriptive statistics or frequency tables.

7.7.4 Safety Analysis

The safety analyses will be performed using the Safety Set. The safety results including ADE and immunogenicity will be listed and summarized by each treatment group. The results of other safety analyses will be presented using descriptive statistics or shift tables,

as appropriate.

7.7.4.1 Demographics, Baseline, and Background Characteristics

Demographics (e.g., age, sex, race, and ethnicity), baseline and background characteristics will be presented by means of summary tables (descriptive statistics for quantitative variables, or frequency for qualitative variables).

7.7.4.2 Adverse Events

Severity of AEs will be graded according to the CTCAE Version 5.0 and AEs will be coded to system organ class and preferred term according to MedDRA. A TEAE is defined as described in Section 6.2.1.1. The following AE summaries will be reported by system organ class, preferred term, and each treatment group, as appropriate:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 TESAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with AESIs (infusion related reaction including hypersensitivity/anaphylaxis reaction)

If more than one AE is recorded for a patient within any system organ class or preferred term, the patient will be counted only once within the respective summary. Adverse events will also be summarized by maximum intensity and relationship to study drug with the percentage of patients in each category. All AE data will be presented in the data listings, and additional TEAE analyses may be performed as detailed in the SAP.

7.7.4.3 Clinical Laboratory Test

Actual values and changes from baseline for numeric clinical laboratory test (clinical chemistry, hematology and urinalysis) results will be summarized by each treatment group at each scheduled visit using descriptive statistics. Shift tables will be generated for categorical clinical laboratory test results.

Individual clinical laboratory and pregnancy tests results will be presented in data listings.

7.7.4.4 Electrocardiogram, Physical Examination, and Vital Sign

Actual values and change from baseline for vital sign measurements will be summarized by each treatment group at each scheduled visit using descriptive statistics. Shift tables comparing the categorical investigator interpretation of 12-lead ECGs and physical

examinations at each scheduled visit with those at baseline will be summarized by each treatment group.

Individual ECG results and the investigator's interpretation, physical examination findings, and vital sign measurements (including hypersensitivity monitoring) will be presented in data listings.

7.7.4.5 Prior, Concomitant Medications and Standard of Care

Prior and concomitant medications will be coded to drug class and preferred term using the WHO Drug Dictionary. All prior and concomitant medications data (including medications used as part of SoC) will be listed and summarized by each treatment group.

7.7.4.6 Immunogenicity

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

7.7.4.7 SARS-CoV-2 Infection Related Signs and Symptoms

The SARS-CoV-2 infection related signs and symptoms will be assessed at each scheduled visit with those at baseline and the results will be summarized by the scheduled visit and by treatment group.

7.7.4.8 Potential Effects of the Incidence of Antibody-dependent Enhancement

The number and percentage of patients with suspicious ADE will be presented by treatment group.

7.7.5 Exploratory Analysis

7.7.5.1 Pharmacokinetic Analysis

All PK analyses will be conducted in the PK set (Part 1 only). The PK parameters of CT-P59 will be analyzed using non-compartmental methods based on the actual sampling time points. All parameters will be calculated using Phoenix WinNonlin (Pharsight, St Louis, Missouri, USA).

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

Dose proportionality for CT-P59 will also be assessed for C_{max} and $AUC_{0\text{-}last}$ using the Power model.

Additional PK analyses may be performed as detailed in the SAP.

7.7.5.2 Virology and Serology Analysis

Exploratory virology (viral shedding based on RT-qPCR and cell culture, genotyping and phenotyping of SARS-CoV-2 viral isolates, and viral serology for SARS-CoV-2 antibody) analysis will be conducted in the ITTI set.

For viral shedding in nasopharyngeal swab specimen based on RT-qPCR and cell culture, the 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 each treatment group at each scheduled visit using descriptive statistics or frequency tables. Mean viral load titer will be plotted for each scheduled time point in log scale.

Genotype, phenotype and serology results will be presented in data listing by treatment groups.

7.8 Interim Analysis

No interim analyses are planned for both Part 1 and Part 2 of this study.

7.9 Institutional Review

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 harmonised guideline E6(R2): GCP and the Declaration of Helsinki (World Medical Association, 2013) 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 supply the sponsor or its designee with written documentation of continued review of clinical research.

7.10 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH GCP guidelines on quality and risk management.

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 lab database. The eCRF will be reviewed for accuracy and completeness by the monitor during on-site monitoring visits and after their return to the sponsor or its designee; 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.

Central laboratory data will be sent directly to the sponsor using their standard procedures to handle and process the electronic transfer of these data. 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 eCRF. 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.

8 Investigator's Obligations

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

8.1 Confidentiality and Data Protection

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.

8.2 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 the ICF is revised during the course of the study, all active participating patients must sign the revised form in case new information becomes available that may be relevant to the patient's willingness to continue participation in the clinical study.

Before recruitment and enrollment, each prospective patient/legal guardian will be given a full explanation of the study by the investigator or designee and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient /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 will be given to the patients.

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.

8.3 Adverse Events and Study Reporting Requirements

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs to sponsor and/or IRB/IEC 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 the relevant IRB/IEC as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

8.4 Financial Disclosure and Obligations

CELLTRION, Inc. is the sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, investigator, and CRO. The sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. The sponsor will indemnify all investigators

participating in this study against future claims by study patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The investigator is required to take out liability insurance for all patients included in the study as required by local law and/or regulations and/or ICH GCP, whichever is applicable.

The investigator and the sponsor will sign a clinical study agreement before the start of the study. The agreement will outline overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the costs based on the calculated expenses of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract.

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 pre-existing disease.

The sponsor undertakes to compensate the patient for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

8.5 Investigator Documentation

Before beginning the study, the investigator will be asked to comply with ICH harmonised guideline and Code Of Federal Regulations Title 21 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.

8.6 Study Conduct

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

8.7 Data Collection

8.7.1 Electronic Case Report Forms and Source Documents

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), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly.

The eCRF are accessed through the appropriate system, which allows for on-site data entry and data management. Study center users will have access to read and write in 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.

8.8 Coding Dictionaries

Medical history, as well as all AEs, will be coded using MedDRA. Previous and concomitant medications will be coded using the WHO Drug Dictionary.

Versions of coding dictionaries will be stated in the study report.

8.9 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.

8.10 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.

8.11 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 will be retained until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product. 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.

8.12 Patients Identification Register

The investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed by the investigator in the Study Center Master File. Otherwise, all reports

and communications relating to the study will identify patients by assigned number only.

8.13 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, 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.

9 Study Management

9.1 Sponsor

CELLTRION, Inc.
23, Academy-ro, Yeonsu-gu, Incheon
22014, Republic of Korea
Phone: +82 32-850-5000
Fax: +82 32-850-5050
Email: contact@celltrion.com

Sponsor Representative
Sung Hyun Kim
Head of Clinical Planning Department
Phone: +82 32 850 5778
Fax: +82 32 837 1203
Email: SungHyun.Kim@celltrion.com

9.2 Vendor Contact

CRO
PPD Global
PPD Granta Park
Great Abington
Cambridge CB21 6GQ
United Kingdom

SAE Reporting
PPD PVG
Email: emeaasiasafetycentral.sm@ppdi.com

9.3 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. Details of analytical facilities are presented in the Lab Manual.

9.4 Data Safety Monitoring Board

This study will be monitored by the independent DSMB. The DSMB will review and evaluate accumulating safety data to ensure the safety of trial subjects. The study will be temporarily stopped if any safety concern or study drug-related TEAE is raised during

monthly SAE listings review by DSMB. The DSMB will evaluate and review available data and will make a recommendation on continuation of study.

The DSMB will provide recommendations for the study to continue as designed for Part 2 based on the review of all available data after all patients have reached Day 28 in Part 1. If, following the review of the data, there are safety concerns, the DSMB may consider recommending modifications or early termination on safety grounds.

Further details will be provided in the independent DSMB charter.

9.5 Monitoring

9.5.1 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 Decrees 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 (SDV) could be performed remotely by the CRAs 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. 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 ICH E6(R2) and SOPs.

9.5.2 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 and CRO of any audits scheduled by any regulatory authorities.

9.6 Management of Protocol Amendments and Deviations

9.6.1 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 IRB/IEC 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.

9.6.2 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 may include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unblinding. Investigators will be notified in writing by the monitor of deviations. The IRB/IEC will be notified of protocol deviations, if applicable, in a timely manner.

9.7 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, if the study is not discontinued by sponsor decision before this date.

9.8 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 harmonised tripartite guideline E3: Structure and content of CSRs.

The sponsor plans to prepare 4 CSRs to report the following:

- Synoptic CSR with data up to Day 28 of last enrolled patient in Part 1
- Clinical study report with all data after completion of Part 1
- Clinical study report with data up to Day 28 of last enrolled patient in Part 2
- Clinical study report with all data after completion of Part 2

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

10 Reference List

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11 Appendices

11.1 Schedule of Assessments

Table 11-1 Schedule of Assessments

	Screening [1]	Treatment Period												EOT [2]	Follow-Up Period [3]
Study Day (Visit windows) [4]	**-7 to 1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**14 (±1)**	**21 (±1)**	**28 (±3)**	**56 (±5)**	**90 (±5)**	**Biweekly up to 180 (±5)**
Telephone Follow-Up Visit															**X**
Informed consent	X														
Medical history	X														
Demographics	X														
Weight, BMI and height [5]	X	X [6]												X	
Urine drug abuse check (only subgroup [PK] cohort) [7]	X														
Hepatitis B/C and HIV test (central) [8]	X														
Serum pregnancy test [9]	X													X	
Inclusion/exclusion criteria	X	X [6]													
Randomization		X [6]													
Administration of study drug [10]		X													
Nasopharyngeal swab [11]															
• SARS-CoV-2 infection by sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR [12]	X														
• Viral shedding (central, RT-qPCR and cell culture), genotyping and phenotyping of SARS-CoV-2 viral isolates (central) [13]		X [6]	X	X	X	X	X	X	X	X	X	X		(X) [14]	

Study Day (Visit windows) [4]	Screening [1]	Treatment Period												EOT [2]	Follow-Up Period [3]
	-7 to 1	1	2	3	4	5	6	7	10	14 (±1)	21 (±1)	28 (±3)	56 (±5)	90 (±5)	Biweekly up to 180 (±5)
Telephone Follow-Up Visit															X
Patient diary [15]	X	X											(X)		
SARS-CoV-2 infection related signs and symptoms assessment [16]	X	X [6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling (central)		X [6]						X		X		X	X	X	
Viral serology for SARS-CoV-2 antibody [17]		X [6]						X		X		X	X	X	
Pharmacokinetic sampling (central, only subgroup [PK] cohort) [18]		X	X	X		X		X	X	X		X	X	X	
Physical Examination	X	X [6]												X	
Clinical laboratory analyses (central) [19]	X		X	X		X		X	X	X		X	X	X	
Vital Signs (blood pressure, heart rate, respiratory rate, SpO_2 and body temperature) [20]	X	X [6]	X	X	X	X	X	X	X	X	X	X	X	X	
NYHA class assessment	X	X [6]													
12-lead ECG [21]	X	X [6]	X					X		X		X	X	X	
Radiography [22]	X														
Hypersensitivity monitoring [23]		X													
Disease status monitoring [24]	X														
Restriction assessment [25]	X														
Prior, concomitant medication [26]	X														
Adverse events monitoring [27]	X														

Abbreviations: ADE=antibody-dependent enhancement; ADR=adverse drug reaction; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; CRP=c-reactive protein; CT=computed tomography; ECG=electrocardiogram; EOT=End-of-Treatment; ESR= erythrocyte sedimentation rate; HBcAb=hepatitis B core antibody, HBsAg=hepatitis B surface antigen; HIV=Human immunodeficiency virus; ICF=informed consent form; NYHA=New York Heart Association; PK=pharmacokinetics; RT-PCR=reverse transcription polymerase chain reaction; RT-qPCR= reverse transcription quantitative polymerase chain reaction ; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2= saturation of peripheral oxygen.

1. If Screening visit date and the date of study drug administration are the same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the same day 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 patients including patients who withdraws prematurely after the study drug administration, each telephone call follow-up will occur biweekly from EOT up to Day 180. During the Follow-up Period, SARS-CoV-2 infection related signs and symptoms will be assessed by telephone calls to capture the suspicious ADE occurrence. For patients with suspicious ADE occurrence, all assessments specified in Table 11-2 will be conducted on unscheduled visit.
4. All patients will complete the study visits during the treatment period either by visiting the study center, confinement in the study center, or home visiting services by health care professionals, whichever applicable according to the local regulations or discretion of investigator.
5. Measurement of height and BMI will be performed once at Screening.
6. These assessments should be performed prior to the study drug administration.
7. A urine drug tests will be performed at Screening for the patients from Part 1 who decide to participate the PK sub-study. The screening for drug abuse includes methamphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates. The urine test can be repeated once at the discretion of the investigator. Patients with positive results at Screening will not be eligible for the study if the patient is on drug abuse in the discretion of investigator.
8. 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 virus antibody, hepatitis C virus ribonucleic acid, and HIV-1 and -2 tests will be performed in all patients. Hepatitis B, hepatitis C virus antibody, and HIV analysis will be performed at the central laboratory.
9. For females patients with childbearing potential, serum pregnancy test will be performed locally at Screening and EOT visit. However, if serum pregnancy test is not available at study site, urine pregnancy test can be performed. Only female patients of childbearing potential with a negative pregnancy test results can be enrolled.
10. Study drug will be administered as an IV infusion over 90 minutes (±15 minutes) on Day 1. When calculating total volume of study drug to be administered, the body weight of each patient measured on Day 1 will be used.
11. Nasopharyngeal swabbing will be performed by trained site personnel. A nasopharyngeal swab sampling time points and acceptable tolerance windows are specified in Table 6-2.
12. If the patient had a RT-PCR result (within 72 hours before the study drug administration) confirming SARS-CoV-2 infection even if before signing the informed consent, the patient can be enrolled. During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.
13. Nasopharyngeal swabbing will be performed in each of the patient's two nostrils; therefore, two nasopharyngeal swabs in one sample bottle will be collected for each assessment visits.
14. If the RT-qPCR result on Day 28 shows positive of SARS-CoV-2 infection, additional viral shedding will be conducted on Day 90.
15. Patients will be instructed to complete the patient diary for SARS-CoV-2 Infection Symptom Checklist twice a day at approximately 12-hour intervals in the morning (between 6 and 10 AM, approximately) and in the evening (between 6 and 10 PM, approximately) from Day 1 until Day 28. The patient diary will be recorded once at Screening. On the date of study drug administration (Day 1), the patient diary will be recorded twice; before and after the study drug administration. If Screening visit date and the date of study drug administration are the same, patient diary will be also recorded twice; before and after the study drug administration. After Day 28, additional recording of the diary will be required if following conditions are met:
    - For patient who achieves clinical recovery on Day 28, the patient will record the diary until Day 29 to confirm whether the patient's condition is maintained at least 24 hours.
    - For patient who shows deterioration (at the discretion of the investigator) or is still not recovered, the patient will record the diary until achievement of clinical recovery.
    - For patients with suspicious ADE occurrence, the patient will record the diary for 7 days from the day of suspicious ADE occurrence (specified in Table 11-2). If suspicious ADE has not resolved or has worsened during the 7 days, same procedure of recording patient diary for 7 days will be repeated until the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

    Body temperature for the patient diary will be collected for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection in the SARS-CoV-2 Infection Symptom Checklist at Screening, or the patients who record feeling feverish in the SARS-CoV-2 Infection Symptom Checklist at any time throughout the study.
    However, if patient's condition is not available to record the diary at the discretion of investigator (e.g. sedation state for mechanical ventilator therapy), recording can be discontinued. Recording will be resumed when the patient's condition becomes available to record the patient diary.
16. SARS-CoV-2 infection related signs and symptoms should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs and the assessment for potential complications of SARS-CoV-2 infection throughout the study. During the Follow-up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone calls.
17. Viral serology for SARS-CoV-2 antibody test with assays detecting serum antibodies against SARS-CoV-2 will be performed locally using the serum samples (if the assay is available).

18. PK sub-analysis will be performed at the central laboratory on the patients in Part 1 who signed informed consent to participate in a PK sub-study. Blood sampling time points and acceptable tolerance windows for PK assessments are specified in Table 6-1 and below:
    - Day 1: pre-dose, at the end of infusion (within 15 minutes after the end of study drug infusion), and 1 hour (+15 minutes) after the end of the study drug infusion.
    - Day 2: 24 hours (±2 hours) after the start of the study drug infusion.
    - Day 3: 48 hours (±2 hours) after the start of the study drug infusion.
    - Day 5: 96 hours (±4 hours) after start of infusion.
    - Day 7: 144 hours (±4 hours) after the start of the study drug infusion.
    - Day 10: 216 hours (±4 hours) after start of the infusion.
    - Day 14: 312 hours (±1 day) after start of the infusion.
    - Day 28 (±3 days), Day 56 (±5 days), and Day 90 (±5 days)/EOT visit.
19. To determine eligibility, clinical laboratory testing will be performed at the local laboratory at Screening. Clinical laboratory testing (clinical chemistry, hematology, and urinalysis) for all visits including Screening will be analyzed at the central laboratory.

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, ESR (local), 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.

20. Blood pressure, heart and respiratory rates, SpO_2 and body temperature will be measured after the patient has rested quietly for at least 5 minutes. SpO_2 will be measured while breathing normal room air. Temperature will be measured using tympanic thermometer throughout the study.
21. All scheduled 12-lead ECGs must be performed locally 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.
22. Radiography (chest x-ray or chest CT) will be performed at Screening and when the investigator considers it is clinically necessary (e.g., abnormal values of SpO_2). An additional radiography can be performed at the investigator's discretion based on the judgment per the signs and symptoms (e.g., abnormal values of SpO_2).
23. Hypersensitivity monitoring at Day 1 pre-dose (within 30 minutes), 30 minutes (±15 minutes) and 60 minutes (±15 minutes) after the start of the study drug administration, 15 minutes after the end of study drug administration (±15 minutes), 2 hours (±15 minutes) and 4 hours (±15 minutes) from the start of study drug administration (specified in Section 6.2.5). Additional vital signs including blood pressure, heart rate, respiratory rate and body temperature will be evaluated for possible hypersensitivity reactions. Hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed.
24. Disease status including requirement of supplemental oxygen, intensive care unit transfer, mechanical ventilation use, hospitalization, and additional prescription medication will be monitored during the study period (from signing of ICF to EOT).
25. Restriction assessments will be performed only for the patients in the PK sub-study in Part 1.
26. Use of all prior and concomitant medications for the treatment of SARS-CoV-2 infection from the diagnosis of disease until the EOT visit, will be recorded in both the source documents and the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 1) or from when the ICF is signed, whichever is earlier, will be recorded until the EOT visit.
27. Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOT visit. Where an 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. AEs of special interest (infusion related reactions [hypersensitivity/anaphylactic reactions]) should be closely monitored.

Table 11-2 Schedule of Assessments for Patients with Suspicious ADE Occurrence (Unscheduled Visits)

Evaluation	Suspicious ADE Assessment				
	Day of occurrence [1]	Day 2	Day 3	Day 5	Day 7 [2]
Nasopharyngeal swab					
• RT-PCR (local) [3]	(X)				
• Viral shedding (central, RT-qPCR and Cell culture)	X	X	X	X	X
• Genotype and phenotype of SARS-CoV-2 viral isolates (central) [4]	(X)				
Patient diary [5]	X	X	X	X	X
SARS-CoV-2 infection related signs & symptoms assessment [6]	X	X	X	X	X
Vital Signs [7]	X	X	X	X	X
12-lead ECG [8]	X		X		X
Troponin test (I or T, only one applicable) (central) [9]	X		X		X

Abbreviations: ADE=antibody-dependent enhancement; ECG=electrocardiogram; RT-qPCR= reverse transcription quantitative polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2= saturation peripheral oxygen.

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 outpatient visit. The assessments designated with an (X) will be performed in selected visits under the conditions explained in the relevant document of virology analysis.

1. The day of suspicious ADE occurrence.
   - If a patient has excessive progression of symptoms regarded as related to viral infection (e.g., excessive infiltration of inflammatory cells in the lung), OR
   - If a 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 until 7 days after the day of suspicious ADE occurrence, same procedure will be repeated from the beginning 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 genotyping and phenotyping will be performed using the biologic samples for patients.
5. For patients with suspicious ADE occurrence, patient will record the patient diary for SARS-CoV-2 Infection Symptom Checklist for 7 days from the day of suspicious ADE occurrence. Body temperature for the patient diary will be collected for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection in the SARS-CoV-2 Infection Symptom Checklist on suspicious ADE occurrence, or the patients who record feeling feverish in the SARS-CoV-2 Infection Symptom Checklist at any time throughout the suspicious ADE assessment. Patients will be instructed to complete the diary twice a day at approximately 12-hour intervals in the morning (between 6 and 10 AM, approximately) and in the evening (between 6 and 10 PM, approximately).
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. Blood pressure, heart rate and respiratory rate, SpO_2 and body temperature will be measured after the patient has rested quietly for at least 5 minutes. SpO_2 will be measured while breathing normal room air. Temperature will be measured using tympanic thermometer throughout the study.
8. 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.
9. Troponin test will be analyzed at the central laboratory. However, analysis of the test can be also conducted at local laboratory at discretion of investigator.

11.2 SARS-CoV-2 Infection Symptom Checklist

All patients will complete the checklist twice a day at approximately 12-hour intervals in the morning (between 6 and 10 AM) and in the evening (between 6 and 10 PM) from Day 1 to Day 28. The patient diary will be recorded once at Screening. On the date of study drug administration, the patient diary will be recorded twice; before and after the study drug administration. Additional assessment will be performed as specified in Section 6.1.1.

Please check a matching box that describes the intensity for each of your SARS-CoV-2 infection symptoms.

	Intensity (score) / 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

11.3 New York Heart Association Functional Classification

As defined in Zhang et al, 2018, the New York Heart Association (NYHA) classification is used in patients with heart failure.

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea.
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.