CLINICAL STUDY PROTOCOL

A Pilot Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Virology of CT-P59 in Patient with Mild Symptoms of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

PROTOCOL NUMBER CT-P59 1.2

EudraCT Number:	2020-003165-19
Study Drug	CT-P59
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SAE Reporting :	[redacted]
Version and Date of Protocol	Protocol Version 1.3, 27 July 2020

Protocol Approval

Study Title	A Pilot, Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Virology of CT-P59 in Patient with Mild Symptoms of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection
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Protocol accepted and approved by:

Head of Clinical Planning Department
Sung Hyun Kim
CELLTRION, Inc.
23, Academy-ro, Yeonsu-gu, Incheon
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[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled 'A Pilot Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Virology of CT-P59 in Patient with Mild Symptoms of 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 1.3, dated 27 July 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:

Address:

Phone:

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PROTOCOL SYNOPSIS

Protocol Number: CT-P59 1.2

Title: A Pilot Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Virology of CT-P59 in Patient with Mild Symptoms of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

Study Phase: Phase 1

Sponsor: CELLTRION, Inc.

Study Center: Approximately 5 centers in Republic of Korea, Romania and United Kingdom

Test Drug Formulation, Dose, and Regimen:
CT-P59 (960 mg/16 mL): 20 mg/kg, 40 mg/kg or 80 mg/kg, intravenous (IV) infusion for 90 minutes (± 15 minutes)

Reference Drug Formulation, Dose, and Regimen:
Placebo (16 mL): matching in volume to each dose of CT-P59, IV infusion for 90 minutes (± 15 minutes)

Objectives:

Primary objective

- To evaluate the preliminary safety and tolerability of CT-P59 up to Day 14 of the last enrolled patient

Secondary objectives

- To evaluate the viral efficacy and characterization of SARS-CoV-2 viral isolates
- To evaluate the efficacy of CT-P59
- To evaluate the PK of CT-P59
- To evaluate additional safety of CT-P59 including immunogenicity

Main Selection Criteria:
Adult male or female patients aged 18 to 60 years (both inclusive), with mild symptoms of SARS-CoV-2 infection diagnosed by reverse transcription polymerase chain reaction (RT-PCR) and no more than 7 days prior to the study drug administration from the onset of symptom will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

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

1. Adult male or female patient, aged between 18 to 60 years (both inclusive).
2. Patient with laboratory confirmed SARS-CoV-2 infection by RT-PCR at Screening.
   Note: But, if the patient had RT-PCR result confirming SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 7 days from the onset of symptoms), the result can be allowed.
   Note: During the Screening Period, only one retest for RT-PCR will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the retest results.
3. Patient has mild conditions meeting all of the following criteria:
   a. Oxygen saturation ≥ 94% on room air.
   b. Not requiring supplemental oxygen.
4. Patient has one or more of the following 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
5. 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

6. 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 symptom of the SARS-CoV-2 infection.
7. Patient with a body weight between 50 kg and 100 kg (both inclusive) and a body mass index of ≥ 18.0 kg/m^2.
8. Patient is able to understand and to comply with protocol requirements, instructions, and restrictions.
9. Patient voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the Screening procedures.
10. Patients and their partners of childbearing potential must agree to use a highly effective method of contraception or two acceptable methods of contraception until 6 months after the study drug administration as specified in Section 5.8.2. A woman is considered of childbearing following menarche and until becoming post-menopausal unless permanently sterile. A menopausal female must have no menses more than 12 months without an alternative medical cause prior to the date of informed consent to be classified as not of childbearing potential. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. 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 medically acceptable methods of contraception.

Exclusion Criteria:

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

1. Patient with severe condition meeting one of the following:
   a. Respiratory distress with respiratory rate ≥ 30 breaths/min.
   b. Requires supplemental oxygen.
   c. Experience shock.
   d. Complicated with other organs failure, and intensive care unit monitoring treatment is needed by Investigator's discretion.
   e. Any other conditions suspected of being severe symptoms of SARS-CoV-2 infection, in the opinion of the Investigator, including but not limited to radiographic findings in lung.
2. Patient has a medical history or current presence of disease including one or more of the following(s):
   a. Clinical hematology results of neutrophil count < 1.0×10^3 cells/μL (International System of Units < 1.0×10^9 cells/L) at Screening and Day 1.
   b. Clinically significant condition of allergic reaction (e.g., urticaria, angio-oedema), atopic condition (asthma and eczematous dermatitis) in the Investigator's opinion and/or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any monoclonal antibody or any components of study drugs.
   c. History of and/or current medical condition, classed as clinically significant by the Investigator, including gastrointestinal, renal, endocrine, neurologic, autoimmune, hepatic, hematological, metabolic (including known diabetes mellitus), cardiovascular, or psychiatric condition.
   d. History or any concomitant active malignancy.
   e. History of and/or current infection with human immunodeficiency virus, hepatitis B or hepatitis C.
   f. History of serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 6 months before the study drug administration and/or current infection, other than SARS-CoV-2 infection, requiring a course of systemic anti-infective therapy.
   g. History of an illness, other than SARS-CoV-2 infection, within 28 days prior to the study drug administration that is identified as clinically significant by the Investigator and/or requires hospitalization.
   h. History of surgical intervention and/or an operation within 28 days prior to the study drug administration or plans to have a surgical procedure during the study period.

3. Patient had a history of or concurrent use of medications including any prior therapy of following(s):
   a. Any vaccinations within 4 weeks prior to the study drug administration.
   b. Blood transfusion, or participated in another clinical trial within 3 months prior to the study drug administration.
   c. Treatment with any monoclonal antibody, fusion protein, or biologics within 6 months prior to the study drug administration.
   d. Any off-label or other investigational drugs prescribed for the treatment of SARS-CoV-2 infection.
   e. Potential antiviral drugs and/or immune-based therapy under evaluation for treatment of SARS-CoV-2 infection.
   f. Use of medications that are contraindicated with standard of care (SoC).
4. A male patient plans to father a child or donate sperm or a female patient is lactating or planning to be pregnant or to breastfeed within 6 months from the study drug administration.
5. Patient shows reasonable evidence of drug/alcohol/nicotine abuse prior to the study drug administration as opinion of the Investigator or has following(s):
   a. Positive result for drug urine test during Screening and/or the opinion of the Investigator.
   b. History or presence of regular consumption exceeding an average weekly intake of > 14 units of alcohol in recent 3 months prior to the study drug administration.
   c. Consuming more than 10 cigarettes or equivalent per day within a month prior to the study drug administration.
6. Patient is unwilling to avoid the use of alcohol or alcohol containing foods, medications, or beverage within 48 hours prior to admission and 24 hours prior to each study visit throughout the study or unable to refrain from smoking during the in-house stays.
7. Patient donated or lost 400 mL or more whole blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration.
8. 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.
9. Patient is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalized persons by law enforcement).
10. Patient is not likely to complete the study for whatever reason other than criteria listed above in the opinion of the Investigator.

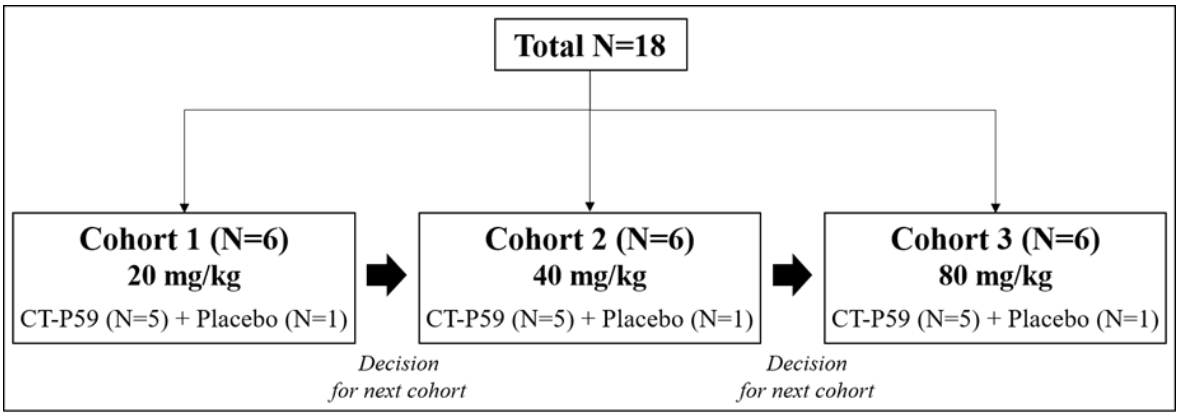
Study Design:

This 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 SoC, except potential antiviral drugs and/or immune-based therapy under evaluation for treatment of SARS-CoV-2 infection, in patients with mild symptoms of SARS-CoV-2 infection.

Approximately 18 patients in 3 cohorts are planned for enrollment and each cohort will consist of 6 patients, 5 of whom will receive CT-P59 and 1 of whom will receive a placebo. In each cohort, patients will be randomized in a 5:1 ratio to receive CT-P59 or placebo.

This study will be started with the lowest dose that will maximize safety and the dose levels will be escalated to the higher doses. The overview of the study is presented in Figure 1.

Figure 1. Study Design Overview



After each study drug administration, patients will be observed for 48 hours for evaluation of the safety and tolerability of the study drug.

When escalating dose from previous cohort to next cohort, Dose Escalation Committee (DEC) will review all available safety data of all patients in each cohort, within an observation period of 48 hours after study drug administration. If no safety or tolerability concern is observed, patients in next cohort will receive study drug.

The dose escalation from a previous cohort to the next cohort will be stopped if one or more of the following stopping criteria are met:

- Two or more patients in one cohort experience TEAEs of grade 3 or higher, which are considered to be related to study drug.
- Four or more patients in one cohort experience TEAEs of grade 2 or higher, which are considered to be related to study drug.
- One or more patients in one cohort experience a treatment-emergent serious AE (TESAE), which are considered to be related to study drug.

If an event corresponding to the above criteria occurs within the observation period of 48 hours in each cohort and the dosing is temporarily stopped under the decision of DEC, the appointed independent Data and Safety Monitoring Board (DSMB) members will evaluate the relationship to CT-P59 of the event with unblinded manner and make a decision on continuation and the dose escalation of the study.

If an event corresponding to the above criteria occurs after observation period of 48 hours in the previous cohort, further progression to next cohort will be temporarily stopped and the appointed independent DSMB members will review data and make a decision on continuation and the dose escalation of the study.

If it was revealed that an event corresponding to the above criteria occurs and all the TEAEs are related to CT-P59 as reviewed by DSMB members, the study will be temporarily stopped and the information will be submitted to regulatory authority for further evaluation and confirmation on continuation of the dose escalation of the study.

Study Procedure:

The total duration of this study will be approximately 27 weeks for the individual patient, including Screening Period and Follow-Up Period.

Screening *(Day -7 to Day 1)*

Patients will sign and date the informed consent form and undergo procedures to determine eligibility. During the Screening Period, retest for Screening is permitted only once by the Investigator's judgement. If the repeated test result is again not suitable or indeterminate for inclusion, the patient will be screen failed. Only one retest for RT-PCR will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on retest results. And, if there is available RT-PCR result confirming SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 7 days from the onset of symptoms), the result can be allowed.

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

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

Inclusion and exclusion criteria will be re-confirmed on Day 1. If it is concluded that the patients are not eligible in Day 1 assessments, the patient will be considered as Screening failure even if he/she was eligible based on assessments results performed during Screening Period.
Patients will be randomized in 5:1 ratio to receive CT-P59 or placebo once all eligibility criteria have been confirmed. Patients will receive a single dose of CT-P59 or placebo on Day 1.
All patients will be admitted to the study center on Day 1 and it is recommended to be confined up to Day 7. In-house stay period can be determined by Investigator considering the isolation regulation and/or public health capacity of the country, however all patients should be confined to the study center for at least 72 hours (until completion of all assessments on Day 3).
After discharge, the consecutive study visits will be carried out on an out-patient basis. During the isolation period according to the local regulation, patients will visit the study center using the transportation provided by Sponsor.

End-of-Treatment Visit *(Day 90)*

End-of-treatment (EOT) visit assessments will be performed on Day 90. If a patient early terminated from the study, the patient will be asked to return to the study center as soon as possible for the safety assessments predefined for EOT visit.

Follow-Up Period *(From End-of-Treatment Visit to Day 180)*

For all patients including a patient who early terminated from the study, each telephone call follow-up will occur bi-weekly from 2 weeks after the EOT visit to Day 180. During the Follow-Up Period, SARS-CoV-2 infection related signs and symptoms will be assessed by telephone call to capture the suspicious antibody dependent enhancement (ADE) occurrence. For patients with suspicious ADE occurrence, additional assessments will be conducted on unscheduled visit.

Study Endpoint:

Primary endpoints

Primary endpoints will be analyzed based on the data up to Day 14 of the last enrolled patient.

Safety

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AEs of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Potential effects on the incidence of ADE
- Vital signs (blood pressure, heart rate, body temperature, SpO_2 and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead electrocardiogram (ECG)
- Severe Acute Respiratory Syndrome Coronavirus infection related signs and symptoms
- Radiography (chest x-ray and/or chest CT)
- Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)

Secondary endpoints

Secondary virology, efficacy, PK, and safety endpoints will be analyzed.

Virology

- Viral shedding in nasopharyngeal swab specimens based on quantitative polymerase chain reaction (qPCR) and cell culture
- Genotyping of SARS-CoV-2 viral isolates

Efficacy

- Time to clinical recovery up to Day 28
- Proportion of patients with clinical recovery up to Day 7, 14, 28
- Proportion of patients requiring supplemental oxygen up to Day 7, 14, 28
- Proportion of patients with intensive care unit transfer up to Day 7, 14, 28
- Proportion of mechanical ventilation up to Day 7, 14, 28
- Proportion of patients with all-cause mortality up to Day 14, 28
- Proportion of patients with hospital admission up to Day 14, 28

Pharmacokinetics

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)

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

Safety

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AEs of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Potential effects on the incidence of ADE
- Incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)
- Vital signs (blood pressure, heart rate, body temperature, SpO_2 and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead electrocardiogram (ECG)
- Severe Acute Respiratory Syndrome Coronavirus infection related signs and symptoms
- Radiography (chest x-ray and/or chest CT)
- Clinical laboratory test (clinical chemistry, hematology, and urinalysis)
- Physical examinations

Sample Size:

The total sample size of 18 patients is not based on a formal statistical hypothesis. A sample size justification based on statistical hypotheses is not relevant in this study. The proposed number of 6 patients (5 patients for CT-P59 and 1 patient for placebo) in each cohort is set empirically based on sample sizes in other Phase 1 studies investigating the safety and tolerability of their study drugs and is considered to be sufficient to achieve the objectives of the study.

Statistical Methods:

Statistical Analysis

The statistical analysis will be performed using Statistical Analysis System Software Version 9.4 or higher (SAS institute Inc., Cary, North Carolina, US). 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 clinical study reports.

Analysis Sets

Intent-to-treat (ITT) Set: The ITT Set is defined as all randomly assigned patients to study drug.
Safety Set: The Safety Set will include all randomized patients who received a full or partial dose of the study drug.
Pharmacokinetic Set: The PK Set will include all patients in the Safety Set who received a full dose of CT-P59 and provide at least 1 evaluable post-treatment PK concentration result.

Safety analysis

Safety analyses will be performed in the Safety Set, unless otherwise indicated. Adverse events will be recorded according to the Common Terminology Criteria for Adverse Events Version 5.0 and will be coded to system organ class and preferred term according to Medical Dictionary for Regulatory Activities. The AE summaries will be reported by system organ class, preferred term, and the cohort of CT-P59 groups and pooling of placebo group, as appropriate. If more than 1 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. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Safety data on results of clinical laboratory test, ECG, physical examinations, vital signs, prior and concomitant medications, immunogenicity, SARS-CoV-2 infection related signs and symptoms, potential effects on the incidence of ADE, hypersensitivity monitoring, radiography, and pregnancy tests will be listed and summarized by visits as well as by the cohort of CT-P59 groups and pooling of placebo group.

Virology analysis

Characterization of SARS-CoV-2 viral isolate (viral shedding based on qPCR and cell culture and genotype) will be analyzed on the ITT 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 the cohort of CT-P59 groups and pooling of placebo group 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 results will be presented in data listing by the cohort of CT-P59 groups and pooling of placebo group.

Efficacy analysis

The secondary efficacy endpoints will be analyzed on ITT set and will be summarized by the cohort of CT-P59 groups and pooling of placebo group using descriptive statistics or frequency tables.

Pharmacokinetic analysis

All PK analyses will be conducted in the PK set. The PK parameters of CT-P59 will be analyzed using noncompartmental methods based on the actual sampling time points. All parameters will be calculated using Phoenix WinNonlin (Pharsight, St Louis, Missouri, US). Pharmacokinetic parameters and PK concentration data will be presented in listings and summarized in tables by cohort of CT-P59 groups. The tables will display the following descriptive statistics: the number of observations (n), mean, standard deviation (SD), median, minimum, maximum, geometric mean and coefficient of variation.

LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
ABV	alcohol by volume
ACE2	angiotensin-converting enzyme 2
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}last}$	area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-}24hr}$	area under the concentration-time curve over a 24 hour dosing interval
$AUC_{0\text{-}48hr}$	area under the concentration-time curve over a 48 hour dosing interval
$AUC_{0\text{-}72hr}$	area under the concentration-time curve over a 72 hour dosing interval
BMI	body mass index
CL	total body clearance
C_{max}	maximum serum concentration
COVID-19	corona virus disease 19
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DEC	Dose Escalation Committee
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EOT	end-of-treatment
ESR	erythrocyte sedimentation rate
GCP	Good Clinical Practice
HBcAb	hepatitis B core 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
ITT	Intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
NAb	neutralizing antibody
OTC	over-the-counter
PK	pharmacokinetic
qPCR	quantitative polymerase chain reaction
RBD	receptor binding protein
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SoC	standard of care
SOP	standard operating procedure
SpO_2	peripheral capillary oxygen saturation
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse events of special interest
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to C_{max}
V_z	Volume of distribution during the elimination phase
WHO	World Health Organization
λ_z	Terminal elimination rate constant

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 [WHO] disease outbreak news, 2020).

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

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

Coronavirus entry into host cells is an important determinant of viral infectivity and pathogenesis. It is also a major target for host immune surveillance and human intervention strategies. It has been established that SARS-CoV-2 binds via the angiotensin-converting enzyme 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 protein (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 this 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 strain (70%) and is more aggressive. Additionally, individuals appear to be affected to different degrees 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 monoclonal antibody targeted against SARS-CoV-2 spike RBD as a treatment for SARS-CoV-2 infection. 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 binding to SARS-CoV-2 RBD and the cellular receptor, ACE2, thus blocking the SARS-CoV-2 infection. Although it is known that in many virus infections antibodies can remove the virus-infected cells via antibody Fc-dependent function such as antibody dependent cellular cytotoxicity, it's unlikely that CT-P59 induces antibody Fc-dependent virus clearance, considering the life cycle of SARS-CoV-2 which is assembled inside cells and released via exocytosis. However, it is postulated that there are additional mechanisms of CT-P59 mediated virus clearance by 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 and toxicology of CT-P59 can be found in the Investigator's brochure (IB).

1.2.2 Clinical Studies

CT-P59 has not been administered in humans yet.

1.3 Study Rationale

There are currently no approved monoclonal antibody therapies available to treat coronaviruses such as SARS-CoV-2 and there is an urgent public health need for the rapid development of such interventions. On 11 March 2020, the WHO declared the SARS-CoV-2 infection outbreak a global pandemic as there were more than 118,000 cases in 114 countries, and 4,291 people had lost their lives. According to the WHO coronavirus disease situation report-135, about 6.28 million people were confirmed to have SARS-CoV-2 infection in 216 countries and fatalities exceeded about 380,000.

CT-P59 is currently being developed by the Sponsor 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 this study, safety, tolerability, and virology of CT-P59 will be evaluated in patients with mild symptoms of SARS-CoV-2 infection.

1.3.1 Rationale for Study Population

The study population depend on the clinical data and recommendation from the regulatory authority and CELLTRION's development program is focusing on evaluating safety and tolerability in patients with mild symptoms of SARS-CoV-2 infection. The expected patient population is adults only.

1.3.2 Rationale for Dose Selection

In this study, there will be three dose levels and an approximate 2-fold increase between doses. The planned starting dose is 20 mg/kg and the proposed top dose is 80 mg/kg.

The pharmacokinetic (PK) profile of CT-P59 is expected to be similar to those of CT-P27, an anti-influenza antibody drug to treat influenza under development by the Sponsor. CT-P27 drug product is a combination of the two human immunoglobulin G1 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 immunoglobulin G1 Fc region backbone with the two monoclonal antibodies of CT-P27.

Doses of CT-P27 in the range of 7.5 to 30 mg/kg were shown to exhibit increasing efficacy in virus-challenged mice and ferrets and are also within the range of doses for other approved human monoclonal antibodies for IV infusion.

The efficacious dose of CT-P59 in ferrets was determined as 30 mg/kg based on viral load and pathology. The nonhuman primate efficacious doses estimated as partial areas under the concentration-time curve (AUCs) ($AUC_{0\text{-}24hr}$, $AUC_{0\text{-}48hr}$, $AUC_{0\text{-}72hr}$) equivalent to the ferret

partial AUCs at 30 mg/kg were about 12-18 mg/kg. Taking the assumption of no PK difference (partial AUCs) between human and nonhuman primates as well as the similar PK assumed between CT-P27 and CT-P59 into account, 20 mg/kg of CT-P59 will be likely to be efficacious in patients as well. Thus, the starting dose of 20 mg/kg of CT-P59 was selected as an effective dose for clinical trials of CT-P59.

In the 2-week repeat dose nonhuman primate toxicity study of CT-P27, the no-observable-adverse effect-level was 320 mg/kg. 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 human. In clinical trials, doses up to 90 mg/kg of CT-P27 were well tolerated. As 400 mg/kg of top dose is selected for 2-week repeat dose toxicology of CT-P59, greater safety factor over that of CT-P27 is expected to support the clinical trials.

The half-lives of the components of CT-P22 and CT-P23, comprising CT-P27, are approximately 17 days and 18 days, respectively. Assuming that the PK of CT-P59 and CT-P27 will be similar, due to the structural similarity between the CT-P27 and the CT-P59, in that an identical human immunoglobulin G1 Fc region backbone, the expected half-life of CT-P59 is 18 days in human.

The further nonclinical results of CT-P59 will be updated in the IB and will serve as the rationale behind dose selection. Safety data from cohort 1 and 2 (10 mg/kg, 20 mg/kg respectively) up to Day 7 in Study CT-P59 1.1 to be conducted in healthy subjects will be submitted for the regulatory's review prior to the dosing of this study, Study CT-P59 1.2, in addition to the nonclinical data. The Data and Safety Monitoring Board (DSMB) members of the healthy and the mild patient studies (Studies CT-P59 1.1 and CT-P59 1.2, respectively) will consist of the same members and the DSMB will be required not to proceed with the dosing of the next cohort in the patient study if there is any safety concern raised in the dose already evaluated in healthy subjects.

CT-P59 will be administrated intravenously. Several human antibodies are approved for IV infusion, which is the same route of administration of CT-P59.

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 and/or prophylaxis of coronaviruses such as SARS-CoV-2 at present.

CT-P59 has not been administered in humans yet, and therefore, the benefits or risks in humans are unknown at this time.

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.

The same global independent DSMB will ensure continued review of emerging data for both Studies CT-P59 1.1 and CT-P59 1.2.

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 and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the preliminary safety and tolerability of CT-P59 up to Day 14 of the last enrolled patient

2.1.2 Secondary Objectives

- To evaluate the viral efficacy and characterization of SARS-CoV-2 viral isolates
- To evaluate the efficacy of CT-P59
- To evaluate the PK of CT-P59
- To evaluate additional safety of CT-P59 including immunogenicity

2.2 Study Endpoints

2.2.1 Primary Endpoints

Primary endpoints will be analyzed based on the data up to Day 14 of the last enrolled patient.

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AEs of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Potential effects on the incidence of antibody-dependent enhancement (ADE)
- Vital signs (blood pressure, heart rate, body temperature, SpO_2 and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead electrocardiogram (ECG)
- Severe Acute Respiratory Syndrome Coronavirus infection related signs and symptoms
- Radiography (chest x-ray and/or chest CT)
- Clinical laboratory test (clinical chemistry, hematology, and urinalysis)

2.2.2 Secondary Endpoints

Secondary virology, efficacy, PK, and safety endpoints will be analyzed.

2.2.2.1 Virology

- Viral shedding in nasopharyngeal swab specimens based on quantitative polymerase chain reaction (qPCR) and cell culture
- Genotyping of SARS-CoV-2 viral isolates

2.2.2.2 Efficacy

- Time to clinical recovery up to Day 28
- Proportion of patients with clinical recovery up to Day 7, 14, 28
- Proportion of patients requiring supplemental oxygen up to Day 7, 14, 28
- Proportion of patients with intensive care unit transfer up to Day 7, 14, 28
- Proportion of mechanical ventilation up to Day 7, 14, 28
- Proportion of patients with all-cause mortality up to Day 14, 28
- Proportion of patients with hospital admission up to Day 14, 28

2.2.2.3 Pharmacokinetics

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Dose normalized $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}inf}$/Dose)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Dose normalized $AUC_{0\text{-}last}$ ($AUC_{0\text{-}last}$/Dose)
- Maximum serum concentration (C_{max})
- Dose normalized C_{max} (C_{max}/Dose)
- Time to C_{max} (T_{max})
- Terminal half-life ($t_{1/2}$)

- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)
- Terminal elimination rate constant (λ_z)
- Total body clearance (CL)
- Volume of distribution during the elimination phase (V_z)

2.2.2.4 Safety

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AEs of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Potential effects on the incidence of ADE
- Incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)
- Vital signs (blood pressure, heart rate, body temperature, SpO_2 and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead electrocardiogram (ECG)
- Severe Acute Respiratory Syndrome Coronavirus infection related signs and symptoms
- Radiography (chest x-ray and/or chest CT)
- Clinical laboratory test (clinical chemistry, hematology, and urinalysis)
- Physical examinations

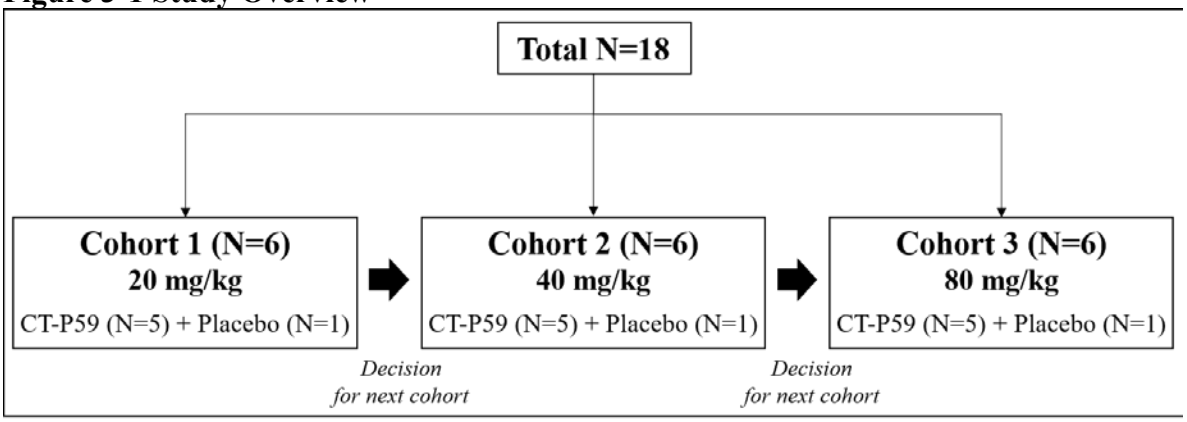
3 Investigational Plan

3.1 Study Design

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

This study will be started with the lowest dose that will maximize safety and the dose levels will be escalated to the higher doses. The details of dose escalation and stopping criteria is specified in Section 3.3. The overview of the study is presented in Figure 3-1.

Figure 3-1 Study Overview



The study will be performed in a double-blind manner. To minimize the risk of unblinding, the study drug will be dispensed by unblinded study center personnel. The unblinded personnel who are responsible for dispensing study drugs will not be permitted to conduct any patient assessments.

3.2 Rationale for Study Design

The design of this clinical trial follows the recommendation of the European Medicines Agency (EMA) Guideline on Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal product (EMA, 2017).

In line with the standard approach to early phase dose escalation study, the Sponsor is planning a pilot dose escalating Phase 1 study in patients with mild symptoms of SARS CoV-2 Infection to evaluate safety, tolerability and virology of CT-P59.

The dose escalation study has been designed to carefully assess the safety and tolerability of CT-P59 in patients with mild symptoms of SARS-CoV-2 infection, before progressing into the subsequent studies.

3.3 Dose Escalation and Stopping Criteria

3.3.1 Dose Escalation Criteria

After each study drug administration, patients will be observed for 48 hours for evaluation of the safety and tolerability of the study drug. Despite the relatively long expected half-life of 18 days for CT-P59, the 48 hours of safety evaluation is justified given the expectation that any significant safety findings from the study drug administration should be apparent within post-48 hours considering the study drug is IV infusion.

When escalating dose from previous cohort to next cohort, Dose Escalation Committee (DEC) will review all available safety data of all patients in each cohort, within an observation period of 48 hours after study drug administration. If no safety or tolerability concern is observed, patients in next cohort will receive study drug.

Patients will be admitted for 72 hours post-study drug administration, and the duration of hospitalization may be extended at the discretion of the Investigator, so safety will be continuously monitored after the observation period of 48 hours.

If any safety concern including stopping rule specified in Section 3.3.2 is raised, study can be temporarily stopped and the case will be immediate escalated to be reviewed at a DSMB meeting. The appointed independent DSMB members will evaluate the relationship to CT-P59 of the event with unblinded manner and review all available data and make a decision on continuation and the dose escalation of the study.

3.3.2 Dose Stopping Rules

The dose escalation from a previous cohort to the next cohort will be stopped if one or more of the following stopping criteria are met:

- Two or more patients in one cohort experience TEAEs of grade 3 or higher, which are considered to be related to study drug.

- Four or more patients in one cohort experience TEAEs of grade 2 or higher, which are considered to be related to study drug.
- One or more patients in one cohort experience a TESAE, which are considered to be related to study drug.

If an event corresponding to the above criteria occurs within the observation period of 48 hours in each cohort and the dosing is temporarily stopped under the decision of DEC, the appointed independent DSMB members will evaluate the relationship to CT-P59 of the event with unblinded manner and make a decision on continuation and the dose escalation of the study.

If an event corresponding to the above criteria occurs after observation period of 48 hours in the previous cohort occurrence, further progression to next cohort will be temporarily stopped and the appointed independent DSMB members will review data and make a decision on continuation and the dose escalation of the study.

If it was revealed that an event corresponding to the above criteria occurs and all the TEAEs are related to CT-P59 as reviewed by DSMB members, the study will be temporarily stopped. If it is decided to restart the trial and continue dose escalation based on further review of all available data, the supporting data will be submitted to the regulatory authority and agreed prior to trial restart.

3.4 Study Overview

The total duration of this study will be up to 27 weeks for the individual patient, including Screening Period and Follow-Up Period. All study procedures will be performed at the time points specified in Table 11-1 and Table 11-2.

3.4.1 Screening Period (Day -7 to Day 1)

Patients will sign and date the informed consent form (ICF) and undergo procedures to determine eligibility. During the Screening Period, retest for Screening is permitted only once by the Investigator's judgement. If the repeated test result is again not suitable or indeterminate for inclusion, the patient will be screen failed. Only one retest for reverse transcription polymerase chain reaction (RT-PCR) will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the retest results. And, if there is available RT-PCR result confirming SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 7 days from the onset of symptoms), the result can be allowed.

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

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

Inclusion and exclusion criteria will be re-confirmed on Day 1. If it is concluded that the patients are not eligible in Day 1 assessments, the patients will be considered as screening failure even if he/she was eligible based on assessments results performed during Screening Period.

Patients will be randomized in 5:1 ratio to receive CT-P59 or placebo once all eligibility criteria have been confirmed. Patients will receive a single dose of CT-P59 or placebo on Day 1.

All patients will be admitted to the study center on Day 1 and it is recommended to be confined up to Day 7. In-house stay period can be determined by Investigator considering the isolation regulation and/or public health capacity of the country, however all patients should be confined to the study center for at least 72 hours (until completion of all assessments on Day 3).

After discharge, the consecutive study visits will be carried out on an out-patient basis. During the isolation period according to the local regulation, patients will visit the study center using the transportation provided by Sponsor.

Patients will undergo the procedures at the time points specified in Table 11-1 and Table 11-2.

3.4.3 End-of-Treatment Visit (Day 90)

End-of-treatment (EOT) visit assessments will be performed on Day 90. Patients will undergo the assessments specified in Table 11-1 and Table 11-2.

If a patient early terminated from the study, the patient will be asked to return to the study center for the safety assessments predefined on an EOT visit.

3.4.4 Follow-Up Period (From End-of-Treatment Visit to Day 180)

For all patients including a patient who early terminated from the study, if possible, each telephone call follow-up will occur bi-weekly from 2 weeks after the EOT visit to Day 180. During the Follow-Up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone call to capture the suspicious ADE occurrence. For patients with suspicious ADE occurrence, all assessments specified in Table 11-2 will be conducted on unscheduled visit.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 18 patients will be enrolled. Male or female patients aged 18 to 60 years (both inclusive), with mild symptoms of SARS-CoV-2 infection diagnosed by RT-PCR and no more than 7 days prior to the study drug administration from the onset of symptom will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

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

1. Adult male or female patient, aged between 18 to 60 years (both inclusive).

2. Patient with laboratory confirmed SARS-CoV-2 infection by RT-PCR at Screening.

   Note: But, if the patient had RT-PCR result confirming SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 7 days from the onset of symptoms), the result can be allowed.

   Note: During the Screening Period, only one retest for RT-PCR will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the retest results.

3. Patient has mild conditions meeting all of the following criteria:

   a. Oxygen saturation ≥ 94% on room air.

   b. Not requiring supplemental oxygen.

4. Patient has one or more of the following 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

5. 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

6. 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 symptom of the SARS-CoV-2 infection.

7. Patient with a body weight between 50 kg and 100 kg (both inclusive) and a BMI of ≥ 18.0 kg/m^2.

8. Patient is able to understand and to comply with protocol requirements, instructions, and restrictions.

9. Patient voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the Screening procedures.

10. Patients and their partners of childbearing potential must agree to use a highly effective method of contraception or two acceptable methods of contraception until 6 months after the study drug administration as specified in Section 5.8.2. A woman is considered of childbearing following menarche and until becoming post-menopausal unless permanently sterile. A menopausal female must have no menses more than 12 months without an alternative medical cause prior to the date of informed consent to be classified as not of childbearing potential. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. 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 medically acceptable methods of contraception.

4.3 Exclusion Criteria

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

1. Patient with severe condition meeting one of the following:

    a. Respiratory distress with respiratory rate ≥ 30 breaths/min.

    b. Requires supplemental oxygen.

    c. Experience shock.

    d. Complicated with other organs failure, and intensive care unit monitoring treatment is needed by investigator's discretion.

    e. Any other conditions suspected of being severe symptoms of SARS-CoV-2 infection, in the opinion of the investigator, including but not limited to radiographic findings in lung.

2. Patient has a medical history or current presence of disease including one or more of the following(s):

    a. Clinical hematology results of neutrophil count < 1.0×10^3 cells/μL (International System of units < 1.0×10^9 cells/L) at Screening and Day 1.

    b. Clinically significant condition of allergic reaction (e.g., urticaria, angio-oedema), atopic condition (asthma and eczematous dermatitis) in the investigator's opinion

and/or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any monoclonal antibody or any components of study drugs.

c. History of and/or current medical condition, classed as clinically significant by the investigator, including gastrointestinal, renal, endocrine, neurologic, autoimmune, hepatic, hematological, metabolic (including known diabetes mellitus), cardiovascular, or psychiatric condition.

d. History or any concomitant active malignancy.

e. History of and/or current infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C.

f. History of serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 6 months before the study drug administration and/or current infection, other than SARS-CoV-2 infection, requiring a course of systemic anti-infective therapy.

g. History of an illness, other than SARS-CoV-2 infection, within 28 days prior to the study drug administration that is identified as clinically significant by the investigator and/or requires hospitalization.

h. History of surgical intervention and/or an operation within 28 days prior to the study drug administration or plans to have a surgical procedure during the study period.

3. Patient had a history of or concurrent use of medications including any prior therapy of following(s):

a. Any vaccinations within 4 weeks prior to the study drug administration.

b. Blood transfusion, or participated in another clinical trial within 3 months prior to the study drug administration.

c. Treatment with any monoclonal antibody, fusion protein, or biologics within 6 months prior to the study drug administration.

d. Any off-label or other investigational drugs prescribed for the treatment of SARS-CoV-2 infection.

e. Potential antiviral drugs and/or immune-based therapy under evaluation for treatment

of SARS-CoV-2 infection.

f. Use of medications that are contraindicated with SoC.

4. A male patient plans to father a child or donate sperm or a female patient is lactating or planning to be pregnant or to breastfeed within 6 months from the study drug administration.

5. Patient shows reasonable evidence of drug/alcohol/nicotine abuse prior to the study drug administration as opinion of the Investigator or has following(s):

   a. Positive result for drug urine test during Screening and/or the opinion of the Investigator.

   b. History or presence of regular consumption exceeding an average weekly intake of > 14 units of alcohol in recent 3 months prior to the study drug administration.

   c. Consuming more than 10 cigarettes or equivalent per day within a month prior to the study drug administration.

6. Patient is unwilling to avoid the use of alcohol or alcohol containing foods, medications, or beverage within 48 hours prior to admission and 24 hours prior to each study visit throughout the study or unable to refrain from smoking during the in-house stays.

7. Patient donated or lost 400 mL or more whole blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration.

8. 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.

9. Patient is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalized persons by law enforcement).

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

4.4 Patient Withdrawal and Replacement

Patients are free to withdraw from the study at any time for any reason. The Investigator may also discontinue the patient from the study at any time in the interest of patient safety.

If premature withdrawal occurs for any reason, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information in the patient's medical record and in the electronic case report form (eCRF). The primary reasons for premature withdrawal are as following:

- Withdrawal of consent
- Lost to follow-up
- Adverse event
- Death
- Investigator's decision
- Study termination by the Sponsor

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show due diligence by documenting in the source documents steps taken to contact the patients, e.g., dates of telephone calls, registered letters, etc. Patients who fail to return for final assessments will be contacted by the center in an attempt to have them comply with the protocol. The status of patients who fail to complete final assessments will be documented in the eCRF.

When possible, the Sponsor should be notified of the withdrawal of a patient from the study. If necessary, the investigator may discuss with the Sponsor or its designee any patient's reason for withdrawal from the study. The Sponsor may be contacted if clarification is required on a case-by-case basis. All patients who are terminated from the study will retain their patient identification number.

4.4.1 Recruitment of Additional Patients

Generally, patients who receive study drug and discontinue before the study completion will not be replaced. However, if a patient who receives the study drug discontinues the study for a

reason other than patient's safety, the patient can be replaced upon decision of DEC. If a patient who is randomized but not receive study drug discontinues the study, the patient can be replaced.

Patients who failed Screening, for any reason, can be rescreened only once. If there is unusual situation so that additional rescreening should be considered, the Investigator is recommended to discuss with the Sponsor. Rescreened patient will be assigned with new patient identification number.

4.5 Premature Termination of the Clinical Trial

Reason for premature termination of this study may include a failing to meet the requirements of regulatory authority, change in opinion of the independent ethics committee (IEC)/ institutional review board (IRB), unexpected or significant safety risk, or at the discretion of sponsor. 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.

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 Independent Ethics Committee (IEC; or Institutional Review Board, where applicable) of any premature termination or suspension of the study.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Group

Randomization will be performed using an interactive voice response system (IVRS) or interactive web response system (IWRS). Unblinded biostatisticians will generate the randomization schedule for IVRS or IWRS, which will link sequential patient randomization numbers to treatment codes. Patients will be allocated to each treatment group with the pre-specified ratio.

5.2 Treatment Administered

On Day 1, patients who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to one of 2 treatment groups, CT-P59 or placebo, according to randomization scheme. The CT-P59 or placebo will be administered as an IV infusion over 90 minutes (±15 minutes) with SoC (except potential antiviral drugs and/or immune-based therapy under evaluation for treatment of SARS-CoV-2 infection).

Patients in each cohort will receive study drug as follows:

- Cohort 1: CT-P59 20 mg/kg or placebo
- Cohort 2: CT-P59 40 mg/kg or placebo
- Cohort 3: CT-P59 80 mg/kg or placebo

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.

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

5.2.1 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 IV 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 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 Packaging, Labeling, and Storage

The Sponsor will provide the Investigator and study center with adequate quantities of CT-P59 and placebo. 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
- Directions for use
- Storage instructions
- Caution statement (for clinical study use only)
- Sponsor's contact name and address
- Expiry date

CT-P59 drug product 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. In case an on-site monitoring visit cannot be made because of the SARS-CoV-2 pandemic situation, the Sponsor and contract research organization (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 another 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 the center's standard operating procedures (SOPs), 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 center agreed upon with the Sponsor. Details on study drugs accountability and destruction will be followed according to the pharmacy manual.

5.4 Blinding

This study will be double-blind until the end of the study. The randomization codes will not be revealed to study patients, Investigator, and study center personnel, except for delegated unblinded staff who will handle the study drug and predefined unblinded teams in the Sponsor and CRO until all final clinical data have been entered into the database and the database is locked and released for analysis.

Pharmacy personnel (trained by a delegated pharmacist) at the study center who has no other patient contact and who is not directly involved with the clinical aspects of the study will prepare and dispense the study medication and will be aware of the randomization code. All study drugs will be delivered to the study center and will be assigned to treatment groups by the pharmacy personnel in accordance with the provided randomization schedule. The pharmacy personnel will also be provided kit list that provides the kit number and corresponding treatment arm. The pharmacy personnel will select the kit based on the randomization and kit lists provided. All study drugs will be supplied to the trained clinical staff member in a sealed carton marked with the kit number.

5.5 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should only be broken if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the Investigator may, in emergency, determine the identity of the study drug by using the IWRS (or applicable procedure if IWRS is not available).

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

The DSMB and the statistician(s) who provides the safety analyses for the DSMB will also be unblinded upon the 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 14 of the last enrolled patient. The unblinded personnel will be predefined and documented before performing the analyses.

5.6 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.

5.7 Prior, Concomitant, and Prohibited Medications

Prior and concomitant medication will be recorded for the 30 days prior to the patient signs the ICF (inclusive of the applicable periods for prohibited medication as defined in Section 4.3) until the EOT. Use of SoC will also be properly recorded. Concomitant medication is permitted if indicated by the Investigator for treatment of AE.

Prohibited medications during the study include the following:

- Any vaccinations
- Blood transfusion, or participated in another clinical trial
- Treatment with any monoclonal antibody or fusion protein, or use of biologics
- Any off-label or other investigational drugs prescribed for the treatment of SARS-CoV-2 infection
- Potential antiviral drugs and/or immune-based therapy under evaluation for treatment of SARS-CoV-2 infection
- Use of medications that are contraindicated with SoC

It is the Investigator's responsibility to ensure that details regarding the medication are adequately recorded in both the source documents and eCRF. Any changes in concomitant medications will also be recorded in both the source documents and eCRF.

5.8 Restriction

The Investigator, or delegated clinical staff member, will check if patient 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 24 hours before any study visit and while

patients are confined to the study center. 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 during the confinement period of the study. 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 during the confinement period of the study.

Meals: Patients must abstain from all food and drink (except water) at least 8 hours prior to the study drug administration and at least 4 hours prior to any safety laboratory evaluations. 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. 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 admission until discharge. After discharge, 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.

Lactation: Female patients are prohibited to breastfeed until 6 months from the study drug administration.

Contraception: A woman is considered of childbearing following menarche and until becoming post-menopausal unless permanently sterile. A menopausal female must have no menses more than 12 months without an alternative medical cause prior to the date of informed consent to be classified as not of childbearing potential. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Patients and their partners of childbearing potential must agree to use a highly effective method of contraception or two acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier contraceptive method by female partner) consistent with local regulations until 6 months after the study drug administration regardless of patient withdrawal.

A highly effective method of birth control may be defined as those which result in a low failure rate (e.g., <1% per year, when used consistently and correctly). Examples of acceptable forms of highly effective contraception for female patients include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine devices
- Intrauterine hormone-releasing system
- Bilateral tubal occulusion
- Vasectomized partner
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject. 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

- Spermicide condom (condoms coated with spermicide) use alone is not allowed

6 Study Assessments and Procedures

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

Patients will undergo the procedures at the time points specified in Table 11-1 and Table 11-2.

6.1 Safety Assessments

Safety assessments include monitoring of AEs (including SAEs and AESI [infusion related reactions including hypersensitivity and anaphylactic reactions]), potential effects on the incidence of ADE, immunogenicity including ADAs and NAbs, vital signs, hypersensitivity monitoring, 12-lead ECG, SARS-CoV-2 infection related signs and symptoms, radiography, physical examination, clinical laboratory tests, pregnancy tests, and prior and concomitant medications.

6.1.1 Adverse Events

6.1.1.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in any patient during the study which does not necessarily have a causal relationship with the study drug. Any new condition noted at Screening would be regarded as an AE, but not a TEAE.

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

A 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 this the study drug. 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 clinically significant as evaluated by the Investigator

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

6.1.1.1.1 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

6.1.1.1.2 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.

6.1.1.1.3 Suspected Unexpected Serious Adverse Reactions

The Sponsor will promptly evaluate all suspected unexpected serious adverse reactions against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, 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.

6.1.1.1.4 Adverse Events of Special Interest

Infusion related reaction including hypersensitivity/anaphylactic reactions is considered as 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.

6.1.1.1.5 Eliciting and Documenting Adverse Events

All AEs will be reported by the Investigator via eCRF from the date patients signs the ICF until EOT visit, regardless of the relationship to the study drug. The condition of the patient will be monitored throughout the study for any signs or symptoms.

At every study visit, patient will be asked a standard nonleading 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 medications and over-the-counter drugs).

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

6.1.1.1.6 Reporting Adverse Events

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

Adverse events resulting from concurrent illness, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported from the date patients signs the ICF until EOT visit. Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The Medical Dictionary for Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

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

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Section 6.1.1.2 and Section 6.1.1.3, respectively.

6.1.1.1.7 Reporting Serious Adverse Events

Any AE considered serious by the Investigator or which meets SAE criteria (Section 6.1.1.1.1) must be reported to CRO within 24 hours from the time study center staff first learn about the event. 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 it to CRO [redacted] or via FAX (details on SAE report form) 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 will be followed up as specified in Section 6.1.1.1.8.

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

The Sponsor or its designee is responsible for reporting fatal or life-threatening suspected unexpected serious adverse reaction (expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), Investigators, and IECs by a written safety report within 15 calendar days of notification.

6.1.1.1.8 Follow-up of Adverse Events

All reported AEs will be followed until one of the following: resolution or improvement from baseline, confirmed by the Investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. For patients who withdraw from the study, the last assessed status of AEs will be collected.

6.1.1.2 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 noninvasive 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 nonserious 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.

6.1.1.3 Assessment of Causality

As discussed in Section 6.1.1.1.6, 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. The event reappears or worsens if the study drug is re-administered.

6.1.2 Medical History and Demographic Information

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

6.1.3 Viral Serology Test

Viral serology tests including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, and HIV-1 and -2 tests will be performed at Screening visit. If the HBsAg test result is positive, the patient cannot be enrolled in the study. If the HBcAb test result is positive, the patient also cannot be enrolled. If the hepatitis C antibody, HIV-1 and -2 test result is a positive, the patient also cannot be enrolled in the study.

6.1.4 Urine Drug Test

An urine drug tests will be performed at Screening. The screen for drug abuse includes methamphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates. The urine test can be repeated once at the discretion of the Investigator.

6.1.5 Hypersensitivity Monitoring

Hypersensitivity monitoring will be performed as specified in Table 6-1.

Table 6-1 Schedule of Assessments for Hypersensitivity Monitoring

Day	Time points	Window
Day 1	Predose	Within 30 minutes
	15 minutes from start of infusion	± 5 minutes
	30 minutes from start of infusion	
	60 minutes from start of infusion	
	90 minutes from start of infusion	
	2 hours from start of infusion	± 15 minutes
	3 hours from start of infusion	
	6 hours from start of infusion	
	12 hours from start of infusion	
Day 2	24 hours from start of infusion	± 30 minutes

Hypersensitivity will be assessed by additional vital signs measurements including blood pressure, heart rate, respiratory rate, and body temperature. 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/or artificial ventilation will be available and any type 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.

6.1.6 Vital Signs, Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in Table 11-1 and Table 11-2. Vital signs (including blood pressure, heart rates, respiratory rates,

body temperature and SpO_2) 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. 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 6.1.5).

6.1.7 Electrocardiogram

A 12-lead ECG will be performed at the time points specified in Table 11-1 and Table 11-2 and if the patient experienced cardiac symptoms during 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 or any other abnormalities, the patient will be referred to a cardiologist if required, 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 performed at the Investigator's discretion.

In case of hypersensitivity monitoring, any type of ECG can be performed (Section 6.1.5).

6.1.8 Physical Examination

Physical examinations will be performed at time points specified in 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 delegated clinical staff member, in both the source documents and the eCRF. 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 as such in the source documents and eCRF.

6.1.9 Pregnancy

Serum pregnancy test will be performed for female patients with childbearing potential at Screening and EOT visit as specified in Table 11-1. Only patients who are confirmed as nonpregnant can be enrolled in the study.

The serum pregnancy test samples will be analyzed at the local laboratory. If serum pregnancy test is unavailable, urine pregnancy test can be performed instead.

In an event of unexpected pregnancy within 6 months after the study drug administration, patients will be counselled to inform the Investigator. If a female patient or female 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 and return it to the Sponsor and CRO within 24 hours of pregnancy being detected.

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

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 6.1.1.1.7).

6.1.10 Radiography

Radiography (chest x-ray and/or chest CT) will be performed at the scheduled time points specified in Table 11-1 and when the Investigator considers it is clinically necessary (e.g., abnormal findings of SpO_2).

6.1.11 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments including clinical chemistry, hematology, and urinalysis will be collected at the time points specified in Table 11-1 and Table 11-2. Laboratory analyses will be performed by the local laboratories.

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, 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

6.1.12 Immunogenicity Assessments

The immunogenicity of CT-59 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 Table 11-1. If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PK assessment at the same time point can be used for immunogenicity assessment. Additional immunogenicity will be assessed when immune-related AEs occurs.

Analysis will be performed at the central laboratory.

6.1.13 SARS-CoV-2 Infection Related Signs and Symptoms

During the Screening, Treatment Period, and EOT visit, 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 non-respiratory signs and symptoms and/or potential complications of SARS-CoV-2 infection. During the Follow-Up Period, patients will be asked if they have any SARS-Cov-2 infection related signs and symptoms by telephone call. The assessment will be performed at the scheduled time points specified in Table 11-1 and Table 11-2.

Any signs and symptoms of SARS-CoV-2 infection captured on SARS-CoV-2 infection related signs and symptoms will be reported as AEs at the discretion of the Investigator.

6.1.14 Potential Effects on 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 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.

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 Period. The patient 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 up to Day 7 after the day of suspicious ADE occurrence, same procedure will be repeated until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCT (local).

6.2 Virology Assessments

Viral shedding (qPCR and cell culture) and genotyping will be performed using the nasopharyngeal swab samples. Samples will be secured at the central laboratory for analysis and backup samples will be retained.

Details of nasopharyngeal swab 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
Screening*	Anytime	Day -7 to Day 1
Day 1*	Predose	Predose 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

* If Screening and administration of study drug are occurred on the same day, sampling of nasopharyngeal swab will be performed twice both for RT-PCR (local) of Screening and viral shedding and genotype (central) of Day 1, respectively.

6.3 Efficacy Assessments

6.3.1 Patient Diary for SARS-CoV-2 Infection Symptom Checklist

All patients will be issued a patient diary for SARS-CoV-2 Infection Symptom Checklist at Screening and will be required to record it daily from Day 1 until clinical recovery or Day 28, whichever comes first. 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). 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.

The 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. Study 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. 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.

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).

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

Clinical recovery is defined by all symptoms on the SARS-CoV-2 Infection Symptom Checklist will be recorded as 'absent or mild in intensity' for at least 24 hours. To satisfy the clinical recovery, symptoms of the moderate or severe in intensity at Screening should be scored as mild or absent, or symptoms of the mild or absent in intensity at Screening should be scored as absent, after study treatment.

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

- For patients who will achieve clinical recovery at Day 28, patients will record the diary until Day 29 to confirm whether it is maintained at least 24 hours.
- For patients who will show deterioration (at the discretion of the Investigator) after the achievement of clinical recovery, patient will record the diary until secondary achievement of clinical recovery.
- After Day 28 of regular scheduled study visit, for patients with suspicious ADE occurrence, patient will record the diary for 7 days from the day of suspicious ADE occurrence (specified in Table 11-2).

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. Any signs and symptoms of SARS-CoV-2 infection throughout the study, including the Screening Period, will be captured on the patient diary for SARS-CoV-2 Infection Symptom Checklist and the symptoms recorded on this diary will not be reported as AEs.

All information obtained from the diary will be entered to the eCRF. These results will be used in the assessment of clinical recovery as secondary efficacy endpoints (see Section 2.2.2.2).

6.3.2 Disease Status Monitoring

Disease status including requirement of supplemental oxygen, intensive care unit transfer, mechanical ventilation use, and hospitalization will be monitored during the study period (from signing of ICF to EOT).

6.3.2.1 Requirement of supplemental oxygen

The information of supplemental oxygen during the study period (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.

6.3.2.2 Intensive care unit transfer

The information of intensive care unit transfer during the study period (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.

6.3.2.3 Mechanical ventilation use

The information of mechanical ventilation use during the study period (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.

6.3.2.4 Hospitalization

The information of hospitalization except the in-house stay according to the Section 3.4.2 during the study period (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 hospitalization.

6.4 Pharmacokinetic Assessments

Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 6-3.

Table 6-3 Blood Sampling Time Points for Pharmacokinetic Assessment

Day	Time point	Window
Day 1	Predose	Predose within the day
	End of infusion	+ 15 minutes
	1 hour after end of infusion	
Day 2	24 hours after start of infusion	± 1 hour
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/EOT visit	2,136 hours after start of infusion	

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for immunogenicity assessment at same time point can be used for PK assessment. Analysis will be performed at the central laboratory.

Instructions for the blood collection, storage, and shipment to the central laboratory are described in Section 6.5 and Section 6.6.

6.5 Sample Collection

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. 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.

6.5.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in Table 6-3. All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.2 Immunogenicity Blood Sampling

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

6.5.3 Safety Blood Sampling

Blood samples for clinical chemistry, hematology test, and serum pregnancy tests will be collected for analysis throughout the study at the time points specified in Table 11-1 and Table 11-2. The actual sampling date will be recorded in both the eCRF and source documents.

6.5.4 Safety Urine Sampling

Urine samples for urinalysis will be collected for analysis at the time points specified in Table 11-1. The actual sampling date will be recorded in both the eCRF and source documents.

6.5.5 Virology Sampling

Virology samples of nasopharyngeal swab will be collected for analysis at the time points specified in Table 6-2, Table 11-1 and Table 11-2.

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

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

6.6.2 Sample Storage and Shipment

During the study, blood samples for PK, immunogenicity, and safety analyses and virology samples 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 back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK and immunogenicity will be retained at the central laboratory 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 Sponsor/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. Procedures for storage and shipment will be followed according to the laboratory manual. Virology samples will be secured at the central laboratory for analysis and backup samples will be retained. The samples can be destroyed by a specific authorization of the Sponsor.

7 Statistical Analysis

The statistical analysis will be performed using Statistical Analysis System Software Version 9.4 or higher (SAS institute Inc., Cary, North Carolina, US). The statistical methods for this study will be described in a detailed 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 CSRs.

Full details of the statistical methods will be described in the SAP.

7.1 Sample Size Calculation

The total sample size of 18 patients is not based on a formal statistical hypothesis. A sample size justification based on statistical hypotheses is not relevant in this study. The proposed number of 6 patients (5 patients for CT-P59 and 1 patient for placebo) in each cohort is set empirically based on sample sizes in other Phase 1 studies investigating the safety and tolerability of their study drugs and is considered to be sufficient to achieve the objectives of the study.

7.2 Analysis Sets

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

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

Safety Set: The Safety Set will include all randomized patients who received a full or partial dose of the study drug.

Pharmacokinetic Set: The PK Set will include all patients in the Safety Set who received a full dose of CT-P59 and provide at least 1 evaluable post-treatment PK concentration result.

7.3 Description of Subgroups to be analyzed

Subgroup analysis can be implemented to reflect medical, regulatory, or ethnic consideration, if required.

7.4 Statistical Analysis Methodology

7.4.1 General Consideration

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

7.4.2 Study Population

7.4.2.1 Disposition of Patients

The number and percentage of patients entering and completing the clinical study will be presented by the cohort of CT-P59 groups and pooling of placebo group.

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.

7.4.3 Safety Analysis

Safety analyses will be performed in the Safety Set, unless otherwise indicated.

7.4.3.1 Demographic, Baseline, and Background Characteristics

Baseline demographic and background variables will be summarized by the cohort of CT-P59 groups and pooling of placebo group using the ITT Set.

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

7.4.3.2 Adverse Events

Adverse events will be recorded according to the CTCAE Version 5.0 and will be coded to system organ class and preferred term according to Medical Dictionary for Regulatory Activities. A TEAE is defined as described in Section 6.1.1.1. The following AE summaries will be reported by system organ class, preferred term, and the cohort of CT-P59 groups and pooling of placebo 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 TEAESIs (infusion related reaction including hypersensitivity/anaphylaxis reaction)

If more than 1 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.

7.4.3.3 Clinical Laboratory and Pregnancy Test

Actual values and changes from baseline for numeric clinical laboratory test (clinical chemistry, hematology and urinalysis) results will be summarized by the cohort of CT-P59 groups and pooling of placebo 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.

7.4.3.4 Electrocardiogram, Physical Examination, and Vital Signs

Actual values and change from baseline for vital sign measurements will be summarized by the cohort of CT-P59 groups and pooling of placebo 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 the cohort of CT-P59 groups and pooling of placebo 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.

7.4.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. All prior and concomitant medications data will be listed and summarized by the cohort of CT-P59 groups and pooling of placebo group.

7.4.3.6 Immunogenicity

Immunogenicity test results will be summarized by the cohort of CT-P59 groups and pooling of placebo group at each scheduled visit and presented in a data listing.

7.4.3.7 SARS-CoV-2 Infection Related Signs and Symptoms

The assessment results of SARS-CoV-2 infection related signs and symptoms at each scheduled visit with those at baseline will be summarized by scheduled visit, and by the cohort of CT-P59 groups and pooling of placebo group.

7.4.3.8 Potential Effects on the Incidence of Antibody-dependent Enhancement

The number and percentage of patients with suspicious ADE will be presented by the cohort of CT-P59 groups and pooling of placebo group.

7.4.4 Virology Analysis

The viral efficacy (viral shedding based on qPCR and cell culture) and characterization of SARS-CoV-2 viral isolate (genotyping) will be analyzed on the ITT 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 the cohort of CT-P59 groups and pooling of placebo group 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 results will be presented in data listing by the cohort of CT-P59 groups and pooling of placebo group.

7.4.5 Efficacy Analysis

The secondary efficacy endpoints will be analyzed on ITT set and will be summarized by the cohort of CT-P59 groups and pooling of placebo group using descriptive statistics or frequency tables.

7.4.6 Pharmacokinetic Analysis

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

Pharmacokinetic parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}inf}$ /Dose, $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}$/Dose, C_{max}, C_{max} /Dose, T_{max}, $t_{1/2}$, $\%AUC_{ext}$, λ_z, CL, and V_z will be presented in data listings and summarized by the cohort of CT-P59 groups at each scheduled visit using descriptive statistics.

Serum concentration data will be presented in data listings and summarized by the cohort of CT-P59 groups at each scheduled visit using descriptive statistics.

7.5 Interim Analysis

No formal interim analysis will be performed in this study. The Sponsor plans to prepare two CSRs (Section 9.7).

7.6 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.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study center, 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 central and/or local laboratories into the clinical database. The data will be collected via Electronic Data Capture (EDC) using eCRFs. The study center will be responsible for data entry into the EDC system. 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. In the event of discrepant data, the Sponsor will request data clarification from the study center, which the study center will resolve electronically in the EDC system. The Sponsor will be responsible for the data management of this study, including quality checking of the data.

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 changed based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IEC but will not result in a protocol amendment.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be disclosed 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 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 Independent Ethics Committee

Regulations and ICH guidelines require that approval be obtained from an IEC before participation of human 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 IEC. Documentation of all IEC approvals and of the IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the Sponsor or its designee.

All IEC approvals should be signed by the IEC chairman or designee and must identify the 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 IEC. The Investigator must promptly supply the Sponsor or its designee, the IEC, and, where applicable, the institution,

with written reports on any changes significantly affecting the conduct of the study or increasing risk to patients.

8.3 Patient Information and Consent

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

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, IEC members, and regulatory authorities. The Investigator will confirm, by signing and dating the eCRFs, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the Principal Investigator or Sub-Investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.1.1.1.7. In addition, the Principal Investigator or Sub-Investigator agrees to submit annual report to his or her IEC as appropriate.

8.5 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 prior to study participation (Screening).

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.

8.6 Investigator Documentation

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

- Independent Ethics Committee 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 study 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 Ethics Committee-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

8.7 Study Conduct

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

8.8 Data Collection

8.8.1 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 eCRFs 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.

8.9 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 IEC with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

8.11 Record Retention

Correspondence (e.g., with Sponsor, 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 be kept on file.

Essential documents should be retained until at least 15 years after completion or discontinuation of the trial or at least 2 years after the granting of the last marketing authorization in the EU (when there are no pending or contemplated marketing applications in the EU) or for at least 2 years after formal discontinuation of clinical development of the investigational product, whichever is the longest.

These documents can be retained for a longer period, 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 Patient 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 will be reported at a peer-reviewed scientific journal for publication. The Sponsor will be responsible for these activities and will work with the Principal Investigator and Sub-Investigator 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
[redacted]

9.2 Vendor Contact

CRO
IQVIA Limited
Green Park 3 Forbury Place
23 Forbury road, Reading Berkshire
RG1 3JH United Kingdom

SAE Reporting
IQVIA Lifecycle Safety
[redacted]

9.3 Central Analytical Facility

Analyses of PK, virology and immunogenicity samples will be performed in following central analytical facility:

PPD Bioanalytical Lab
2244 Dabney Road Richmond,
VA 23230-3323 United States
Phone: +1 804 359 1900

Viroclinics Bioscience BV
Rotterdam Science Tower, Marconistraat 16,
3029 AK Rotterdam, The Netherlands
Phone: +31 88 668 4787

The information of other facilities not listed above will be provided in the Laboratory Manual. Analytical facility and any procedures utilized for this study must be Good Laboratory Practice compliant.

9.4 Monitoring

9.4.1 Dose Escalation Committee

The DEC is consist of Investigator, representatives of the Sponsor, and medical monitor of CRO. The DEC will be appointed for safety oversight and will make decision on continuation of next group dosing or dose escalation according to the criteria specified in Section 3.3.

Further details will be provided in DEC charter.

9.4.2 Data and Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician.

The appointed DSMB members will review the safety data and make a decision on continuation the study according to the criteria specified in Section 3.3. The DSMB will also review the data up to Day 14 of the last patient to evaluate preliminary safety and make recommendations on conduct of the study.

Further details will be provided in the independent DSMB charter.

9.4.3 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. 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.

9.4.4 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, 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 to access to all study records.

The Investigator should promptly notify the Sponsor and CRO of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 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 IEC and Regulatory Authority for approval before patients are enrolled under an amended protocol. This will be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion and agreement from the Sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant 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.

9.5.2 Protocol Deviations

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

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 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 IEC and agreed to by the Investigator. A significant deviation occurs when there is nonadherence 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 nonadherence to inclusion or exclusion criteria, or nonadherence 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. Principal Investigator will be notified in writing by the monitor of deviations. The IEC will be notified of protocol deviations, if applicable, in a timely manner.

9.6 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.

9.7 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 two CSRs to report the following:

- First CSR: data up to Day 14 of the last enrolled patient
- Final CSR: all data after completion of the study

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

10 Reference List

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). (2017). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. London. EMEA/CHMP/SWP/28367/07 Rev. 1. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

Food and Drug Administration. Code of Federal Regulations Title 21 (regulation 21 CFR 320.38). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.38

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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)	**-7 to 1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**14 (±1)**	**21 (±1)**	**28 (±3)**	**56 (±5)**	**90 (±5)**	**Bi-weekly up to 180 (±5)**
In-house Stay [4]		**X**	**X**	**X**	**(X)**	**(X)**	**(X)**	**(X)**							
Telephone Follow-Up Visit															**X**
Informed consent	X														
Medical history	X														
Demographics	X														
Inclusion/exclusion criteria [5]	X	X [6]													
Weight, BMI and height [7]	X	X [6]												X	
Physical Examination	X	X [6]												X	
Urine drug abuse check [8]	X														
Hepatitis B/C and HIV test [9]	X														
Serum pregnancy test [10]	X													X	
Clinical laboratory analyses [11]	X	X [6]	X	X		X		X	X	X		X	X	X	
Vital Signs (blood pressure, heart rate, respiratory rate, SpO_2 and body temperature) [12]	X	X [6]	X	X		X		X	X	X	X	X	X	X	
12-lead ECG [13]	X	X [6]	X					X		X		X	X	X	
Radiography [14]	X									X					
Randomization		X [6]													
Administration of study drug [15]		X													
Nasopharyngeal swab [16]															
• RT-PCR (local) [17]	X														
• Viral shedding (central, qPCR and Cell culture)		X [6]	X	X	X	X	X	X	X	X	X	X			

Study Day (Visit windows)	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)	Bi-weekly up to 180 (±5)
In-house Stay [4]		**X**	**X**	**X**	**(X)**	**(X)**	**(X)**	**(X)**							
Telephone Follow-Up Visit															**X**
• Genotyping of SARS-CoV-2 viral isolates (central)		X [6]	(X) [18]												
Patient diary for SARS-CoV-2 Infection Symptom Checklist [19]	X	X											(X)	(X)	
SARS-CoV-2 infection related signs and symptoms assessment [20]	X	X [6]	X	X		X		X	X	X		X	X	X	X
Pharmacokinetic sampling [21]		X	X	X		X		X	X	X		X	X	X	
Immunogenicity sampling		X [6]						X		X		X	X	X	
Hypersensitivity monitoring [22]		X	X												
Disease status monitoring [23]	X														
Restriction assessment	X														
Prior, concomitant medication [24]	X														
Adverse events [25]	X														

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

1. If Screening visit date and the administration of study drug date (Day 1) are same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the date before randomization.
2. End-of-Treatment visit assessments will be performed on Day 90. If a patient is early terminated from the study, the patient will be asked to return to the study site for the safety assessments predefined on an EOT visit. If deemed necessary by the investigator, then the patient will be asked to return at the scheduled EOT visit.
3. For all patients, (including a patient who early terminated from the study, if possible) each telephone call follow-up will occur bi-weekly from 2 weeks after the EOT visit to Day 180. During the Follow-Up Period, SARS-CoV-2 infection related signs and symptoms will be assessed by telephone call to capture the suspicious ADE occurrence. For patients with suspicious ADE occurrence, all assessments specified in Table 11-2 will be conducted on unscheduled visit.
4. All patients will be admitted to the study center on Day 1 and it is recommended to be confined up to Day 7. In-house stay period can be determined by investigator considering the isolation regulation and/or public health capacity of the country, however all patients should be confined to the study center for at least 72 hours (until completion of all assessments on Day 3). After discharge, the consecutive study visits will be carried out on an out-patient basis. During the isolation period according to the regulatory of the country, patients will visit the study center using the transportation provided by Sponsor.
5. Inclusion and exclusion criteria will be confirmed at Screening and on Day 1. If it is concluded that the patients are not eligible in Day 1 assessments, the patients will be considered as Screening failure even if he/she was eligible based on assessments results performed during Screening Period.

6. These assessments should be performed prior to the study drug administration.
7. Measurement of height and BMI will be performed once at Screening.
8. A urine drug tests will be performed at Screening. The screen for drug abuse includes methamphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates. The urine test can be repeated once at the discretion of the Investigator.
9. At Screening, HBsAg, HBcAb, hepatitis C antibody, HIV-1 or -2 test must be assessed in all patients (mandatory). If HBsAg test result is positive, the patient cannot be enrolled in the study. If HBcAb test is positive, the patient also cannot be enrolled. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study.
10. For female patients with childbearing potential, serum pregnancy test will be performed at Screening and EOT visit. If serum pregnancy test is unavailable, urine pregnancy test can be performed instead. Only patients who are confirmed as nonpregnant can be enrolled in the study.
11. Clinical laboratory testing (clinical chemistry, hematology, and urinalysis) 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, ESR, total white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination of white blood cell count, red blood cell count, and bacteria

12. Blood pressure, heart rate, 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.
13. 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.
14. Radiography (chest x-ray and/or chest CT) will be performed at the scheduled time point and when the investigator considers it is clinically necessary (e.g., abnormal findings of SpO_2).
15. Study drug will be administered as an IV infusion for 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.
16. 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 and below:
    - Screening: If Screening and administration of study drug occur on the same day, sampling of nasopharyngeal swab will be performed twice both for RT-PCR (local) of Screening and viral shedding and genotype (central) of Day 1, respectively.
    - Day 1: predose (within the day)
    - Day 2: 24 hours (±4 hours) after the start of the study drug infusion.
    - Day 3: 48 hours (±4 hours) after the start of the study drug infusion.
    - Day 4: 72 hours (±4 hours) after the start of the study drug infusion.
    - Day 5: 96 hours (±4 hours) after the start of the study drug infusion.
    - Day 6: 120 hours (±4 hours) after the start of the study drug infusion.
    - Day 7: 144 hours (±4 hours) after the start of the study drug infusion.
    - Day 10: 216 hours (±4 hours) after the start of the study drug infusion.
    - Day 21 (±1 day)
    - Day 14 (±1 day)
    - Day 28 (±3 days)

17. If the patient had RT-PCR result confirming SARS-CoV-2 infection prior to obtaining written informed consent (but no more than 7 days from the onset of symptoms), the result can be allowed. During the Screening Period, only one retest for RT-PCR will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on retest results.
18. The genotyping will be performed on samples at time point when resistance is suspected, but not limited to.
19. After study drug administration, 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 clinical recovery or Day 28, whichever comes first. 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. After Day 28, additional recording of the diary will be required if following conditions are met:
    - For patients who will achieve clinical recovery at Day 28, patients will record the diary until Day 29 to confirm whether it is maintained at least 24 hours.
    - For patients who will show deterioration (at the discretion of the investigator) after the achievement of clinical recovery, patient will record the diary until secondary achievement of clinical recovery.
    - After Day 28 of regular scheduled study visit, for patients with suspicious ADE occurrence, patient will record the diary for 7 days from the day of suspicious ADE occurrence (specified in Table 11-2).

    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.
20. During the Screening, Treatment Period, and EOT visit, 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. During the Follow-Up Period, patients will be asked if they have any SARS-Cov-2 infection related signs and symptoms by telephone call.
21. PK analysis will be performed at the central laboratory. Blood sampling time points and acceptable tolerance windows for PK assessments are specified in Table 6-3 and below:
    - Day 1: predose (within the day), end of infusion (+15 minutes), and 1 hour (+15 minutes) after the end of infusion.
    - Day 2: 24 hours (±1 hour) after start of infusion.
    - Day 3: 48 hours (±1 hour) after start of infusion.
    - Day 5: 96 hours (±4 hours) after start of infusion.
    - Day 7: 144 hours (±4 hours) after start of infusion.
    - Day 10: 216 hours (±4 hours) after start of the infusion.
    - Day 14 (±1 day), Day 28 (±3 days), Day 56 (±5 days), and Day 90 (±5 days)/EOT visit.
22. Hypersensitivity monitoring will be performed at Day 1 predose (within 30 minutes), 15 minutes (±5 minutes), 30 minutes (±5 minutes), 60 minutes (±5 minutes), 90 minutes (±5 minutes), 2 hours (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 12 hours (±15 minutes), 24 hours (±30 minutes) from the start of infusion (specified in Table 6-1). Vital signs including blood pressure, heart rate, respiratory rate and body temperature will be evaluated for possible hypersensitivity reactions. Any type of ECG will be performed if a patient experiences cardiac symptoms. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (inhalational therapy, oxygen and artificial ventilator) must be available.
23. Disease status including requirement of supplemental oxygen, intensive care unit transfer, mechanical ventilation use, hospitalization will be monitored during the study period (from signing of ICF to EOT).
24. Prior and/or concomitant medication use will be recorded for the 30 days before the signed date of ICF until the EOT visit.
25. Adverse events will be assessed from the date the ICF is signed until up to EOT visit, regardless of the relationship to the study drug. All incidences of ADE occurring during the follow-up period will be reported as an AE, irrespective of causal relationship.

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, qPCR and Cell culture)	X	X	X	X	X
• Genotyping of SARS-CoV-2 viral isolates (central) [4]	(X)				
Patient diary for SARS-CoV-2 Infection Symptom Checklist [5]	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)	X		X		X

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

Note: For suspicious ADE assessment, patients can be hospitalized based on the investigator's decision. If required, additional assessments can be performed by investigator's discretion during the hospitalization period. Otherwise, the assessment will be done by out-patient visit. The genotype assessment marked as (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 up to Day 7 after the day of suspicious ADE occurrence, same procedure will repeat until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).
3. If required, RT-PCR (local) can be performed at any time by Investigator's discretion.
4. The genotyping will be performed on samples at time point when resistance is suspected, but not limited to.
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. 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, 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.

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 until clinical recovery or Day 28, whichever comes first.

After Day 28, additional recording of the diary will be required if following conditions are met (specified in Section 6.3.1):

- For patients who will achieve clinical recovery at Day 28, patients will record the diary until Day 29 to confirm whether it is maintained at least 24 hours.
- For patients who will show deterioration (at the discretion of the Investigator) after the achievement of clinical recovery, patient will record the diary until secondary achievement of clinical recovery.
- After Day 28 of regular scheduled study visit, for patients with suspicious ADE occurrence, patient will record the diary for 7 days from the day of suspicious ADE occurrence (specified in Table 11-2).

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

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

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

Source: National Institute of Allergy and Infectious Diseases. Adaptive platform treatment trial for outpatients with COVID-19. 31 May 2020.