CLINICAL STUDY PROTOCOL

A Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CT-P59 in Healthy Subjects

PROTOCOL NUMBER CT-P59 1.1

EudraCT Number:	2020-003065-19
Study Drug	CT-P59
Sponsor:	CELLTRION, Inc. [redacted]
Sponsor Contact :	[redacted]
SAE Reporting :	Email: [redacted]
Version and Date of Protocol	Protocol Version 1.3, 03 July 2020

Protocol Approval

Study Title	A Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CT-P59 in Healthy Subjects
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Protocol Date	Protocol Version 1.3, 03 July 2020

Protocol accepted and approved by:

[redacted]

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled 'A Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CT-P59 in Healthy Subjects' 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 03 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 subjects. I agree to administer study drug only to subjects 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. Subject 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 1.1

Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CT-P59 in Healthy Subjects

Study Phase: Phase 1

Sponsor: CELLTRION, Inc.

Principal Investigator: [redacted]

Study Center:
[redacted]

Test Drug Formulation, Dose, and Regimen:
CT-P59 (960 mg/16 mL): 10 mg/kg, 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 subject

Secondary objectives
- To evaluate the pharmacokinetic (PK) of CT-P59
- To evaluate additional safety of CT-P59 including immunogenicity

Main Selection Criteria:
Healthy male or female subjects who are negative on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection test with 19 to 55 years (both inclusive) of age, a body weight of ≥ 50 kg and a body mass index between 18.0 and 29.9 kg/m^2 (both inclusive) will be considered for enrollment in the study if they meet all of inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:
Each subject must meet all of the following criteria to be randomized in this study:
1. Subject is a healthy male or female subject, aged between 19 to 55 years (both inclusive). Health is defined as no clinically relevant abnormalities identified by Investigator's decision based on a detailed medical history, full physical examination, including blood pressure, heart rate, respiratory rate, and body temperature measurements, 12-lead electrocardiogram (ECG) and clinical laboratory tests prior to the study drug administration.
2. Subject is confirmed as negative in SARS-CoV-2 infection test on screening and Day -1 visits.
3. Subject with a body weight of ≥ 50 kg and a body mass index between 18.0 and 29.9 kg/m^2 (both inclusive).
4. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.
5. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the screening procedures.
6. Subjects 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 man or woman is of childbearing potential if he or she is biologically capable of having children and is sexually active in the opinion of the Investigator. Subjects 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 Subject meeting any of the following criteria will be excluded from the study:
1. Subject has a medical history or current presence of disease including one or more of the following(s):
   a. History of or current allergic reaction such as asthma, urticaria, angioedema, and eczematous dermatitis considered as clinically significant in the Investigator's opinion or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any monoclonal antibody or any component of study drug
   b. History of or current medical condition including gastrointestinal, renal, endocrine, neurologic, autoimmune, hepatic, hematological metabolic (including known diabetes mellitus), cardiovascular, or psychiatric condition classed as clinically significant by the Investigator

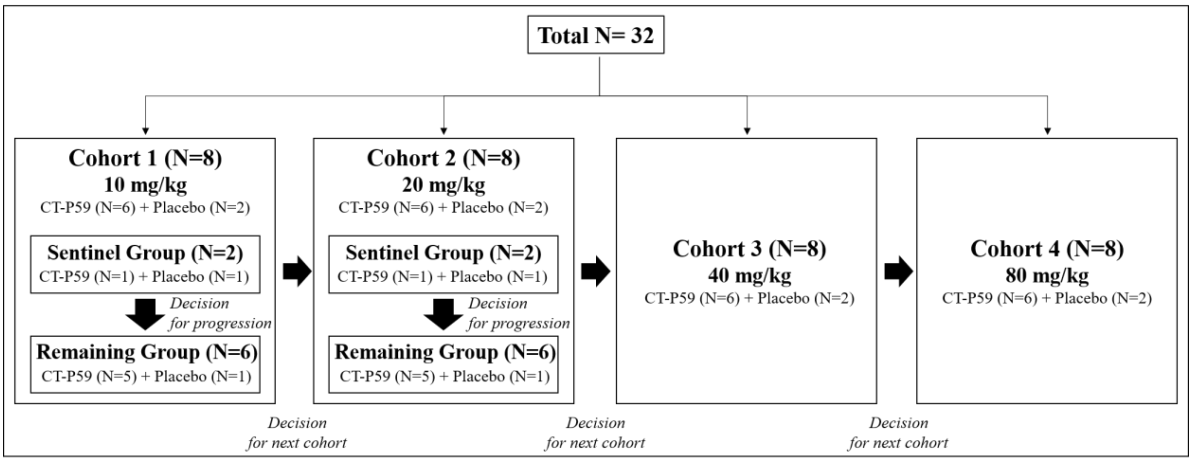
c. History of or any concomitant active malignancy
d. History of or current infection with human immunodeficiency, syphilis, hepatitis B or hepatitis C
e. History of or current infection requiring a course of systemic anti-infective that was completed within 28 days prior to the study drug administration or a serious infection (associated with hospitalization or which required IV antibiotics) within 6 months before the study drug administration
f. History of an illness within 28 days prior to the study drug administration that is identified as clinically significant by the Investigator or requires hospitalization
g. History of surgical intervention or an operation within 28 days prior to the study drug administration or plans to have a surgical procedure during the study period

2. Subject had a history of or concurrent use of medications including any prior therapy of following(s):
   a. Prescription medication (excluding hormonal birth control), over-the-counter drug, dietary supplements or herbal remedies within 7 days or 5 half-lives (whichever is longer) prior to the study drug administration
   b. Any vaccination within 4 weeks prior to the study drug administration
   c. Treatment with any monoclonal antibody, fusion protein, or blood transfusion within 6 months or 5 half-lives (which is longer) prior to the study drug administration or current use of biologics
   d. Treatment with any other investigational drug within 6 months or 5 half-lives (which is longer) prior to the study drug administration
3. A male subject plans to father a child or donate sperm or a female subject is lactating or planning to be pregnant or to breastfeed within 6 months from the study drug administration.
4. Subject 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 or Day -1
   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
5. Subject 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.
6. Subject donated or lost 400 mL or more whole blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the study drug administration.
7. Subject 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 subject to comply with the protocol requirements in the opinion of the Investigator.
8. Subject 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).
9. Subject 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 study to evaluate the safety, tolerability and PK of CT-P59 in healthy subjects. Approximately 32 subjects in 4 cohorts are planned for enrollment and each cohort will consist of 8 subjects, 6 of whom will receive CT-P59 and 2 of whom will receive a placebo. In cohorts 1 and 2, each cohort includes a sentinel group of 2 subjects and a remaining group of 6 subjects. In a sentinel group, 2 subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo. In a remaining group, 6 subjects will be randomized in a 5:1 ratio to receive CT-P59 or placebo. In cohorts 3 and 4, 8 subjects will be randomized in 3:1 ratio to receive CT-P59 or placebo.

Figure S 1. Study Design Overview



This study will be started with the lowest dose that will maximize safety and the dose levels will be escalated to the higher doses. In cohorts 1 and 2, the first study drug administration will be administered as IV infusion to the each sentinel group. In cohorts 3 and 4, all subjects in each cohort will randomly receive study drug without group sequence. Dose Escalation Committee will review all available safety data after an observation period of 48 hours and will decide whether to proceed dosing of remaining group and next cohort. If any safety concern including predefined stopping rule is raised under decision of committee, the study will be temporarily stopped and Data and Safety Monitoring Board will evaluate and review all available data and evaluate the relationship to CT P59 of the event with unblinded manner and will make a decision on continuation of the study.
This study is consist of screening period (Day -21 to Day -2), admission (Day -1), study period (Day 1 to prior to end-of-study visit), and end-of-study visit (Day 90). The total duration of this study will be approximately 16 weeks for the individual subject. Subjects will sign the informed consent at screening visit and undergo procedures to determine eligibility. Eligible subjects will have admission visit on Day -1 and under go baseline assessments and recheck eligibility. Subjects will be randomized to receive a single dose of CT-P59 or placebo on Day 1. All subjects will be confined to the study center on Day -1 until completion of the 72-hour (Day 4) assessments after the study drug administration and confinement can be extended depending on the subjects' and study center's availability up to Day 14. The subsequent study visits will be carried out on an out-patient basis. Subjects will return to the study center on Day 90 and undergo predefined end-of-study visit assessments.

Safety Assessments:

Primary endpoints

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

- Treatment-emergent AEs (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AE of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead ECG
- Physical examination findings
- Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)

Secondary endpoints

Secondary endpoints will be analyzed for whole study period.

- Treatment-emergent AEs (including TESAEs and TEAESI)
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Twelve-lead ECG
- Physical examination findings
- Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)
- Incidence of anti-drug antibodies and neutralizing antibodies

Pharmacokinetic Assessments:

Secondary endpoints

- 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)

Sample Size:

The total sample size of 32 subjects 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 8 subjects (6 subjects for CT-P59 and 2 subjects 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:

Data Analyses

The study will be unblinded for the reporting purposes after database lock for data up to Day 14 of the last enrolled subject. The unblinded team will be predefined and documented before performing the analyses. The study will remain blinded to the Investigators, subjects, predefined blinded study center staffs, blinded teams in the Sponsor, and contract research organization until all subject have completed the study and the database has been finalized for study termination.

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 Set: The Intent-to-treat Set is defined as all randomly assigned subjects to study drug.

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

Pharmacokinetic Set: The PK Set will include all subjects 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

All safety analyses including immunogenicity will be conducted on the Safety Set and will be listed and summarized by the cohort of CT-P59 groups and pooling of placebo group. Adverse events will be listed and summarized by severity and relationship to the study drug using system organ class and preferred term. Serious adverse events will be summarized separately. Terminology and severity grading of AEs will be recorded based on Common Terminology Criteria for Adverse Events Version 5.0. All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Safety data on results of vital signs, ECG, clinical laboratory tests, pregnancy test, hypersensitivity monitoring, and physical examination, prior and concomitant medications, and immunogenicity will be listed and summarized by visits as well as by the cohort of CT-P59 groups and pooling of placebo group.

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 concentrations

will be presented in listings and summarized in tables by cohort of CT-P59 groups. The tables will display the following descriptive statistics: n, mean, 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
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
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
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
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
EOS	end-of-study
ESR	erythrocyte sedimentation rate
GCP	Good Clinical Practice
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
NAb	neutralizing antibody
OTC	over-the-counter
PK	pharmacokinetic
RBD	receptor binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure
$t_{1/2}$	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
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. The current study is the first-in-human study.

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 pharmacokinetics of CT-P59 will be evaluated in healthy subjects.

1.3.1 Rationale for Study Population

Healthy subject is selected as study population since this healthy population allows for the collection of information which is not confounded by pathogens or medications likely used for treatment of the condition, easier access to a full pharmacokinetic profile, and higher internal validity of collected data due to lower variability of factors affecting the study subjects (Association of the British Pharmacology Industry, 2018).

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 subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global SARS-CoV-2 infection outbreak.

A global independent Data and Safety Monitoring Board (DSMB) would monitor the preliminary analysis with safety data up to Day 14 of the last subject and available pharmacokinetic (PK) data (central) to evaluate initial safety of CT-P59.

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 subjects 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 subject

2.1.2 Secondary Objectives

- 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 subject.

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious AEs (TESAEs)
- Treatment-emergent AEs of special interest (TEAESI; infusion related reactions including hypersensitivity/anaphylactic reaction)
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Hypersensitivity monitoring
- Twelve-lead electrocardiogram (ECG)
- Physical examination findings
- Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)

2.2.2 Secondary Endpoints

Secondary safety and PK endpoints will be analyzed for whole study period.

2.2.2.1 Safety Endpoints

- Treatment-emergent AEs (including TESAE and TEAESI)
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Twelve-lead ECG
- Physical examination findings
- Clinical laboratory tests (clinical chemistry, hematology, and urinalysis)
- Incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

2.2.2.2 Pharmacokinetic Endpoints

- Area under the concentration-time curve (AUC) 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)

3 Investigational Plan

3.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel group, single ascending dose, Phase 1 study to evaluate the safety, tolerability and PK of CT-P59 in healthy subjects. Approximately 32 subjects in 4 cohorts are planned for enrollment and each cohort will consist of 8 subjects, 6 of whom will receive CT-P59 and 2 of whom will receive a placebo.

In cohorts 1 and 2, each cohort includes a sentinel group of 2 subjects and a remaining group of 6 subjects. In a sentinel group, 2 subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo. In a remaining group, 6 subjects will be randomized in a 5:1 ratio to receive CT-P59 or placebo. In cohorts 3 and 4, 8 subjects will be randomized in 3:1 ratio to receive CT-P59 or placebo.

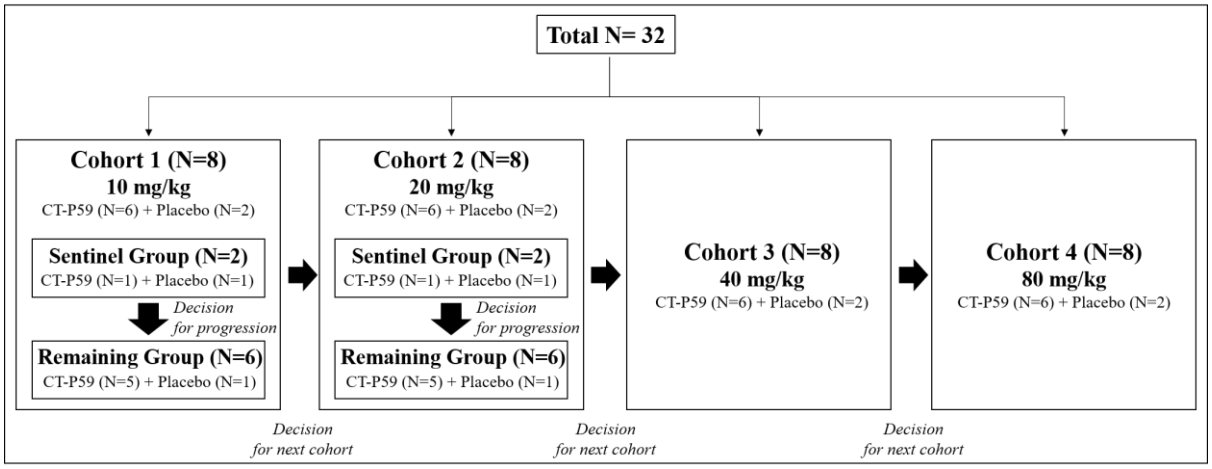
This study will be started with the lowest dose that will maximize safety and the dose levels will be escalated to the higher doses.

Subjects will be admitted to the study center on Day -1 and will be discharged on Day 4 after completion of the 72-hour assessments after study drug administration to identify any subsequent reactions.

In cohorts 1 and 2, the first study drug administration will be administered as IV infusion to the each sentinel group. In cohorts 3 and 4, all subjects in each cohort will randomly receive study drug without group sequence. The details of dose escalation and stopping criteria is specified in Section 3.2.

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 subject 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 first-in-human studies, the Sponsor is planning an initial dose escalating Phase 1 study in healthy subjects to evaluate safety and tolerability of CT-P59.

The dose escalation study has been designed to carefully assess the safety and tolerability of CT-P59 in healthy subjects, before progressing into the subsequent studies.

3.3 Dose Escalation and Stopping Criteria

3.3.1 Criteria for Proceeding from Sentinel Group to Remaining Group

In cohorts 1 and 2, 2 subjects in sentinel group will receive study drug first. One subject will receive CT-P59 and the other subject will receive placebo. After an observation period of 48 hours, all available safety data (including TEAE, vital signs, 12-lead ECG, hypersensitivity monitoring, and clinical laboratory tests, etc.) of subjects in sentinel group will be reviewed by the Dose Escalation Committee (DEC) and they will decide whether to proceed dosing of remaining group or stop dosing. If no safety or tolerability concern is observed, the 6 subjects of remaining group in same cohort will proceed to dosing. If any safety concern including

stopping rule specified in Section 3.3.3 is raised under decision of DEC, the study will be temporarily stopped and DSMB meeting will be held. The appointed 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 of the study.

3.3.2 Dose Escalation Criteria

When escalating dose to next cohort, DEC will review all available safety data of all subjects in current cohort, after an observation period of 48 hours after study drug administration. If no safety or tolerability concern is observed in the current cohort, dose will be escalating to next cohort.

When escalating dose from cohort 1 to 2, DEC will review all available safety data of all subjects in the cohort 1, after an observation period of 48 hours after study drug administration of remaining group. If no safety or tolerability concern is observed in the cohorts 1, 2 subjects in sentinel group of cohort 2 will receive study drug.

When escalating dose from cohort 2 to 3, DEC will review all available safety data of all subjects in the cohort 2, respectively, after an observation period of 48 hours after study drug administration of remaining group. If no safety or tolerability concern is observed in the cohort 2, 8 subjects in cohort 3 will receive study drug.

When escalating dose from cohorts 3 to 4, DEC will review all available safety data of all subjects in the cohort 3 after observation period of 48 hours after study drug administration of cohort 3. If no safety or tolerability concern is observed, 8 subjects in cohort 4 will receive study drug.

If any safety concern including stopping rule specified in Section 3.3.3 is raised under decision of DEC, the dose escalation and study will be temporarily stopped and DSMB meeting will be held. The appointed 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 of the study.

3.3.3 Dose Stopping Rules

The continuation of dosing after the sentinel group or 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:

- One or more subjects experience a study drug-related TESAE

- Two or more subjects in one cohort experience study drug-related TEAEs of grade 3 or higher
- Four or more subjects in one cohort experience study drug-related TEAEs of grade 2 or higher

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

3.4 Study Overview

The total duration of this study will be approximately 16 weeks for the individual subject, including Screening Period. All study procedures will be performed at the time points specified in Table 11-1.

3.4.1 Screening Period (Day -21 to Day -2)

Subjects 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 subject will be screen failed.

If screening visit date and the admission date (Day -1) are same, all assessments scheduled for the screening and Day -1 visit can be performed only once on the date.

3.4.2 Admission (Day -1)

Subjects who successfully complete the screening visit will be confined in the study centers as scheduled on Day -1. Eligible criteria will be reviewed to confirm subject eligibility. If it is concluded that the subject is not eligible in Day -1 assessments, the subject will be considered as a screening failure even if he was eligible based on assessments results performed during the screening visit.

3.4.3 Study Period (Day 1 to prior to End-of-Study Visit)

Subjects will be randomized to receive a single dose of CT-P59 or placebo on Day 1. In cohorts 1 and 2, 2 subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo in the sentinel group. If it is decided to proceed to remaining group based on criteria specified in Section 3.3.1, 6 subjects in the remaining group of cohorts 1 and 2 will be randomized in a 5:1 ratio to receive CT-P59 or placebo. If it is decided to proceed to cohorts 3 and 4, 8 subjects will be randomized in 3:1 ratio to receive CT-P59 or placebo.

All subjects will be confined to the study center until completion of the 72-hour (Day 4) assessments after the study drug administration and confinement can be extended depending on the subjects' and study center's availability up to Day 14. The subsequent study visits will be carried out on an out-patient basis.

3.4.4 End-of-Study Visit (Day 90)

End-of-study (EOS) visit assessments will be performed on Day 90. Subjects will undergo the assessments specified in Table 11-1.

If a subject withdraws prematurely after study drug administration, the subject will be asked to return to the study center for the safety assessments predefined on EOS visit. If deemed necessary by the Investigator, the subject will be asked to return for the scheduled EOS visit.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

The study population will consist of healthy male or female subjects who are negative on SARS-CoV-2 infection test with 19 to 55 years (both inclusive) of age, a body weight of ≥ 50 kg and a body mass index (BMI) between 18.0 and 29.9 kg/m^2 (both inclusive). Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria, according to the criteria outlined below (Section 4.2 and Section 4.3).

4.2 Inclusion Criteria

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

1. Subject is a healthy male or female subject, aged between 19 to 55 years (both inclusive). Health is defined as no clinically relevant abnormalities identified by Investigator's decision based on a detailed medical history, full physical examination, including blood pressure, heart rate, respiratory rate, and body temperature measurements, 12-lead ECG and clinical laboratory tests prior to the study drug administration.

2. Subject is confirmed as negative in SARS-CoV-2 infection test on screening and Day -1 visits.

3. Subject with a body weight of ≥ 50 kg and a BMI between 18.0 and 29.9 kg/m^2 (both inclusive).

4. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.

5. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to undergoing any of the screening procedures.

6. Subjects 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 man or woman is of childbearing potential if he or she is biologically capable of having children and is sexually active in the opinion of the Investigator. Subjects 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 subject meeting any of the following criteria will be excluded from the study:

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

    a. History of or current allergic reaction such as asthma, urticaria, angioedema, and eczematous dermatitis considered as clinically significant in the Investigator's opinion or hypersensitivity including known or suspected clinically relevant drug hypersensitivity to any monoclonal antibody or any component of study drug

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

    c. History of or any concomitant active malignancy

    d. History of or current infection with human immunodeficiency (HIV), syphilis, hepatitis B or hepatitis C

    e. History of or current infection requiring a course of systemic anti-infective that was completed within 28 days prior to the study drug administration or a serious infection (associated with hospitalization or which required intravenous antibiotics) within 6 months before the study drug administration

    f. History of an illness within 28 days prior to the study drug administration that is identified as clinically significant by the Investigator or requires hospitalization

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

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

    a. Prescription medication (excluding hormonal birth control), over-the-counter (OTC) drug, dietary supplements or herbal remedies from 7 days or 5 half-lives (whichever is longer) prior to the study drug administration

b. Any vaccination within 4 weeks prior to the study drug administration

c. Treatment with any monoclonal antibody, fusion protein, or blood transfusion within 6 months or 5 half-lives (which is longer) prior to the study drug administration or current use of biologics

d. Treatment with any other investigational drug within 6 months or 5 half-lives (which is longer) prior to the study drug administration

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

4. Subject 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 or Day -1

   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

5. Subject 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.

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

7. Subject 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 subject to comply with the protocol requirements in the opinion of the Investigator.

8. Subject 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).

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

4.4 Subject Withdrawal and Replacement

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

If premature withdrawal occurs for any reason, the Investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the subject'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 subjects who are lost to follow-up (i.e., those subjects 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 subjects, e.g., dates of telephone calls, registered letters, etc. Subjects 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 subjects who fail to complete final assessments will be documented in the eCRF.

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

4.4.1 Recruitment of Additional Subjects

Subjects who receive study drug and discontinue before the study completion will generally not be replaced. However, if a subject who receives study drug discontinues the study for a reason other than subject's safety, additional subject can be recruited upon decision of DEC. If a subject who randomized but did not receive study drug decides to discontinue the study, this subject can be replaced.

Subjects 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 subject will be assigned with new subject identification number.

4.5 Premature Termination of the Clinical Trial

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 subjects will be kept fully informed and an appropriate follow-up examination of the subjects 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 Subjects to Treatment Group

The randomization code will be generated by unblinded statistician prior to the study, and will be provided to unblinded pharmacist in the study center. Enrolled subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to CT-P59 or placebo on Day 1. In cohorts 1 and 2, subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo in sentinel group and in a 5:1 ratio to receive CT-P59 or placebo in remaining group. In cohorts 3 and 4, 8 subjects will be randomized in a 3:1 ratio to receive CT-P59 or placebo.

5.2 Treatment Administered

On day 1, subjects 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.

Subjects in each cohort will receive study drug as follows:

- Cohort 1: CT-P59 10 mg/kg or placebo
- Cohort 2: CT-P59 20 mg/kg or placebo
- Cohort 3: CT-P59 40 mg/kg or placebo
- Cohort 4: CT-P59 80 mg/kg or placebo

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

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 subject 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 intravenous infusion. One vial (16 mL) delivers 960 mg SARS-CoV-2 RBD binding monoclonal antibody, 13.12 mg of L-histidine, 15.84 mg of L-histidine monohydrochloride monohydrate, 8.0 mg of polysorbate 80, 505.584 mg of L-Arginine monohydrochloride, and water for injection. The container closure system includes type I borosilicate glass vial, Fluroetec Film coated rubber stopper and flip-off type aluminum cap.

5.2.2 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 Rationale for Dose Selection

In this study, there will be four dose levels and an approximate 2-fold increase between doses. The planned starting dose is 10 mg/kg and the proposed top dose is 80 mg/kg.

The 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.

In the 2-week repeat dose nonhuman primate toxicity study of CT-P27, which included safety pharmacology endpoints (e.g., clinical observations, body temperature, respiratory rate, heart rate, blood pressure, and electrocardiogram) and full histopathology, there were no treatment

related adverse effects at IV doses up to 320 mg/kg. The main finding was a minimal to mild inflammatory response at the catheter infusion sites; however, the effects were fully reversible and not considered adverse.

In this study, the first dose will be 10 mg/kg via IV infusion. The nonhuman primate repeat dose toxicity study of CT P27 had no-observed-adverse-effect level of 320 mg/kg, which was the highest dose tested and no adverse effects were observed. Applying a safety factor of 10, it is expected that a dose of up to 32 mg/kg could be supported as posing a very low risk of inducing adverse effects in this study as well. However, to maximize the safety in this first-in-human study, a lower dose of 10 mg/kg will be adapted as the starting dose. In addition, since this study is being conducted in healthy subjects, a pharmacologically-active dose is not relevant for the initial dose setting.

The proposed top dose of 80 mg/kg is expected to ensure 2.8 times of the margin of exposure based on the CT-P27 studies results (AUC results of the no-observed-adverse-effect level in nonclinical study and expected AUC value of 80 mg/kg in a clinical study with healthy volunteers).

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

The further nonclinical results of CT-P59 will be updated in the IB and will serve as the rationale behind dose selection.

5.2.4 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 subject 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
- Subject 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 CRO will discussed 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 subjects participating in the study. Study drug may not be relabeled or reassigned for use by another subjects 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 SOPs, and keep tear-off labels for accountability. This

authorization may also be granted to destroy used vials immediately after administering to subjects. 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 subjects, 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 subject contact and who are 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 applicable procedure.

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 subjects 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 subject. The unblinded personnel will be predefined and documented before performing the analyses.

5.6 Treatment Compliance

Subject 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 subjects' compliance with the study visits.

5.7 Prior, Concomitant, and Prohibited Medications

Prior and concomitant medication use will be recorded for the 30 days prior to the subject signs the ICF (inclusive of the applicable periods for prohibited medication as defined in Section 4.3) until the EOS visit. Concomitant medication use is permitted if indicated by the Investigator for treatment of AE.

Prohibited medications during the study include the following:

- Prescription medications (excluding hormonal birth control), OTC drugs, dietary supplements or herbal remedies
- Any vaccinations
- Treatment with any other investigational drug, any monoclonal antibody, fusion protein, or biologics, and blood transfusion.

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 subject 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

subjects are confined to the study center. Subjects must abstain from alcohol-containing products for 24 hours prior to each PK sampling time point. Subject 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: Subjects 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. Subjects must abstain from caffeine or xanthine-containing products for 24 hours prior to each PK sampling time point.

Nicotine: Subjects 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: Subjects 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 96 hours prior to admission until discharge. After discharge, mild physical activity can be resumed, but strenuous physical activity is prohibited 96 hours prior to each study visit.

Hygiene: Subjects 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 subjects are prohibited to breastfeed until 6 months from the study drug administration.

Contraception: Subjects and their female 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 subject 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 females include: abstinence, simultaneous use of hormonal contraceptives starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study and condom for the male partner, simultaneous use of intra-uterine contraceptive device placed at least 4 weeks prior to study drug administration and condom for the male partner, or a sterilized male partner (vasectomized since at least 6 months). Examples of acceptable forms of highly effective contraception for male subjects include: abstinence, simultaneous use of a male condom and, for the female partners include: combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation, intra-uterine or intrauterine hormone-releasing system (placed since at least 4 weeks). Examples of nonacceptable methods of contraception include solo use of a barrier method (including use of a diaphragm, cervical cap, or condom), periodic abstinence, the withdrawal method, or use of spermicide. Subjects are not permitted to donate sperm or plan to have a child until 6 months after the study drug administration.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects 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 subject. The investigator will also sign the ICF.

Subjects will undergo the procedures at the time points specified in Table 11-1.

6.1 Safety Assessments

Safety assessments include monitoring of AEs (including SAEs and AESI [infusion related reactions including hypersensitivity and anaphylactic reactions]), hypersensitivity monitoring, immunogenicity including ADAs and NAbs, vital sign assessments, physical examination, clinical laboratory tests, pregnancy test, 12-lead ECG, and prior and concomitant medications.

6.1.1 Medical History and Demographic Information

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

6.1.2 Other Baseline Characteristics

6.1.2.1 SARS-CoV-2 Infection Test

A SARS-CoV-2 infection test will be performed at Screening and Day -1 visit to confirm a subject is not infected to SARS-CoV-2. Only subjects who are negative on both screening and Day -1 tests can be enrolled in study. If the scheduled SARS-CoV-2 infection test seemed unavailable on Day -1, it can be performed on Day -2 or Day -3 instead.

6.1.2.2 Viral Serology Test

Viral serology tests including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, rapid plasma reagin and anti-HIV tests will be performed at screening visit. If the HBsAg test result is positive, the subject cannot be enrolled in the study. If the HBcAb test result is positive, the subject is also cannot be enrolled. If the hepatitis C antibody, rapid plasma reagin or anti-HIV test result is a positive, the subject also cannot be enrolled in the study.

6.1.2.3 Urine Drug Test

A urine drug tests will be performed at screening and Day -1 visit. 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.

6.1.2.4 Chest X-ray

A chest X-ray will be performed on screening visit for baseline data collection purposes. An additional assessment can be performed when the Investigator considers it is clinically necessary.

6.1.3 Adverse Events

6.1.3.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in any subject 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 subject. Treatment due to an AE will be recorded.

A TEAE includes any untoward medical occurrence in a subject 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.

6.1.3.1.1 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 subject 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 subject 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., subject 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 subject

6.1.3.1.2 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.

6.1.3.1.3 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.

6.1.3.1.4 Adverse Events of Special Interest

Infusion related reaction including hypersensitivity/anaphylactic reactions is considered as AESI and will be reported using the same process as for AEs.

6.1.3.1.5 Eliciting and Documenting Adverse Events

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

At every study visit, subject 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 OTC drugs).

In addition to subject 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 subject safety will be documented on the AE page in the eCRF.

6.1.3.1.6 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 subjects signs the ICF until EOS 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 subject 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 6.1.3.2 and Section 6.1.3.3, respectively.

6.1.3.1.7 Reporting Serious Adverse Events

Any AE considered serious by the Investigator or which meets SAE criteria (Section 6.1.3.1.1) 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 [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 6.1.3.1.8.

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.

6.1.3.1.8 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 subjects who withdraw from the study, the last assessed status of AEs will be collected.

6.1.3.2 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the subject'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.

6.1.3.3 Assessment of Causality

As discussed in Section 6.1.3.1.6, 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.

6.1.4 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 (prior to dosing on Day 1)	Within 30 minutes
	15 minutes from start of infusion	± 5 minutes
	30 minutes from start of infusion	
	60 minutes from start of infusion	
	End 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 subject experiences cardiac symptoms.

For subjects 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.

6.1.5 Vital Signs, Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in Table 11-1. Vital signs (including blood pressure, heart rates, respiratory rates, and body temperature) will be measured after the subject has rested quietly for at least 5 minutes. Body temperature will be measured using tympanic thermometer throughout the study. Height 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 6.1.4).

6.1.6 Electrocardiogram

A 12-lead ECG will be performed at the time points specified in Table 11-1 and if the subject experienced cardiac symptoms during study drug administration. All scheduled 12-lead ECGs will be performed after the subject 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 subject 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 6.1.4).

6.1.7 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.

6.1.8 Pregnancy

A serum pregnancy test will be performed at screening and EOS visits, and urine pregnancy test will be performed on female subjects with childbearing potential on Day -1 as specified in Table 11-1. Only subjects who are confirmed as nonpregnant by both serum pregnancy test at screening and urine pregnancy test on Day -1 can be enrolled in the study.

Throughout the study, a urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive or equivocal.

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

In an event of unexpected pregnancy within 6 months after the study drug administration, subjects will be counselled to inform the investigator. If a female subject or a female subject or female partner of a male subject 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. Once the pregnancy is confirmed with a serum pregnancy test, female subjects must be withdrawn from the study. 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 subjects or partners of subjects 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 subjects or female partners of subjects, 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 6.1.3.1.7).

6.1.9 Clinical Laboratory Tests

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

The following clinical laboratory tests will be performed.

Clinical chemistry: Total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-myocardial band isoenzyme, troponin I, albumin, sodium, potassium, total calcium, chloride, phosphorus, glucose, lactate dehydrogenase, total cholesterol, gamma-glutamyltransferase, estimated glomerular filtration rate (eGFR), uric acid and C-reactive protein.

(Direct bilirubin, troponin T, triglyceride and high-density lipoprotein cholesterol will be analyzed at screening visit and when the Investigator consider it is clinically necessary.)

Hematology: Red blood cell count, white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, monocyte count, basophil count, platelet, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit

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

6.1.10 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.

6.2 Pharmacokinetic Assessments

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

Table 6-2 Blood Sampling Time Points for Pharmacokinetic Assessment

Day	Time point	Window
Day 1	Predose	Predose within the day
	End of infusion	+ 5 minutes
	1 hour after end of infusion	± 15 minutes
	4 hours after end of infusion	
	8 hours after end of infusion	
	12 hours after end of infusion	
Day 2	24 hours after start of infusion	± 1 hours
Day 3	48 hours after start of infusion	
Day 5	96 hours after start of infusion	± 4 hours
Day 7	144 hours after start of infusion	
Day 10	216 hours after start of infusion	
Day 14	312 hours after start of infusion	± 1 day
Day 28	648 hours after start of infusion	± 3 days
Day 56	1,320 hours after start of infusion	± 5 days
Day 90	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 is describe in Section 6.3 and Section 6.4.

6.3 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.

6.3.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each subject at the time point specified in Table 6-2. 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.

6.3.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained in accordance with the laboratory manual from each subject 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.

6.3.3 Safety Blood Sampling

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

6.3.4 Safety Urine Sampling

Urine samples for urinalysis and urine pregnancy test 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.

6.4 Labeling, Storage, and Transportation of Samples

6.4.1 Sample Labeling

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

6.4.2 Sample Storage and Shipment

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

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.

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 32 subjects 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 8 subjects (6 subjects for CT-P59 and 2 subjects 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 subjects to study drug.

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

Pharmacokinetic Set: The PK Set will include all subjects 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 subjects within a particular category. Data will be listed in data listings.

7.4.2 Study Population

7.4.2.1 Disposition of Subjects

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

The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects 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 6.1.3.1. 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 subjects reporting at least 1 TEAE
- Number and percentage of subjects reporting at least 1 TESAE
- Number and percentage of subjects discontinuing the study drug due to a TEAE
- Number and percentage of subjects with TEAESIs (infusion related reaction including hypersensitivity/anaphylaxis reaction)

If more than 1 AE is recorded for a subject within any system organ class or preferred term, the subject 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 subjects 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 Tests

Actual values and changes from baseline for numeric clinical laboratory tests (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 tests results.

Individual clinical laboratory and serum and urine 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 Analysis

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.

7.4.4 Pharmacokinetic Analyses

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

Pharmacokinetic parameters of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}inf}$ /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. Subject 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 subject 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 subject (or the subject'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 subjects in research studies. Before study onset; the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject'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 subjects.

8.3 Subject Information and Consent

A written informed consent in compliance with ICH E6(R2) guidelines will be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. 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 subjects must sign the revised form in case new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical study.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the subject understands the implications of participating in the study, the subject 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 subject's right to withdraw from the clinical study at any time without giving reason and without jeopardizing the subject's further course of medical treatment
- The existence of subject insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions will be given to the subjects.

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 subject'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 subject 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 6.1.3.1.7. 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 subjects; 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 subjects 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 subject's pre-existing disease prior to study participation (Screening).

The Sponsor undertakes to compensate the subject 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 subject or legal guardian
- 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 subjects 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 subject 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 subjects, 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 Subject Identification Register

The Investigator agrees to complete a subject 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 subjects by assigned number only.

8.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the 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.

[redacted]

Sponsor Representative

[redacted]

9.2 Vendor Contact

CRO

[redacted]

SAE Reporting

Email: [redacted]

9.3 Central Analytical Facility

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

[redacted]

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 subject 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 subject, 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 subjects 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 subjects 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 subject'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 subjects 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 subject or Investigator that results in a significant and additional risk to the subject'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 subject
- 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

Association of the British Pharmacology Industry. Guidelines for Phase I clinical trials 2018 edition. Available from: https://www.abpi.org.uk/media/4992/guidelines-for-phase-i-clinical-trials-2018-edition-20180626.pdf

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

Food and Drug Administration. Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. January 2010. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

ICH Assembly. Integrated Addendum to ICH E6(R2): Guideline for good clinical practice E6(R2): ICH harmonised guideline. International Council for Harmonisation. 09 November 2016.

Tang X, Wu C, Li X, *et al*. On the origin and continuing evolution of SARS-CoV-2. *National Science Review*. 2020;0:1-12.

US Department of Health and Human Services. (2010). National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Varga Z, Flammer AJ, Steiger P, *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020 May 2;395:1417-18.

World Health Organization. Coronavirus disease (COVID-19) Situation Report-135. 03 June 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/

World Health Organization. Disease outbreak news. 05 January 2020. Available from: http://who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/

World Health Organization Guidelines. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. Available from: https://www.who.int/csr/bioriskreduction/infection_control/publication/en/

11 Appendices

11.1 Schedule of Assessments

Table 11-1 Schedule of Assessments

	Screening[1]	In-house stay					Out-patient visit						EOS[2]
Study day	**-21 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**7**	**10**	**14**	**28**	**56**	**90**
Visit window	**-**						**-**	**-**	**-**	**±1**	**±3**	**±5**	**±5**
Informed consent	X												
Demographic information	X												
Medical history	X	X											
Inclusion/Exclusion criteria[3]	X	X											
Weight and height[4]	X	X											X
Urine drug tests [5]	X	X											
Pregnancy test[6]	X	X											X
SARS-CoV-2 infection test	X	X[18]											
Viral serology test[7]	X												
Chest X-ray[8]	X												
Vital signs	X	X	X[9]	X	X	X	X	X	X	X	X	X	X
Randomization			X[9]										
Study drug administration[10]			X										
Hypersensitivity monitoring[11]			X	X									
Physical examination	X	X	X[9]		X	X	X	X	X	X	X	X	X
Clinical laboratory tests[12]	X	X		X	X			X		X	X	X	X
Twelve-lead electrocardiogram[13]	X			X				X		X	X		X
Pharmacokinetic sampling[14]			X	X	X		X	X	X	X	X	X	X
Immunogenicity sampling[15]			X[9]					X		X	X	X	X
Restriction assessment	X												
Prior and concomitant medication[16]	X												
Adverse events[17]	X												

Abbreviations: BMI = body mass index; ECG = electrocardiogram; EOS = end-of-study; HBcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; IV = intravenous; PK = pharmacokinetics; RPR = rapid plasma reagin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. If screening visit date and the admission date (Day -1) are same, all assessments scheduled for the screening and Day -1 visit will be performed only once on the date.
2. End-of-study visit assessments will be performed on Day 90 (± 5 days). If a subject withdraws prematurely after study drug administration, the subject will be asked to return to the study center for the safety assessments predefined on EOS visit. If deemed necessary by the Investigator, the subject will be asked to return for the scheduled EOS visit.
3. Inclusion and exclusion criteria will be confirmed at screening and will be rechecked on Day -1.
4. Height will be measured only once at screening visit. BMI will be measured once at screening for eligibility check.
5. Drug abuse testing includes drugs specified in Section 6.1.2.3. The urine test for drugs of abuse will be performed at screening and Day -1 visit. The urine test can be repeated once at the Investigator's discretion.
6. For female subjects with childbearing potential, a serum pregnancy test will be performed at screening and EOS visits, and urine pregnancy test will be performed on Day -1. Only subjects who are confirmed as nonpregnant by both serum pregnancy test at screening and urine pregnancy test on Day -1 can be enrolled in the study. A urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive or equivocal throughout the study.
7. Viral serology test including HBsAg, HBcAb, hepatitis C antibody, RPR, and anti-HIV test must be assessed in all subjects (mandatory). If any of the test result is positive, the subject cannot be enrolled in the study.
8. Chest X-ray will be performed at screening visit to collect baseline data. Additional chest X-ray assessments can be performed when the Investigator consider it is clinically necessary.
9. These assessments should be performed on Day 1 prior to the study drug administration.
10. 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 subject measured on Day -1 will be used.
11. Additional vital sign assessments will be evaluated for hypersensitivity monitoring purpose at the time point specified in Table 6-1. Any type of ECG will be performed if a subject experiences cardiac symptoms. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (inhalational therapy, oxygen and/or artificial ventilator) must be available.
12. Hematology, clinical chemistry, and urinalysis will be performed and detail analyses are listed in Section 6.1.9.
13. All scheduled 12-lead ECG assessments must be performed after the subject has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the Investigator's discretion.
14. Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 6-2. Analysis will be performed at the central laboratory.
15. In addition to sampling time point specified, serum samples for immunogenicity testing may be collected if a subject experiences immune-related AEs. Analysis will be performed at the central laboratory.
16. Prior and/or concomitant medication use will be recorded within 30 days before the signed date of ICF (inclusive of the applicable periods for prohibited medications as defined in Section 5.7) until the EOS visit.
17. Adverse events will be assessed from the date the ICF is signed until up to EOS visit, regardless of the relationship to the study drug.
18. If the scheduled SARS-CoV-2 infection test seemed unavailable on Day -1, it can be performed on Day -2 or Day -3 instead.