

CELLTRION Inc.
CT-P59 3.2

A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

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Statistical Analysis Plan

Part 2 – Final Version 2.0

Prepared by:

CELLTRION, Inc.
23, Academy-ro,
Yeonsu-gu, Incheon
22014
Republic of Korea

Prepared by:

[Redacted signature and name]

Approved:

[Redacted signature and name]

Upon review of this document, including table, listing and figure shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

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List of Abbreviations

Abbreviation	Definition
ADA	Anti-drug Antibody
ADE	Antibody-dependent Enhancement
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID	Corona Virus Disease
CPK	Creatine Kinase
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOT	End-of-Treatment
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
GGT	γ -Glutamyl Transferase
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRR	Infusion Related Reaction
ITT	Intent-to-Treat
ITTI	Intent-to-Treat Infected
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
LOD	Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
NEWS2	National Early Warning Score 2
NYHA	New York Heart Association
PT	Preferred Term
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RT-qPCR	Reverse Transcription-quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SI	System International
SoC	Standard of Care
SOC	System Organ Class
SpO ₂	Saturation Peripheral Oxygen
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Event
TEAESI	Treatment-emergent Adverse Events of Special Interest
TESAE	Treatment-emergent Serious Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal
WHO	World Health Organization

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc. (hereinafter referred to as “CELLTRION”). The clinical monitoring, medical writing and bioanalytical lab analysis are being performed under contract with [REDACTED] in collaboration with CELLTRION. Virology analysis is being performed under contract with [REDACTED] in collaboration with CELLTRION. Randomization is being performed under contract with [REDACTED], in collaboration with CELLTRION. The data management and statistical analysis are being performed by CELLTRION.

2. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data for Part 2 of CELLTRION study number CT-P59 3.2, entitled as “A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection”.

Two clinical study reports (CSRs) will be generated during entire study period of Part 2 as follows:

- Clinical study report with available data up to and including Day 28 in Part 2. The following data will be included.

	Ongoing at Day 28	Withdrawal prior to Day 28
Scheduled Visit (including EOT)	Up to and including Day 28 for each patient	All available data
Unscheduled Visit	On or before Day 28 visit date for each patient	All available data up to the latest date of the all patient’s Day 28 visit date.
Non-visit based data (e.g. adverse events and medications)	All available data having a start date or imputed start date on or before Day 28 visit date for each patient.	

- Clinical study report with all data after completion of Part 2

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

This SAP covers all specified analysis for Part 2 and is based on the following documents:

- Study Protocol Version 7.0 – 30th April 2021

- Unique CRF for Version 3.0 – 23th October 2020

3. STUDY OBJECTIVES

Primary, key secondary, secondary and exploratory objectives are described as below.

3.1. Primary Objective

The primary objective of this study for Part 2 is as follows:

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

Details of definition of ‘requiring hospitalization due to SARS-CoV-2 infection’, ‘requiring oxygen therapy due to SARS-CoV-2 infection’ and ‘experiencing mortality due to SARS-CoV-2 infection’ for statistical analyses are described in [Section 9.1](#).

“High-risk patients” are defined as patients who are at high risk for progressing to severe COVID-19 and/or hospitalization and who meet at least one of the following criteria (high-risk criteria):

- Advanced age (Age >50 years)
- Obesity (Body Mass Index [BMI] >30 kg/m²)
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescriber’s assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of acquired immune deficiency syndrome), sickle cell anemia, thalassemia, and prolonged use of immune weakening medications.

For the criteria other than advanced age and obesity, a detailed terminology for each criterion will be confirmed by medical reviewers and a list of high-risk patients will be confirmed before unblinding.

3.2. Key Secondary Objectives

The key secondary objectives of this study for Part 2 are as follows:

- To demonstrate the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 in high-risk patients
- To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 in all randomized patients

Definition of clinical recovery and the time to clinical recovery is described in [Section 9.2](#).

3.3. Secondary Objective

The secondary objectives of this study for Part 2 are as follows:

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

3.4. Exploratory Objective

The exploratory objectives of this study for Part 2 are as follows:

- To assess the viral efficacy, genotype and phenotype of SARS-CoV-2 viral isolates
- To assess the serology of SARS-CoV-2 antibody

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Part 2 of this study is a phase 3, randomized, parallel-group, placebo-controlled, double-blind study to evaluate the efficacy, safety, virology of CT-P59 in combination with Standard of Care (SoC) (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs) in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy. ‘Outpatient’ in this study includes patients visiting the study center, and patients confined in the study center or quarantine at home due to local regulation or at discretion of the investigator.

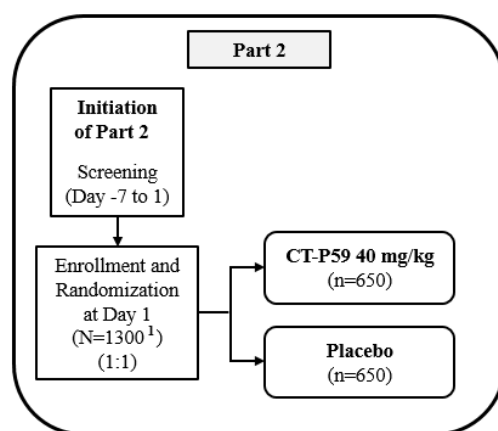
In Part 2, approximately 1300 patients will be randomly assigned in a 1:1 ratio to CT-P59

40 mg/kg or placebo.

The study will be unblinded to the predefined unblinded teams of sponsor and Contract Research Organization (CRO) for reporting purposes after completion of the Day 28 assessments of the last enrolled patient in Part 2. However, the treatment assignment will remain blinded to the investigators, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staff designated to prepare the study drug for infusion), and patients until the final CSR is generated.

The overview of study design for Part 2 is illustrated in [Figure 1](#).

Figure 1. Schematic Diagram of Study Patients for Part 2



Note: In Part 2, patients with body weight at or above 200 kg will receive 8,000 mg of CT-P59 or matching volume of placebo.

1. Of 1300 patients in Part 2, 822 high-risk patients will be included based on the sample size calculation.

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

Screening (Day-7 to 1): Screening will take place between Days –7 and 1, prior to the study drug administration. No study procedures will be performed prior to informing the patient about the study and obtaining written informed consent form (ICF). It is critical that patients receive study drug no more than 7 days from the onset of symptoms.

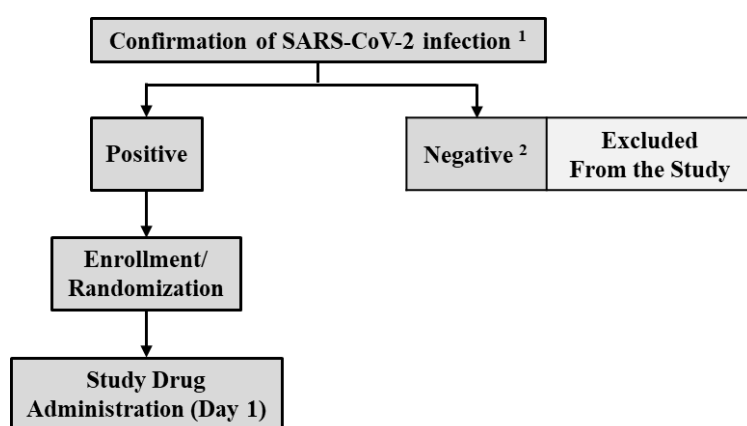
Screening evaluations will be completed prior to the randomization on Day 1. Outpatients with mild to moderate symptoms of SARS-CoV-2 infection not requiring supplemental oxygen therapy will be eligible for enrollment. Patients must have a local confirmation of SARS-CoV-2 infection by positive test result from a sponsor-supplied rapid SARS-CoV-2 diagnostic test or reverse transcription polymerase chain reaction (RT-PCR). If the patient had a RT-PCR result (sample collected within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the

patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.

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

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

Figure 2. Enrollment Process



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

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

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

Approximately 1300 patients will be randomly assigned in a 1:1 ratio (650 patients, respectively) to receive either a single dose of CT-P59 40 mg/kg, or placebo on Day 1. All patients will be given optimal SoC (except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs).

Randomization will be stratified by age (≥ 60 years vs. < 60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia) and region (United States vs. Asia vs. European Union vs. other) in Part 2.

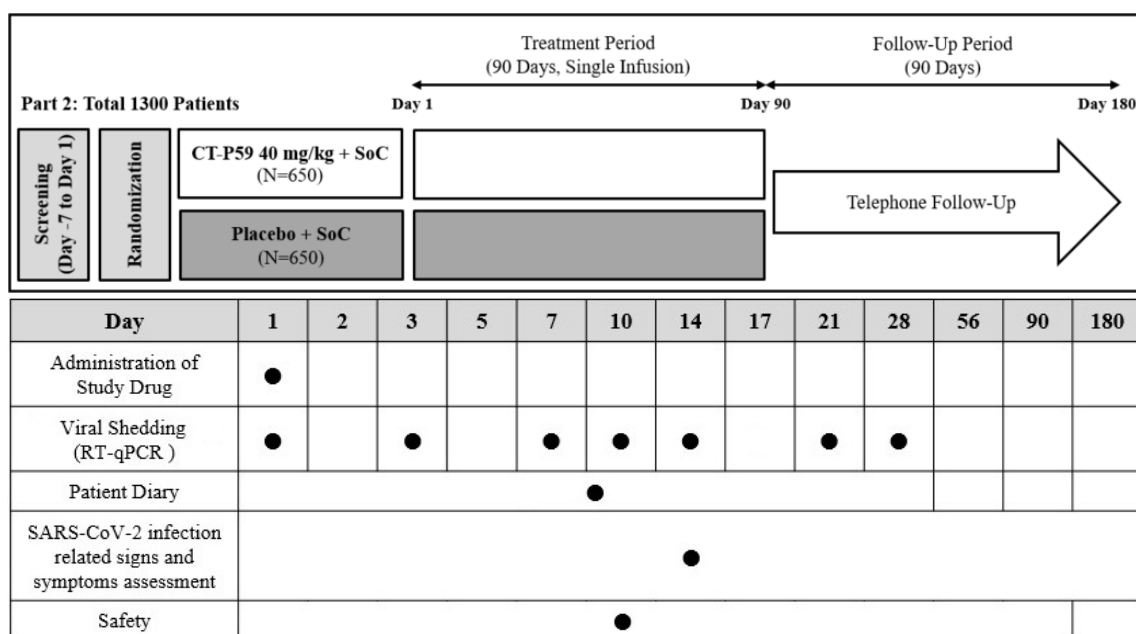
All enrolled patients in the study will complete the study visits during the treatment period either by visiting the study center, confinement in the study center, or home visiting services by health care professionals, whichever applicable according to the local regulation or at discretion of investigator.

Patients will comply with all appropriate visits and assessments. If a patient withdraws prematurely after the study drug administration, the patient will be asked to return to the study site on the next scheduled visit for the EOT assessments.

Follow-Up Period (From End-of-Treatment Visit to Day 180): For all patients including patients who withdraw prematurely after the study drug administration, each telephone call follow-up will occur biweekly from EOT visit up to Day 180. During the Follow-up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone calls to capture the suspicious ADE occurrence.

The schedule of assessments is presented in [Appendix 1](#).

Figure 3. Study Design Scheme for Part 2



Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoC = standard of care; RT-qPCR = reverse transcription quantitative polymerase chain reaction.

Notes: a) In Part 2, patients with body weight at or above 200 kg will receive 8,000 mg of CT-P59 or matching volume of placebo. b) Of 1300 patients in Part 2, 822 high-risk patients will be included based on the sample size calculation.

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: number of patients (n), mean, standard deviation (SD), minimum, median and maximum unless otherwise specified. The descriptive statistics will be calculated using raw data before rounding although rounded values are listed. The following rules will be followed with regard to the number of decimal places:

- Minimum and maximum will be displayed without rounding from values in the source listing.
- Mean and median will be rounded to one more decimal place than the maximum decimal place of values in the source listing.
- Standard deviation and standard error (SE) will be rounded to one more decimal place than mean.
- Point estimate and confidence interval (CI) obtained from statistical procedures will be displayed to two decimal places.
- P-value obtained from statistical procedures will be displayed to four decimal places if the value is greater than 0.0001, otherwise <.0001.

Categorical data will be summarized in a frequency table showing the numbers and percentages of patients. Percentages and corresponding CIs will be rounded to one decimal place and will be suppressed when the count is zero. P-value will be displayed using the same rule as continuous data. The denominator for all percentages will be the number of patients within each treatment group for the population of interest, unless otherwise specified.

Unscheduled and EOT visit will not be summarized in visit-based tables, unless otherwise specified. But, all data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, patient number, and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality sign will be displayed, unless otherwise specified.

5.1. Software

All analyses will be conducted using [REDACTED]

5.2. Sample Size

In Part 2, to demonstrate the efficacy of CT-P59 40 mg/kg compared to placebo by proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patients, a total of 822 high-risk patients (411 patients per group) will provide 80% power to detect 4.2% difference (60% reduction) at a significance level of 5% (2-sided test) assuming placebo rate of 7.1% and CT-P59 rate of 2.9%. As it is expected that high-risk patients will account for 64% of all patients, approximately a total of 1300 (650 patients per group) patients will be enrolled to this study.

Approximately, a total of 1300 (for high-risk patients, 822) patients will provide following statistical power for the key secondary endpoints at the 2-sided significance level of 5%:

- At least 80% power for proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients, assuming placebo rate of 5.5% and CT-P59 rate of 2.5% (3% difference [55% reduction])
- At least 90% power for time to clinical recovery up to Day 14 in high-risk patients, assuming 90% of patients with clinical symptoms at baseline for analysis and clinical recovery ratio of 1.5 with 66% of patients achieving clinical recovery
- At least 90% power for time to clinical recovery up to Day 14 in all randomized patients, assuming 90% of patients with clinical symptoms at baseline for analysis and clinical recovery ratio of 1.35 with 65% of patients achieving clinical recovery

5.3. Randomization, Stratification, and Blinding

On Day 1, eligible patients will be randomly assigned in a 1:1 ratio to receive either a single dose of CT-P59 40 mg/kg or placebo.

An Interactive Web Response System (IWRS) will be used for the randomization. Unblinded biostatisticians will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes. The randomization numbers will be blocked, and within each block the pre-specified ratio of patients will be allocated to each treatment group. The block size will not be revealed.

Randomization will be stratified by age (≥ 60 years vs. < 60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia) and region (United States vs. Asia vs. European Union vs. other) in Part 2.

This study will be double-blind, and will remain blinded to the investigator, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staffs designated to prepare the study drug for infusion and predefined unblinded teams in the sponsor and CRO), and patients until the final CSR is generated.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management or regulatory requirement (e.g., for serious adverse event [SAE] and death). In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure.

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

The DSMB and the statistician(s) who provide the safety analyses for the DSMB will also be unblinded upon request from DSMB members during closed session. The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Day 28 of the last enrolled patient in Part 2. The unblinded personnel will be predefined and documented before performing the analyses.

5.4. Analysis Sets

The following patient analysis sets are defined: Intent-to-Treat (ITT) Set, ITT Set – High Risk, Intent-to-Treat Infected (ITTI) Set, ITTI Set – High Risk and Safety Set.

Analysis of the ITT Set, ITT Set – High Risk, ITTI Set and ITTI Set – High Risk will be performed according to the treatment they were randomized to. The Safety Set will be analyzed according to actual treatment group. The actual treatment group will be assigned according to their actual treatment, not according to the randomized group, even if there is a discrepancy between the actual treatment administered and the randomized group.

For analysis of time to event endpoints, the following patients will be included in the analysis set:

- Time to clinical recovery: Patients who report at least one symptom at baseline
- Time to negative conversion: Patients who have positive result confirmed based on the negative threshold (as defined in [Section 11.1.1](#)) in the analysis at baseline (or Day 2/Day 3). The same analysis set will be used for the proportion of negative conversion.
- Time to NEWS2 of 0: Patients who have NEWS2 > 0 at baseline

The number of patients in each analysis set will be tabulated by the treatment group. A listing will also be produced displaying data on ITT Set, unless otherwise specified.

5.4.1. Intent-to-Treat Set

The ITT Set is defined as all randomly assigned patients to study drug. All patients assigned randomization ID according to the “Randomization” page of the eCRF will be included.

5.4.2. Intent-to-Test Set – High Risk

The ITT Set – High Risk is defined as all randomly assigned patients to study drug, who are at high risk for progressing to severe COVID-19 and/or hospitalization and who meet at least one of the high-risk criteria. The ITT Set – High Risk consist of patients in ITT set who meet at least one of the high-risk criteria described in [Section 3.1](#).

5.4.3. Intent-to-Treat Infected Set

The ITTI Set is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of reverse transcription quantitative polymerase chain reaction (RT-qPCR) who receive a complete or partial dose of the study drug. The SARS-CoV-2 infection will be confirmed based on the negative threshold of 2.33 log₁₀cp/mL. If the pre-infusion result at Day 1 is confirmed negative or missing and the Day 2 or Day 3 result is confirmed positive, this patient will also be considered as confirmed SARS-CoV-2 infection. A patient will be considered to have received a study drug if the patient is recorded as ‘Yes’ on the “Study Drug Administration” page of the eCRF.

5.4.4. Intent-to-treat Infected Set – High Risk

The ITTI Set – High Risk is defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of RT-qPCR, who receive a complete or partial dose of study drug, who are at high risk for progressing to severe COVID-19 and/or hospitalization and who meet at least one of the high-risk criteria. The ITTI Set – High Risk consist of patients in ITTI set who meet at least one of the high-risk criteria described in [Section 3.1](#).

5.4.5. Safety Set

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

5.5. Definition of Baseline

The baseline value will be considered to be the last non-missing value before the study drug administration. Post-baseline values will be considered to be all values collected after the study drug administration.

5.6. Protocol Deviations

Protocol deviation will be categorized as “major” or “minor”. Category of protocol deviation will be identified during the blinded Data Review Meeting (DRM). A major protocol deviation is one that may affect the interpretation of study results or the patient’s rights, safety or welfare.

Major protocol deviations are defined as follow (but not limited to):

- Significant GCP non-compliance: CELLTRION will identify the sites which have been closed or patients who have been affected due to suspected scientific misconduct and/or serious GCP non-compliance.
- Non-compliance of inclusion or exclusion criteria which affect the efficacy result: CELLTRION will identify via review of data sourced from the site monitoring database.
- Mis-randomizations: Patients who received the other treatment than that to which they were assigned will be defined as mis-randomized.

The major protocol deviations will be summarized for ITT Set by treatment group. A listing of major protocol deviations for each patient will also be provided by treatment group for the ITT Set.

6. PATIENT DISPOSITION

The total number of patients who were screened and failed at screening will be displayed along with the primary reason for screening failure based on the “Eligibility Criteria” page of eCRF.

The reasons for screening failure will be displayed using the following categories and ordering:

- Inclusion/Exclusion Criteria not met
- Subject withdrew consent
- Other

A listing of patients for eligibility criteria will be provided.

The number of patients who were randomized, treated study drug, discontinued and completed in each period, and entered in follow-up period will also be displayed on the ITT Set along with percentage, if applicable.

Patient disposition will be defined as follows:

- A patient will be considered to have failed the Screening if the screening failure date is recorded on the “Eligibility Criteria” page of eCRF.

- A patient will be considered to be randomized if the patient was allocated a randomization ID based on the “Randomization” page of the eCRF.
- A patient will be considered to have been treated study drug if it is recorded as ‘Yes’ on the “Study Drug Administration” page of the eCRF.
- A patient will be considered to have discontinued in Treatment Period if it is recorded that they ended (box checked other than ‘Completion of Treatment Period’) in the “End of Treatment Period” page of eCRF.
- Conversely, a patient will be considered to have completed Treatment Period if it is recorded that they completed (‘Completion of Treatment Period’ box checked) in the “End of Treatment Period” page of eCRF.
- A patient will be considered to have been entered in Follow-Up Period if it is recorded in the “End of Treatment Period” page of eCRF that they enter the Follow-Up Period (‘Yes’ box checked).
- A patient will be considered to have discontinued in Follow-Up Period if it is recorded that they ended (box checked other than ‘Completion of Follow-Up Period’) in the “End of Follow-Up Period” page of eCRF.
- Conversely, a patient will be considered to have completed Follow-Up Period if it is recorded that they completed (‘Completion of Follow-Up Period’ box checked) in the “End of Follow-Up Period” page of eCRF.
- A patient will be considered to have completed the study if it is recorded that they completed (‘Completion of Treatment Period’ box checked) in the “End of Treatment Period” page of eCRF and they completed (‘Completion of Follow-Up Period’ box checked) in the “End of Follow-Up Period” page of eCRF.

The number and percentage of patients who discontinued the study in the Treatment Period will be presented by primary reason and treatment group. The number and percentage of patients who discontinued the study in the Follow-Up Period will also be displayed by primary reason and treatment group. The reasons for discontinuation will be displayed using the following categories and ordering:

- Adverse Event
- Lost to Follow-Up
- Death
- Investigator’s decision
- Withdrawal by Subject
- Other

In addition, the time on study prior to discontinuation will also be summarized using descriptive statistics by treatment group, if applicable, for those patients who have discontinued study prematurely in the Treatment Period or Follow-Up Period, respectively. The study duration in days will be calculated as (Date of last visit of each period - Date of study drug administration + 1).

The date of administration will be taken as the date on the “Study Drug Administration” page of the eCRF. Date of last visit of each period will be taken as the date on the “End of Treatment Period” or “End of Follow-up Period” page of the eCRF.

The patient disposition data collected for the ITT Set will be listed by treatment group.

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics and Stratification Details

The following demographic measures will be summarized for the ITT Set and ITT Set – High Risk by treatment group: Age (years); Sex (Male, Female); Female fertility status (Pre-Menarche, Surgically Sterilized, Post-Menopausal, Potentially Able to Bear Children); Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Not Allowed by Investigator Country Regulations, Other); Ethnicity (Hispanic or Latino, Non-Hispanic or Non-Latino, Unknown); Height (cm), Weight (kg) and BMI (kg/m^2) as recorded at the screening visit.

Age will be automatically calculated in the eCRF system based on the date of the informed consent visit and the year of birth considering whether birth date has passed the informed consent date or not.

The following stratification details will also be summarized for the ITT Set and ITT Set – High Risk by treatment group: age (≥ 60 years vs. < 60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia) and region (United States vs. Asia vs. European Union vs. other) for Part 2. If there is a difference for data entered between IWRS and eCRF, the stratification factors will be summarized using the final data collected on the eCRF.

The following Baseline characteristics will also be summarized for the ITT Set and ITT Set – High Risk by treatment group: high-risk status (Yes vs. No); screening obesity ($\text{BMI} > 30 \text{ kg}/\text{m}^2$ vs. $\text{BMI} \leq 30 \text{ kg}/\text{m}^2$); screening disease severity (Mild vs. Moderate); baseline viral load titer ($\log_{10}\text{cp}/\text{mL}$; negative titer threshold: $2.33 \log_{10}\text{cp}/\text{mL}$); day1 serostatus (Sero Positive, Sero Negative and Other);

Baseline characteristics will be defined as follows:

- Screening disease severity (Mild vs. Moderate):
 - A patient will be considered to have mild disease severity if the question “Are there any radiological findings of pneumonia and clinical signs of pneumonia?” is answered ‘No’ on the ‘Radiography’ page of eCRF at the screening visit.
 - A patient will be considered to have moderate disease severity if the question “Are there any radiological findings of pneumonia and clinical signs of pneumonia?” is answered ‘Yes’ on the ‘Radiography’ page of eCRF at the screening visit.

- Day1 serostatus (Sero Positive, Sero Negative and Other):
 - A patient will be considered to have seropositive serostatus if there is at least one positive result of viral serology for SARS-CoV-2 Antibody IgG and IgM at Day 1.
 - A patient will be considered to have seronegative serostatus if there are both negative results of viral serology for SARS-CoV-2 Antibody IgG and IgM at Day 1.
 - Otherwise, a patient will be considered to have other serostatus.

Demographics and stratification details will be listed for the ITT Set by treatment group.

7.2. SARS-CoV-2 Infection by Sponsor-supplied Rapid Diagnostic Test or RT-PCR

A Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection by sponsor-supplied rapid diagnostic test or RT-PCR will be completed prior to the randomization on Day 1 to confirm patient is infected to SARS-CoV-2. Patients must have a local confirmation of SARS-CoV-2 infection by positive test result from a sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR. If the patient had a RT-PCR result (within 72 hours prior to the study drug administration) confirming SARS-CoV-2 infection even if before signing the ICF, the patient can be enrolled without additional confirmation of SARS-CoV-2 infection at Screening.

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

All results of SARS-CoV-2 Infection by sponsor-supplied rapid diagnostic test or RT-PCR will be listed by treatment group for the ITT Set.

7.3. Congestive Heart Failure Assessment

Congestive heart failure will be assessed by New York Heart Association (NYHA) functional criteria at the scheduled time points specified in [Appendix 1](#). If a patient had cardiac disease, corresponding NYHA class will be selected. The criteria for congestive heart failure is defined as [Table 1](#).

Table 1. New York Heart Association Functional Classification

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).

III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea.
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

All NYHA criteria assessment data will be presented in a listing by treatment group for the ITT Set. Patients who have no cardiac disease will be classed as “No Class” in the listing.

7.4. Hepatitis B and C and Human Immunodeficiency Virus Test

At Screening, the following assessments will be performed:

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis C Virus Antibody
- Hepatitis C Virus Ribonucleic Acid
- Human Immunodeficiency Virus (HIV) 1&2

Hepatitis B/C and HIV test results will be summarized by treatment group for the ITT Set. If the parameters are analyzed at both central and local laboratory, the parameter results at central laboratory will be included in summary table. For HIV 1 and HIV 2 parameters analyzed separately at local laboratory, if both results are “Negative”, the results will be summarized as “HIV 1&2 Negative” and if at least one result is missing, the results will not be summarized. A listing will be produced by treatment group for the ITT Set. All collected results will be listed.

7.5. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher. Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the ITT Set. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by treatment group. Medical history will also be listed for the ITT Set by treatment group.

7.6. Disease Characteristic

Disease characteristic is captured at the Screening visit. If disease characteristic is recorded on the “General Comments” page of the eCRF at the Screening visit, then it will be considered as ‘Other’ disease characteristic. The symptoms and time since the earliest symptom start will be summarized by treatment group for the ITT Set and ITT Set – High Risk. Time (days) since the earliest symptom start will be calculated as (date of study drug administration – date of the earliest symptom start).

7.7. Radiography

Radiography (chest x-ray or chest computed tomography [CT]) will be performed at Screening and when the investigator considers it is clinically necessary (e.g., abnormal values of saturation peripheral oxygen [SpO₂] or patient with clinical signs of pneumonia). If the patient has a radiography result performed within 7 days prior to the study drug administration even before signing the ICF, the result can be used for the Screening assessment when this radiography is performed after the onset of first SARS-CoV-2 infection related symptom.

All radiography results will be listed by treatment group for the ITT Set.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

All medications (including medications used as part of SoC) for the treatment of SARS-CoV-2 infection, from the diagnosis of disease until the EOT visit, will be collected on the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the study drug administration of the study drug (Day 1) or from when the Informed Consent Form (ICF) is signed, whichever is earlier, will be recorded until the EOT visit. All medications will be coded according to the World Health Organization drug dictionary (WHO Drug Global B3 Version September, 2020 or later version).

Medications will be classified as either prior or concomitant. For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

If the stop date is incomplete the following rules will be applied:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as Missing.

In the case of the death of a patient, and the imputed stop date is after the date of death, the stop date will be imputed as the date of death.

If the start date is incomplete the following rules will be applied. If the stop date is incomplete, imputed stop date will be used instead of reported stop date:

- Missing day: Assume the first day of the month.
However, if the partial date and the date of study drug administration lie within the same month and year and the date of study drug administration is not after the stop date of the medication, set to the date of study drug administration. Otherwise, set to stop date of the medication.
- Missing day and month: Assume January 1st.
However, if the partial date and the date of study drug administration lie within the same year and the date of study drug administration is not after the stop date of the

medication, set to the date of study drug administration. Otherwise, set to stop date of the medication.

- Missing day, month and year: Assume date of study drug administration, if not after the stop date for the medication. Otherwise, set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:
Medication start: UNJUN2020
Medication stop: 20OCT2020
Date of study drug administration: 16OCT2020
Medication start imputed: 01JUN2020
- Example 2:
Medication start: UNOCT2020
Medication stop: 20OCT2020
Date of study drug administration: 16OCT2020
Medication start imputed: 16OCT2020
- Example 3:
Medication start: UNOCT2020
Medication stop: 20OCT2020
Date of study drug administration: 24OCT2020
Medication start imputed: 20OCT2020

A prior medication is defined as following, and all other medications will be defined as concomitant medication.

- A medication having actual/imputed stop date of medication before the study drug administration date, or
- A medication checked as yes to “If stop date is unknown, was this drug stopped before the study drug administration?” on eCRF.

The prior medications will be summarized by treatment groups, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and Preferred Term (PT) along with the total number of prior medications and the number and percentage of patients with at least one prior medication for the Safety Set. When ATC Level 2 for drug class is not available, Level 1 will be used instead. The summaries will be repeated in separate tables for concomitant medications.

All prior and concomitant medications will be listed separately by treatment group for the ITT Set.

8.2. Exposure to Study Drug

The table will be provided displaying descriptive statistics of the prescribed dose per weight (mg/kg) and actual administered dose per weight (mg/kg) by treatment group for the Safety Set.

Weight (kg) at Day 1 on the “Vital Signs” page of eCRF will be used to calculate prescribed dose per weight (mg/kg) and actual administered dose per weight (mg/kg).

A listing will be provided by treatment group for the ITT Set showing the details of study drug administration. This listing will include all data collected on the “Study Drug Administration” page of eCRF.

9. EFFICACY ANALYSIS

All efficacy data will be listed for the ITT Set by treatment group unless otherwise specified. Efficacy endpoints will be analyzed in the ITT Set and/or ITTI Set unless otherwise specified.

9.1. Primary Efficacy Analysis

The primary efficacy endpoint of Part 2 is proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patients.

Patients who have hospitalization record (≥ 24 hours of acute care) in “Disease Status Monitoring” page of eCRF and received treatment such as oxygen therapy due to SARS-CoV-2 infection (as defined in this section), remdesivir or tocilizumab (from “Prior & Concomitant Medications” page of eCRF) during period of the hospitalization will be considered to have required hospitalization due to SARS-CoV-2 infection. If the start date and stop date are the same in “Disease Status Monitoring” page of eCRF, the duration of hospitalization is considered as < 24 hours. List of treatment will be determined by medical review before unblinding.

Patients who have supplemental oxygen record (at least 24 hours) in “Disease Status Monitoring” page of eCRF and SpO₂ measure in room air shows $\leq 94\%$ before applying supplemental oxygen will be considered to have required oxygen therapy due to SARS-CoV-2 infection. If the start date and stop date are the same in “Disease Status Monitoring” page of eCRF, the duration of supplemental oxygen is considered as < 24 hours. The SpO₂ measure of $\leq 94\%$ in room air will be confirmed based on “Vital Signs” page of eCRF on the starting day of supplemental oxygen. If there is no record of SpO₂ on the starting day of supplemental oxygen in the “Vital Signs” page of eCRF or the SpO₂ does not meet $\leq 94\%$ in room air, the SpO₂ will be identified based on description on “Disease Status Monitoring” page of eCRF.

Patients whose ‘Reason for End of Treatment Period’ on “End of Treatment Period” page of eCRF or ‘Reason for End of Follow-Up Period’ on “End of Follow-Up Period” page of eCRF is recorded as death and the cause of death is SARS-CoV-2 infection will be considered as experiencing mortality due to SARS-CoV-2 infection. The cause of death will be confirmed through “General Comments” page of eCRF or ‘If death, Reason of Death’ on End of Follow-Up Period” page of eCRF.

Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patients will be presented along with 95% Wilson (score) CI for the proportion in each treatment

group. For the comparison between treatment groups, the primary efficacy endpoint will be tested at the 2-sided significance level of 5% on the ITT set – High Risk using Cochran-Mantel-Haenszel (CMH) test stratified by age (≥ 60 years vs. < 60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other). For the region, the patients in Asia are included in other category as the number of patients in Asia was confirmed to be around 1% during blinded DRM. The difference of proportions between two treatment groups estimated using CMH weights will also be provided along with the 95% stratified Newcombe CI with CMH weights. Supportive analysis will be performed on ITTI set – High Risk using the same analysis method for the primary efficacy analysis. For sensitivity analysis, Fisher's exact test will be conducted on ITT set – High Risk. The 95% exact CI (Chan and Zhang 1999) for the treatment difference will also be provided. Additionally, sensitivity analysis will be performed for the primary analysis excluding 7 patients randomized in site 6179 which terminated its participation in the study by Institutional Review Board (IRB)'s decision due to serious and continuing non-compliance to the protocol and GCP.

In addition, the analysis for the following subgroups will be conducted on ITT set – High Risk:

- Age (< 60 years, ≥ 60 years, ≥ 50 years)
- Baseline comorbidities (Yes, No)
- Region (United States, Asia, European Union, Other)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Not Allowed by Investigator Country Regulations, Other)
- Sex (Male, Female)

9.2. Key Secondary Efficacy Analysis

If the primary endpoint is statistically significant, the key secondary endpoints will be tested using the fixed sequence procedure in order to preserve the Type I error. The order of testing is as follows:

- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients.
- Time to clinical recovery up to Day 14 in high-risk patients.
- Time to clinical recovery up to Day 14 in all randomized patients.

The first key secondary endpoint will be tested only if the primary endpoint is statistically significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is statistically significant.

The key secondary endpoints will be tested at the 2-sided significance level of 5% on the ITT set (for high-risk patients, ITT set - High Risk) using the p-value from stratified CMH

test for binary endpoint or stratified log-rank test for time to event endpoints. The same stratified analysis used for the primary endpoint analysis will be applied.

The supportive analysis will be performed on ITTI set (for high-risk patients, ITTI set - High Risk). Additionally, sensitivity analysis will be performed for the key secondary analysis excluding 7 patients randomized in site 6179 which terminated its participation in the study by IRB's decision due to serious and continuing non-compliance to the protocol and GCP.

Binary endpoint (the first key secondary endpoint) will be summarized using frequency table along with 95% Wilson (score) CI for each proportion of treatment, and difference of proportions between two treatment groups estimated using CMH weights and corresponding 95% stratified Newcombe CI with CMH weights will be presented along with p-value from stratified CMH test.

For time to event endpoints (the second and third key secondary endpoints), Kaplan-Meier methodology will be used to estimate the 25th percentile, 50th percentile (median) and 75th percentile in each treatment arm. The Brookmeyer-Crowley methodology (via log-log transformation) will be used to construct the 95% CI for each percentile. The treatment difference will be assessed by the stratified log-rank test presenting p-value. Hazard ratio between two treatment groups and associated 95% CI will be estimated using the stratified Cox proportional hazard model. Since clinical recovery is beneficial outcome, not hazard, the hazard ratio will be expressed as recovery rate ratio.

For time to clinical recovery endpoints, patients who report at least one symptom at baseline will be included in the analysis.

Clinical recovery is defined as all symptoms on the SARS-CoV-2 Infection Symptom Checklist 1 being recorded as 'absent' or 'mild' in intensity for both at least 48 hours. To meet the clinical recovery, all symptoms of SARS-CoV-2 Infection Symptom Checklist 1 defined in [Table 2](#) should satisfy one of the following conditions.

- ✓ Symptoms 'severe' or 'moderate' in intensity at baseline should be changed to 'mild' or 'absent' after the study drug administration for at least 48 hours.
- ✓ Symptoms 'mild' in intensity at baseline should be changed to 'absent' after the study drug administration for at least 48 hours.
- ✓ Symptoms 'absent' in intensity at baseline should maintain as 'absent' for at least 48 hours.
- ✓ Symptoms 'absent' in intensity at baseline becomes 'severe', 'moderate', or 'mild' during the study and changes back to 'absent' for at least 48 hours.
- ✓ Missing symptoms at baseline becomes 'absent' for at least 48 hours.

Patients who meet the clinical recovery criteria for at least two consecutive time points at each symptom will be considered as satisfying condition of 48 hours and achieving clinical

recovery at the first time point. The checklist at Screening or on Day 1 will be used to determine baseline and checklist from Day 2 will be used to determine clinical recovery. If the checklist from Day 2 is recorded twice a day, evening diary will be used to determine clinical recovery. From Day 2, missing time in SARS-CoV-2 Infection Symptom Checklist 1 will be imputed as 10PM for calculation of time to recovery.

Time to clinical recovery is defined as the elapsed time (in days) from the study drug administration to the earliest day satisfying condition for clinical recovery, and calculated as (Date/time of event or censoring – Date/time of study drug administration). The following patients will be considered censored at their scheduled visit of interest (Day 14).

- Patients who are ongoing in the study without event
- Patients with death or early withdrawal for any reason prior to their scheduled visit of interest (Day 14)
- Patients who administered the rescue therapy due to SARS Cov-2 infection (as defined in [Section 9.3](#)) prior to their scheduled visit of interest (Day 14)
- Patients who were hospitalized due to SARS-CoV-2 infection (as defined in [Section 9.1](#)) prior to their scheduled visit of interest (Day 14)

9.3. Other Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed up to Day 14 and up to Day 28, unless otherwise specified:

- Proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection (after study drug administration)
- Proportion of patients with intensive care unit transfer due to SARS-CoV-2 infection (after study drug administration)
- Proportion of patients with all-cause mortality (after study drug administration)
- Time to clinical recovery (after study drug administration)
- Duration of fever defined as the last day in the patient diary on which the temperature >38 °C (100.4 °F) is recorded, or a potentially antipyretic drug (acetaminophen or ibuprofen) is taken.
 - Duration of fever will be calculated for patients with the temperature >38 °C (100.4 °F) or a potentially antipyretic drug on or before study drug administration.
 - A potential antipyretic drug (including but not limited to acetaminophen, paracetamol or ibuprofen) will be identified by medical review.

- Proportion of patients with hospital admission due to SARS-CoV-2 infection (after study drug administration)
- Proportion of patients with mechanical ventilation due to SARS-CoV-2 infection (after study drug administration)
- Proportion of patients requiring rescue therapy due to SARS-CoV-2 infection (after study drug administration)
 - Rescue therapy is defined as prohibited therapy on or after the study drug administration on Day 1.
 - A prohibited therapy due to SARS-CoV-2 infection (including but not limited to remdesivir, chloroquine, hydroxychloroquine, dexamethasone [alternative corticosteroids to dexamethasone], interferon beta-1b, ribavirin, lopinavir-ritonavir, human intravenous immunoglobulin, convalescent plasma, tocilizumab, sarilumab, SARS-CoV-2 vaccine) will be identified by medical review before unblinding.
- Proportion of patient with negative conversion in nasopharyngeal swab specimen based on RT-qPCR at each visit (after study drug administration)
 - Patients who have negative result for at least two consecutive time points will be considered as satisfying negative conversion at the first time point. The two consecutive time points will be determined excluding missing data. If patients who have one negative result followed by all missing results will also be considered as satisfying negative conversion.
- Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR (after study drug administration)
 - Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR will be calculated as (Date/time of event or censoring – Date/time of study drug administration)
- Time to National Early Warning Score 2 (NEWS2) of 0 (after study drug administration)
 - Patients whose sum of each parameter score meet 0 will be considered as satisfying NEWS2 of 0.
 - Time to NEWS2 of 0 will be calculated as (Date of event or censoring – Date of study drug administration).
- Scores of other known SARS-CoV-2 Infection symptoms such as vomiting, diarrhea, loss of taste or smell at each visit

The secondary efficacy endpoints listed in this section will be analyzed on both ITT and ITTI sets. Confidence interval and p-value will be presented for comparison between treatment groups in a descriptive manner with no adjustments for multiple testing.

Binary endpoints and time to event endpoints will be summarized and analyzed using the same statistical method as the key secondary endpoints ([Section 9.2](#)). For time to event endpoint, time to event will be defined as the elapsed time (in days) from the study drug administration to the earliest day satisfying condition for event. The same censoring rules used for clinical recovery of the key secondary endpoints ([Section 9.2](#)) will be applied.

Continuous endpoints will be summarized using descriptive statistics and analyzed using Analysis of Covariance (ANCOVA) presenting a point estimate, p-value and 95% CI for the treatment difference. Covariates for ANCOVA will include stratification factors used for the primary analysis.

For analysis of time to event endpoints, the following patients will be included in the analysis set:

- Time to clinical recovery: Patients who report at least one symptom at baseline
- Time to negative conversion: Patients who have positive result confirmed based on the negative threshold (as defined in [Section 11.1.1](#)) in the analysis at baseline (or Day 2/Day 3). The same analysis set will be used for the proportion of negative conversion.
- Time to NEWS2 of 0: Patients who have NEWS2 > 0 at baseline

9.4. Patient Diary

Patient diary consists of SARS-CoV-2 Infection Symptom Checklist 1 and 2. Patient diary will be issued to all patients at Screening and patients will be required to record the diary daily from Day 1 until Day 28, and after Day 28 if applicable (Protocol Section 6.1.1.1 and 6.1.1.2) after patients got instructed on how to appropriately complete the patient diary. Signs and symptoms of SARS-CoV-2 infection recorded in the patient diary throughout the study will not be reported as AEs.

9.4.1. SARS-CoV-2 Infection Symptom Checklist 1

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

Table 2. SARS-CoV-2 Infection Symptom Checklist 1

	Intensity (score)	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
1	Symptoms				
	Feeling feverish*				

2	Cough				
3	Shortness of breath or difficulty breathing				
4	Sore throat				
5	Body pain or muscle pain				
6	Fatigue				
7	Headache				

* If patient checks ‘Feeling feverish’ as Mild, Moderate, or Severe, body temperature will be recorded in the patient diary.

Mild: no interference with normal daily activity

Moderate: interferes with normal daily activity

Severe: prevents normal daily activity

The SARS-CoV-2 Infection Symptom Checklist 1 will be recorded once at Screening.

On the date of study drug administration (Day 1), the checklist will be recorded once; before the study drug administration. If Screening visit date and the date of study drug administration are the same, the checklist will be also recorded once; before the study drug administration. From Day 2 and up to Day 28, the checklist will be recorded once a day at approximately 24-hour intervals in the evening (between 6 and 10 PM, approximately).

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

- For patient who achieves the clinical recovery on Day 28 (or Day 27), the patient will record the checklist until Day 30 (or Day 29) to confirm whether the patient’s condition is maintained at least 48 hours.
- For patient who shows deterioration (at the discretion of the investigator) or is still not recovered, the patient will record the checklist until the achievement of clinical recovery.
- For patient with suspicious ADE occurrence, the patient will record the whole patient diary for 7 days from the day of suspicious ADE occurrence. If suspicious ADE has not resolved or has worsened during the 7 days, same procedure of recording the whole patient diary for 7 days will be repeated from the beginning until the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

Body temperature will be collected in the SARS-CoV-2 Infection Symptom Checklist 1 for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection at Screening, or for the patients who record feeling feverish at any time throughout the study.

The body temperature will be self-measured by the patients, once a day (at approximately 24-hour interval; in the evening [between 6 and 10 PM, approximately]) from the first day on which the patient records feeling feverish until the day of subsidence of a fever (subsides to ≤ 38.0 °C), except Screening visit.

SARS-CoV-2 Infection Symptom Checklist 1 will be summarized by treatment group and visit for the both ITTI and ITT sets, in the form of a shift table to detect changes from baseline.

9.4.2. SARS-CoV-2 Infection Symptom Checklist 2

SARS-CoV-2 Infection Symptom Checklist 2 consists of 4 symptoms and the frequency or intensity of patient’s self-aware for each SARS-CoV-2 infection symptom. The 4 symptoms of SARS-CoV-2 infection included are vomit, diarrhea, sense of smell, and sense of taste. Frequency of vomit or diarrhea in the last 24 hours and intensity of the sense of smell or taste in the last 24 hours will be recorded, defined as below [Table 3](#):

Table 3. SARS-CoV-2 Infection Symptom Checklist 2

No.	Items	Score
1	How many times did you vomit (throw up) in the last 24 hours?	
	I did not vomit at all	0
	1-2 times	1
	3-4 times	2
	5 or more times	3
2	How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	
	I did not have diarrhea at all	0
	1-2 times	1
	3-4 times	2
	5 or more times	3
3	Rate your sense of smell in the last 24 hours.	
	My sense of smell is THE SAME AS usual	0
	My sense of smell is LESS THAN usual	1
	I have NO sense of smell	2
4	Rate your sense of taste in the last 24 hours.	
	My sense of taste is THE SAME AS usual	0
	My sense of taste is LESS THAN usual	1
	I have NO sense of taste	2

The SARS-CoV-2 Infection Symptom Checklist 2 will be recorded once at Screening. On the date of study drug administration (Day 1), the checklist will be recorded once before the study drug administration. If Screening visit date and the date of study drug administration are the same, the checklist will be also recorded once before the study drug administration. From Day 2 and up to Day 28, the checklist will be recorded once a day at approximately 24-hour interval in the evening (between 6 and 10 PM, approximately).

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

- For patient with suspicious ADE occurrence, the patient will record the whole patient diary for 7 days from the day of suspicious ADE occurrence. If suspicious ADE has not resolved or has worsened during the 7 days, same procedure of

recording the whole patient diary for 7 days will be repeated from the beginning until the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).

9.5. Disease Status Monitoring

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

9.6. NEWS2

NEWS2 physiological parameter including respiratory rate (breaths per minute), SpO₂ Scale 1 (%), SpO₂ Scale 2 (%), Room air or oxygen, Systolic blood pressure (mmHg), Heart rate (beats per minute), Consciousness, Body temperature (°C) will be assessed at time points specified in the schedule of assessment in [Appendix 1](#).

NEWS2 will be calculated by sum of each parameter score in [Appendix 4](#). If there is missing score in some parameter, then NEWS2 will not be calculated. NEWS2 will be summarized by treatment group at each scheduled visit for both ITTI and ITT sets, displaying descriptive statistics.

10. SAFETY ANALYSIS

All safety analyses will be performed in the Safety Set by each treatment group, and all safety listing will be presented for the ITT Set unless otherwise stated.

10.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in any patient during the study which does not necessarily have to have a causal relationship with the study drug. AEs will be collected from the date of the patient signs on the ICF until the end of the patient's participation in the study. All AEs will be coded to SOC and PT using the MedDRA version 23.1 or higher, and will be graded for intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A treatment-emergent adverse event (TEAE) includes any untoward medical occurrence in a patient after administration of a study drug, which does not necessarily have to have a causal relationship with the study drug. This includes any occurrence that is new or aggravated in severity or frequency from the baseline condition. A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the study drug.

For the purpose of inclusion in TEAE tables and categorization of treatment period or Follow-Up period, incomplete AE start and stop dates will be imputed as follows:

If the stop date of an AE is partial or missing, the following rules will be applied.

- Missing day (e.g. XXAUG2020): Assume the last day of the month. (e.g. 31AUG2020)
- Missing day and month (e.g. XXXXX2020): Assume December 31st. (e.g. 31DEC2020)
- Missing day, month and year (e.g. XXXXXXXXXX): Leave it as Missing.

If the start date of an AE is partial or missing the following rules will be applied. If the stop date of the AE is partial, imputed stop date will be used instead of reported stop date.

- If the day of an Adverse Event is missing (e.g. XXAUG2020), the month and year of the partial date will be compared to the date of the first exposure to study drug.
 - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.
 - If the month and year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01AUG2020).
- If the day and month is missing (e.g. XXXXX2020), the year of the partial date will be compared to the date of the first exposure to study drug.
 - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.
 - If the year is not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2020).
- If the AE start date is missing (e.g. XXXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.

In summaries, AEs will be considered to be related if relationship is possible, probable or definite. AEs with no relationship or intensity will be summarized separately under a missing category.

All AEs will be listed including the following information: Safety Set flag, SOC, PT and Verbatim term; start and stop date/time; TEAE flag; intensity (CTCAE Grade 1 to 5); outcome (Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Not recovered/Not Resolved, Fatal, Unknown); type of sequelae (If Recovered/Resolved with Sequelae); relationship with study drug (Unrelated, Possible, Probable, Definite); action taken with study drug (Dose not changed, Drug interrupted, Drug withdrawn); any treatment received (No, Medication, Non-Medication Treatment: Specify, Both Medication and Non-Medication Treatment: Specify the Non-Medication Treatment); whether the event was serious (Yes, No); whether the AE classified as infusion related reaction (IRR); period flag (Treatment Period, Follow-Up Period).

10.1.1. Incidence of Treatment-Emergent Adverse Events

The TEAEs during Treatment Period will be summarized by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The

total number of events and number of patients with at least one TEAE over all SOC's will also be displayed. In addition, TEAEs regardless of relationship will be summarized.

10.1.2. Deaths

All patients who have a SAE with serious criteria of "Death" will be presented in a listing and the following variables will be included; Safety Set flag, ITTI Set flag, date of the study drug administration, date of last visit, date of death, time to death from the study drug administration, TEAE flag, SOC/PT, cause of death, whether an autopsy was performed (yes, no), whether a death certificate was completed (yes, no), relationship to the study drug, period flag. Time (days) to death from the study drug administration will be calculated as (date of death – date of the study drug administration + 1).

10.1.3. Serious Adverse Events

A SAE is defined as any event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment-Emergent Serious Adverse Events (TESAEs) during Treatment Period will be summarized by treatment group, SOC, PT, relationship, intensity or serious criteria, displaying the number and percentage of patients with at least one TESAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TESAE over all SOC's will also be displayed.

Serious criteria and SAE description will be presented in an additional information listing.

10.1.4. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All patients who have a TEAE with an action taken with study drug of "Drug Withdrawn" during Treatment Period will be summarized by treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE leading to study drug discontinuation, using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE leading to study drug discontinuation over all SOC's will also be displayed.

10.1.5. Treatment-Emergent Adverse Events of Special Interest

The AEs checked as infusion related reactions (IRR) including hypersensitivity and anaphylactic reactions on the "Adverse Event" page of eCRF will be classified as treatment-emergent adverse events of special interest (TEAESI). All TEAESI during Treatment Period will be summarized by treatment group, SOC, PT, relationship and

intensity, displaying number and percentage of patients with at least one TEAESI using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAESI over all SOCs will also be displayed. In addition, a table for signs and symptoms regarding IRR will be provided separately by SOC, PT and intensity. Signs and symptoms of IRR including hypersensitivity and anaphylactic reactions will be presented in an additional information listing.

10.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology and urinalysis) will be collected at each scheduled visit specified in [Appendix 1](#).

The following clinical laboratory assessment will be performed:

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

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

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

All summaries will be based on the System International (SI) units based on CTCAE v5.0.

All parameters analyzed at the central laboratory, not limited as specified in the protocol, and ESR analyzed at the local laboratory will be included in summary tables. All parameter results regardless of central or local laboratory will be presented in listings.

Actual value and change from baseline for clinical chemistry and hematology results will be summarized by treatment group at each time point using descriptive statistics. For the

purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality signs will be displayed. Shift tables from baseline visit to each scheduled post-baseline visit will be generated for urinalysis results using “Normal” or “Abnormal” classification as appropriate by treatment group.

Some numeric parameters will be labeled with a CTCAE term, and grading will be applied to post-baseline values for numeric parameters where possible according to CTCAE v 5.0. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. If different grades share the same criteria due to exclusion of clinical input, lower grade will be used. The CTCAE terms and ranges for applicable parameters are listed in [Appendix 3](#). The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as “No Grade”.

The number and percentage of patients with a result for each grade will be summarized by laboratory category, treatment group, CTCAE term and visit. Additional tables will be generated using the most severe grade after study drug administration. The most severe grade will be selected including unscheduled visits.

Clinical chemistry, hematology and urinalysis data will be presented in separate listings along with high and low flags, if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters.

10.3. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart and respiratory rate, saturation peripheral oxygen [SpO₂] and body temperature), will be measured at each scheduled visit specified in [Appendix 1](#). Body weight will be measured at screening, prior to the study drug administration on Day 1 and on Day 90 (EOT). Height and BMI will be assessed at screening only as a baseline measurement.

Actual values and change from baseline for vital signs including weight, except for hypersensitivity monitoring results, will be summarized by treatment group at each time point using descriptive statistics. Individual vital sign measurements including body weight, except for hypersensitivity monitoring, will be presented in a data listing.

10.4. Hypersensitivity Monitoring

For hypersensitivity monitoring, additional vital signs (including systolic and diastolic blood pressure, heart and respiratory rate and body temperature) will be performed at the following time points as specified in [Appendix 1](#).

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

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

Actual values and change from baseline for hypersensitivity monitoring will be summarized by treatment group at each time point using descriptive statistics. Clinically notable hypersensitivity results of each parameter will be summarized by treatment group at each time point. The criteria for clinically notable results are defined as below.

Table 4. The Criteria for Clinically Notable Results

Parameter	Low	High
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Heart rate (beats per minute)	≤ 50	≥ 100
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Body temperature ($^{\circ}\text{C}$)	≤ 35.0	≥ 38.0

Individual vital sign measurements for hypersensitivity monitoring will be presented in a data listing. High and low flags will be included in this listing to show whether a hypersensitivity result is outside of the clinically notable ranges.

10.5. Electrocardiograms

Twelve-lead electrocardiograms (ECG) will be performed at each scheduled visit specified in [Appendix 1](#) and if the patient experienced cardiac symptoms during the study drug administration. Findings of 12-lead ECG will be classified as either “Normal”, “Abnormal, Not Clinically Significant” or “Abnormal, Clinically Significant”. Any type of ECG can be performed in case of hypersensitivity.

A shift table from baseline visit to each scheduled post-baseline visit will be summarized by treatment group. Individual 12-lead results will be presented in a data listing.

10.6. Physical Examination

Physical examinations will be performed at each scheduled visit specified in [Appendix 1](#). The following body systems will be examined:

- General Appearance
- Head and Neck
- Skin
- Cardiovascular System
- Respiratory System
- Abdominal System
- Neurological System

- Musculoskeletal System
- Lymphatic System

Findings of physical examination will be classified as either “Normal”, “Abnormal, not clinically significant” or “Abnormal, clinically significant”.

The physical examination results for each body system will be summarized by treatment group and scheduled visit (including EOT). Individual physical examination results will be presented in a data listing.

10.7. Pregnancy Test

Only female patients of childbearing potential with a negative pregnancy test results can be enrolled. Serum pregnancy test will be performed for female patients with childbearing potential at each scheduled visit specified in [Appendix 1](#). However, if serum pregnancy test is not available at the study site, urine pregnancy test can be performed.

The serum (or urine) pregnancy test samples will be analyzed at the local laboratory, and will be classified as either “Negative”, “Positive” or “Indeterminate”.

The pregnancy test results will be summarized by using the number of female patients with childbearing potential as a denominator by treatment group at each scheduled visit (including EOT), displaying the number and percentage of patients. Individual pregnancy test results will be presented in a data listing.

10.8. Immunogenicity

Blood samples for immunogenicity assessments will be collected at each scheduled visit specified in [Appendix 1](#). Additional immunogenicity test will be performed if a patient experiences any immune-related AEs after the study drug administration.

The anti-drug antibody (ADA) assay will follow a three tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. The test outcome for the screening assay will be “Potential Positive” or “Negative”. Samples that are “Potential Positive” in the screening assay will be undergone further testing in the confirmatory assay to determine if patients are true positive. The test outcome for the confirmatory assay will be “Reactive”, “Negative” or “Not applicable (N/A)”. “Reactive” indicates a true positive test outcome and will be labeled as “Positive” in outputs, “Negative” is considered negative and “N/A” indicates the assay was negative at the screening phase of the process. Patients with a “Negative” test outcome for either screening or confirmatory assays will be considered as negative for the overall ADA assessment. For further characterization, the antibody level will be assessed by titration in confirmed positive samples.

Samples that are positive in the ADA assay will be analyzed further to conduct a neutralizing antibody (NAb) assessment. The test outcome for the screening assay will be “Positive” or “Negative”.

The results of the final ADA and the screening NAb assay at each scheduled visit will be summarized by treatment group, displaying the number and percentage of patients.

In addition, the number of patients and percentages with positive ADA and NAb conversion will be summarized. The rule of ADA and NAb conversion is as follows:

- ADA Conversion is defined as patients who reported at least one ADA positive result after study drug administration in patients who
 - Have at least one ADA result after study drug administration, and
 - Do not have any ADA positive result before study drug administration.
- NAb Conversion is defined as patients who reported at least one NAb positive result after study drug administration in patients who
 - Have at least one ADA result after study drug administration, and
 - Do not have any NAb positive result before study drug administration.

Actual values for ADA titration will be summarized by treatment group at each time point using descriptive statistics. Individual immunogenicity test results will be presented in a data listing.

10.9. SARS-CoV-2 Infection Related Signs and Symptoms

During screening, treatment period and EOT visit, the investigator or designee will perform a respiratory signs and symptoms assessment (including but not limited to the examination of ears, nose, throat, sinuses and lungs, and the assessment for potential complications of SARS-CoV-2 infection throughout the study) at each scheduled visit specified in [Appendix 1](#). During the follow-up period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone calls. The results will be classified as either “Normal” or “Abnormal”.

A shift table from baseline visit to each scheduled post-baseline visit for each category, except for the follow-up period, will be summarized by treatment group. Individual SARS-CoV-2 infection related sign and symptoms will be presented in a data listing.

10.10. Potential Effects of the Incidence of Antibody-dependent Enhancement

A patient will be considered to possibly have antibody-dependent enhancement (ADE) if the date of occurrence of suspicious ADE is filled on the “ADE Occurrence” page of eCRF.

If a patient has suspicious ADE, additional evaluations (including nasopharyngeal swab test, patient diary, SARS-CoV-2 infection related signs and symptoms assessment, vital signs, 12-lead ECG and troponin test) will be performed at each scheduled visit specified in [Appendix 2](#). If symptoms have not resolved or have worsened until 7 days after the day of suspicious ADE occurrence, same procedure will be repeated from the beginning until

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

Suspicious ADE will be summarized by treatment group, displaying the number and percentage of patients. Individual date of occurrence of suspicious ADE will be presented in a data listing, and additional evaluations will be included in the corresponding assessment listings.

11. EXPLORATORY ANALYSIS

11.1. Virology and Serology Analysis

Exploratory virology (viral shedding based on RT-qPCR, genotyping and phenotyping of SARS-CoV-2 viral isolates, and viral serology for SARS-CoV-2 antibody) analysis will be conducted in the ITTI Set and listed ITT Set. Viral shedding will also be analyzed in the ITT Set.

11.1.1. Viral Shedding

For viral shedding in nasopharyngeal swab specimen based on RT-qPCR, the actual values and change from baseline for viral shedding, percentage of patients with positive/negative viral shedding, duration of viral shedding, and AUC of viral levels will be summarized by each treatment group at each scheduled visit using descriptive statistics (n, mean, SE, minimum, median and maximum) or frequency tables. Mean (\pm SE) viral load titer will be plotted for each scheduled time point in log scale. If EOT result is available and the result from patient whose viral titer result at Day 28 is greater than or equal to negative threshold, the result of EOT visit will be included in summary table (the actual values and change from baseline for viral shedding, percentage of patients with positive/negative viral shedding).

The following rules present how viral titers will be treated in descriptive summary and AUC calculation, and categorized to Positive or Negative. AUC will be displayed to two decimal places. The analysis will be based on the 2.33 log₁₀cp/mL. Additionally negative threshold for 3 and 4 log₁₀cp/mL will be also considered although 2.33 log₁₀cp/mL is used to determine the analysis set defined in [Section 5.4](#).

Table 5. Rules of Viral Titers

Reported Value	RT-qPCR	
	Treated as	Categorized as
\geq Negative threshold	Reported value	Positive
< Negative threshold	Negative threshold	Negative
Negative	Negative threshold	Negative

Abbreviations: RT-qPCR= reverse transcription-quantitative polymerase chain reaction.

Duration (days) of viral shedding will be calculated as (Date/Time of post-baseline last positive sample – Date/Time of study drug administration).

AUC of viral level is calculated from date/time of study drug administration to date/time of last measurable value of patients who have at least one post-baseline result using linear trapezoidal rule. Viral level at baseline will be considered as result at study drug administration.

11.1.2. Genotype of SARS-CoV-2 Viral Isolates

Genotype result will be summarized on the ITTI Set by each treatment group at each scheduled visit using frequency table and will be presented in listing.

11.1.3. Viral Serology for SARS-CoV-2 Antibody

Viral serology for SARS-CoV-2 antibody test with assays detecting serum antibodies against SARS-CoV-2 will be performed locally using the serum samples (if the assay is available). Viral serology for SARS-CoV-2 antibody result will be summarized on the ITTI Set by each treatment group at each scheduled visit using frequency table.

12. Changes in the Planned Analysis

- For patients who had negative result at Day 1 or missing Day 1 result of RT-qPCR, the ITTI Set will also include these patients if they are confirmed SARS-CoV-2 infection positive by Day 2 or Day 3. These patients can also be considered as infected since the virus was detected at Day 2 or Day 3.
- All expression or text regarding phenotype will be deleted in SAP since phenotype was not analyzed.

13. Reference List

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14. APPENDICES

Appendix 1: Schedule of Assessments for Part 2

Study Day (Visit windows) ⁴	Screening ¹	Treatment Period											EOT ²	Follow-Up Period ³
	-7 to 1	1	2	3	5	7	10	14 (±1)	17 (±1)	21 (±1)	28 (±3)	56 (±5)	90 (±5)	Biweekly up to 180 (±5)
Telephone Follow-Up Visit														X
Informed consent	X													
Medical history	X													
Demographics	X													
Weight, BMI and height ⁵	X	X ⁶											X	
Hepatitis B/C and HIV test (central) ⁷	X													
Serum pregnancy test ⁸	X												X	
Inclusion/exclusion criteria	X	X ⁶												
Randomization		X ⁶												
Administration of study drug⁹		X												
Nasopharyngeal swab ¹⁰														
<ul style="list-style-type: none"> SARS-CoV-2 infection by sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR¹¹ 	X													
<ul style="list-style-type: none"> Viral shedding (central, RT-qPCR), genotyping and phenotyping of SARS-CoV-2 viral isolates (central)¹² 		X ⁶		X		X	X	X		X	X		(X) ¹³	

Study Day (Visit windows) ⁴	Screening ¹	Treatment Period											EOT ²	Follow-Up Period ³
	-7 to 1	1	2	3	5	7	10	14 (±1)	17 (±1)	21 (±1)	28 (±3)	56 (±5)	90 (±5)	Biweekly up to 180 (±5)
Telephone Follow-Up Visit														X
Patient diary ¹⁴	X	X											(X)	
SARS-CoV-2 infection related signs and symptoms assessment ¹⁵	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	X
NEWS2	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity sampling (central)		X ⁶				X		X			X	X	X	
Viral serology for SARS-CoV-2 antibody ¹⁶		X ⁶				X		X			X	X	X	
Physical Examination	X	X ⁶											X	
Clinical laboratory analyses (central) ¹⁷	X		X		X	X	X	X			X			
Vital Signs (blood pressure, heart rate, respiratory rate, SpO ₂ and body temperature) ¹⁸	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	
NYHA class assessment	X	X ⁶												
12-lead ECG ¹⁹	X	X ⁶				X		X			X			
Radiography ²⁰	X													
Hypersensitivity monitoring ²¹		X												
Disease status monitoring ²²								X						
Prior, concomitant medication ²³								X						
Adverse events monitoring ²⁴								X						

Abbreviations: ADE=antibody-dependent enhancement; ADR=adverse drug reaction; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; CRP=c-reactive protein; CT=computed tomography; ECG=electrocardiogram; EOT=End-of-Treatment; ESR= erythrocyte sedimentation rate; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HIV=Human immunodeficiency virus; ICF=informed consent form; NEWS2= National Early Warning Score 2; NYHA=New York Heart Association; RT-PCR=reverse transcription polymerase chain reaction; RT-qPCR= reverse transcription quantitative polymerase chain reaction ; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO₂= saturation of peripheral oxygen.

1. If Screening visit date and the date of study drug administration are the same, all assessments scheduled for the Screening and Day 1 visit can be performed only once on the same day before randomization.
2. End-of-Treatment visit assessments will be performed on Day 90. If a patient withdraws prematurely after the study drug administration, the patient will be asked to return to the study site on the next scheduled visit for the EOT assessments.

3. For all patients including patients who withdraws prematurely after the study drug administration, each telephone call follow-up will occur biweekly from EOT up to Day 180. During the Follow-up Period, SARS-CoV-2 infection related signs and symptoms will be assessed by telephone calls to capture the suspicious ADE occurrence. For patients with suspicious ADE occurrence, all assessments specified in protocol [Table 11-3](#) will be conducted on unscheduled visit.
4. All patients will complete the study visits during the treatment period either by visiting the study center, confinement in the study center, or home visiting services by health care professionals, whichever applicable according to the local regulations or discretion of investigator.
5. Measurement of height and BMI will be performed once at Screening.
6. These assessments should be performed prior to the study drug administration.
7. HBsAg, HBsAb, HBeAb, hepatitis C virus antibody, hepatitis C virus ribonucleic acid, and HIV-1 and -2 tests will be performed in all patients. Hepatitis B, hepatitis C virus antibody, and HIV analysis will be performed at the central laboratory.
8. For females patients with childbearing potential, serum pregnancy test will be performed locally at Screening and EOT visit. However, if serum pregnancy test is not available at study site, urine pregnancy test can be performed. Only female patients of childbearing potential with a negative pregnancy test results can be enrolled.
9. Study drug will be administered as an IV infusion over 60 minutes (± 15 minutes) on Day 1. When calculating total volume of study drug to be administered, the body weight of each patient measured on Day 1 will be used. Patients with body weight at or above 200 kg will receive 8,000 mg of CT-P59 or matching volume of placebo.
10. Nasopharyngeal swabbing will be performed by trained site personnel. A nasopharyngeal swab sampling time points and acceptable tolerance windows are specified in protocol [Table 6-3](#).
11. If the patient had a RT-PCR result (sample collected within 72 hours before the study drug administration) confirming SARS-CoV-2 infection even if before signing the informed consent, the patient can be enrolled. During the Screening Period, only one re-test for confirmation of SARS-CoV-2 infection will be allowed, if study drug can be administered no more than 7 days from onset of symptom based on the re-test result.
12. Nasopharyngeal swabbing will be performed in each of the patient's two nostrils; therefore, two nasopharyngeal swabs in one sample bottle will be collected for each assessment visits.
13. If the RT-qPCR result on Day 28 shows positive of SARS-CoV-2 infection, additional viral shedding will be conducted on Day 90.
14. Patients will be instructed to complete the patient diary for SARS-CoV-2 Infection Symptom Checklist 1 once a day at approximately 24-hour interval in the evening (between 6 and 10 PM, approximately), and SARS-CoV-2 Infection Symptom Checklist 2 once a day in the evening (between 6 and 10 PM, approximately) from Day 1 until Day 28 (more details specified in protocol [Section 6.1.1.1](#) and [6.1.1.2](#)). After Day 28, additional recording of the diary will be required if following conditions are met:
 - For patient who achieves clinical recovery on Day 28 (or Day 27), the patient will record the SARS-CoV-2 Infection Symptom Checklist 1 until Day 30 (or Day 29) to confirm whether the patient's condition is maintained at least 48 hours. For patient who shows deterioration (at the discretion of the investigator) or is still not recovered, the patient will record the SARS-CoV-2 Infection Symptom Checklist 1 until achievement of clinical recovery.
 - For patients with suspicious ADE occurrence, the patient will record the whole patient diary for 7 days from the day of suspicious ADE occurrence (specified in protocol [Table 11-3](#)). If suspicious ADE has not resolved or has worsened during the 7 days, same procedure of recording the whole patient diary for 7 days will be repeated until the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).Body temperature will be collected in the SARS-CoV-2 Infection Symptom Checklist 1 for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection at Screening, or for the patients who record feeling feverish at any time throughout the study. However, if patient's condition is not available to record the diary at the discretion of investigator (e.g. sedation state for mechanical ventilator therapy), recording can be discontinued. Recording will be resumed when the patient's condition becomes available to record the patient diary.
15. SARS-CoV-2 infection related signs and symptoms should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs and the assessment for potential complications of SARS-CoV-2 infection throughout the study. During the Follow-up Period, patients will be asked if they have any SARS-CoV-2 infection related signs and symptoms by telephone calls.
16. Viral serology for SARS-CoV-2 antibody test with assays detecting serum antibodies against SARS-CoV-2 will be performed locally using the serum samples (if the assay is available).
17. To determine eligibility, clinical laboratory testing will be performed at the local laboratory at Screening. Clinical laboratory testing (clinical chemistry, hematology, and urinalysis) for all visits including Screening will be analyzed at the central laboratory.

Clinical chemistry	Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ -glutamyl transferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-myocardial band isoenzyme, troponin (I or T, only one applicable), albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP
Hematology	Red blood cells, ESR (local), total white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination of white blood cell count, red blood cell count, and bacteria.

18. Blood pressure, heart and respiratory rates, SpO₂ and body temperature will be measured after the patient has rested quietly for at least 5 minutes. SpO₂ will be measured while breathing normal room air. Temperature will be measured using tympanic thermometer throughout the study.
19. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes. Regardless of the 12-lead ECG result, further cardiological evaluation can be performed at the investigator's discretion. If the patient has a 12-lead ECG result performed within 7 days prior to the study drug administration even before signing the ICF, the result can be used for the Screening assessment.
20. Radiography (chest x-ray or chest CT) will be performed at Screening and when the investigator considers it is clinically necessary (e.g., abnormal values of SpO₂ or patient with clinical signs of pneumonia). An additional radiography can be performed at the investigator's discretion based on the judgment per the signs and symptoms (e.g., abnormal values of SpO₂ or patient with clinical signs of pneumonia). If the patient has a radiography result performed within 7 days prior to the study drug administration even before signing the ICF, the result can be used for the Screening assessment when this radiography is performed after the onset of first SARS-CoV-2 infection related symptom.
21. Hypersensitivity monitoring at Day 1 pre-dose (within 30 minutes), 30 minutes (± 15 minutes) and 60 minutes (± 15 minutes) after the start of the study drug administration, 15 minutes after the end of study drug administration ($+15$ minutes), 2 hours (± 15 minutes) and 4 hours (± 15 minutes) from the start of study drug administration (specified in protocol [Section 6.2.5](#)). Additional vital signs including blood pressure, heart rate, respiratory rate and body temperature will be evaluated for possible hypersensitivity reactions. Hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed.
22. Disease status including requirement of supplemental oxygen, intensive care unit transfer, mechanical ventilation use, hospitalization, and rescue therapy will be monitored during the study period (from signing of ICF to EOT).
23. Use of all prior and concomitant medications for the treatment of SARS-CoV-2 infection from the diagnosis of disease until the EOT visit, will be recorded in both the source documents and the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 1) or from when the ICF is signed, whichever is earlier, will be recorded until the EOT visit.
24. Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOT visit. Where an ADR (e.g., related to study drug) is ongoing at the EOT visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. AEs of special interest (infusion related reactions [hypersensitivity/anaphylactic reactions]) should be closely monitored.

Appendix 2: Schedule of Assessments for Patients with Suspicious ADE Occurrence (Unscheduled Visits)

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

Abbreviations: ADE=antibody-dependent enhancement; ECG=electrocardiogram; RT-qPCR= reverse transcription quantitative polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO₂= saturation peripheral oxygen.

Note: For suspicious ADE assessment, patients can be hospitalized based on the investigator's decision. If required, additional assessments can be performed by investigator's discretion during the hospitalization period. Otherwise, the assessment will be done by outpatient visit. The assessments designated with an (X) will be performed in selected visits under the conditions explained in the relevant document of virology analysis.

1. The day of suspicious ADE occurrence.
 - If a patient has excessive progression of symptoms regarded as related to viral infection (e.g., excessive infiltration of inflammatory cells in the lung), OR
 - If a patient has other SARS-CoV-2 infection related signs and symptoms which are judged as possible manifestations of ADE according to the medical opinion of the investigator.
2. If symptoms have not resolved or have worsened until 7 days after the day of suspicious ADE occurrence, same procedure will be repeated from the beginning until when the symptoms are resolved and/or no SARS-CoV-2 infection is confirmed by RT-PCR (local).
3. If required, RT-PCR (local) can be performed at any time by investigator's discretion.
4. The genotyping and phenotyping will be performed using the biologic samples for patients.
5. For patients with suspicious ADE occurrence, patient will record the whole patient diary for 7 days from the day of suspicious ADE occurrence. Body temperature will be collected for the patients who record feeling feverish as the baseline symptoms of SARS-CoV-2 infection in the SARS-CoV-2 Infection Symptom Checklist 1 on suspicious ADE occurrence, or the patients who record feeling feverish in the SARS-CoV-2 Infection Symptom Checklist 1 at any time throughout the suspicious ADE assessment.
6. The investigator or designee will perform a respiratory signs and symptoms assessment (which should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and assessment for potential complications of SARS-CoV-2 infection.
7. Blood pressure, heart rate and respiratory rate, SpO₂ and body temperature will be measured after the patient has rested quietly for at least 5 minutes. SpO₂ will be measured while breathing normal room air. Temperature will be measured using tympanic thermometer throughout the study.
8. All scheduled 12-lead ECGs must be performed after the patient has rested quietly for at least 5 minutes. Regardless of the 12-lead ECG result, further cardiological evaluation can be performed at the investigator's discretion.
9. Troponin test will be analyzed at the central laboratory. However, analysis of the test can be also conducted at local laboratory at discretion of investigator.

Appendix 3: Table of CTCAE v5.0 Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Blood bilirubin increased	Serum Bilirubin (Total)	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Alanine aminotransferase (ALT)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate aminotransferase (AST)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline Phosphatase	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
GGT increased	γ -Glutamyl Transferase	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Creatinine increased	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
CPK increased	Creatine Kinase	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L;	>155 - 160 mmol/L;	>160 mmol/L;
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L;
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L;	>6.0 - 7.0 mmol/L;	>7.0 mmol/L;
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; #	<3.0 - 2.5 mmol/L;	<2.5 mmol/L;

Hypercalcemia	Calcium	High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; @	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; @	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; @	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; @
Hypocalcemia	Calcium	Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; @	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; @	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; @	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; @
Hypoglycemia	Glucose	Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L;
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L;
Leukocytosis	Total White Blood Cell Count	High			>100,000/mm ³	
White blood cell decreased	Total White Blood Cell Count	Low	<LLN - 3000/mm ³ ; <LLN - 3.0 x 10 ⁹ /L	<3000 - 2000/mm ³ ; <3.0 - 2.0 x 10 ⁹ /L	<2000 - 1000/mm ³ ; <2.0 - 1.0 x 10 ⁹ /L	<1000/mm ³ ; <1.0 x 10 ⁹ /L
Neutrophil count decreased	Absolute Neutrophil Count	Low	<LLN - 1500/mm ³ ; <LLN - 1.5 x 10 ⁹ /L	<1500 - 1000/mm ³ ; <1.5 - 1.0 x 10 ⁹ /L	<1000 - 500/mm ³ ; <1.0 - 0.5 x 10 ⁹ /L	<500/mm ³ ; <0.5 x 10 ⁹ /L
Lymphocyte count decreased	Lymphocyte Count	Low	<LLN - 800/mm ³ ; <LLN - 0.8 x 10 ⁹ /L	<800 - 500/mm ³ ; <0.8 - 0.5 x 10 ⁹ /L	<500 - 200/mm ³ ; <0.5 - 0.2 x 10 ⁹ /L	<200/mm ³ ; <0.2 x 10 ⁹ /L
Lymphocyte count increased	Lymphocyte Count	High		>4000/mm ³ - 20,000/mm ³	>20,000/mm ³	
Platelet count decreased	Platelet Count	Low	<LLN - 75,000/mm ³ ; <LLN - 75.0 x 10 ⁹ /L	<75,000 - 50,000/mm ³ ; <75.0 - 50.0 x 10 ⁹ /L	<50,000 - 25,000/mm ³ ; <50.0 - 25.0 x 10 ⁹ /L	<25,000/mm ³ ; <25.0 x 10 ⁹ /L
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	
Hemoglobin increased	Hemoglobin	High	> ULN - Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	

Note: LLN = lower limit of normal, ULN = upper limit of normal. The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory. # indicates that this grade will not be used because this grade shares the same criteria due to exclusion of clinical input. @ indicates that corrected

calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 – serum albumin [g/dL]), where 4.0 represents the average albumin level. For SI units as: Corrected calcium (mmol/l) = total Ca (mmol/l) + 0.02 (40 – serum albumin [g/l]).

Appendix 4: National Early Warning Score 2 (NEWS2)

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

Abbreviations: C = confusion; P = pain; U = unresponsive; SpO₂ = Saturation peripheral oxygen; V= voice.

* For patients with hypercapnic respiratory failure (blood gas analysis may be locally done by the investigator’s discretion) and requiring supplemental oxygen, a prescribed oxygen saturation target range of 88 to 92% is recommended, and SpO₂ Scale 2 will be used to score the oxygen saturation of the NEWS2. The decision to use SpO₂ Scale 2 should be made by the investigator. In all other circumstances, SpO₂ Scale 1 will be used for scoring NEWS2.