CELLTRION Inc.

CT-P59 1.1

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

30th Nov 2020

Statistical Analysis Plan

Version 2.0

Prepared by:

[redacted]

Prepared by: [redacted] Date: [redacted]

Approved by: [redacted] Date: [redacted]

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.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
ADA	Anti-Drug Antibody
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}inf}$	Area under the Concentration-Time Curve from Time zero to Infinity
$AUC_{0\text{-}last}$	Area under the Concentration-Time Curve from time zero to the Last Quantifiable Concentration
BLQ	Below the Lower limit of Quantification
BMI	Body Mass Index
AESI(s)	Adverse Event(s) of Special Interest
CI	Confidence Interval
CL	total body clearance
C_{max}	maximum serum concentration
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
%CV	percent Coefficient of Variation
DEC	Dose Escalation Committee
DRM	Date Review Meeting
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End-Of-Study
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HBcAb	Hepatitis B Core Antibody
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ITT	Intent-to-treat
IV	intravenous
LS	Least Square
NAb	neutralizing antibody
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Abbreviation	Definition
SD	Standard Deviation
SOC	System Organ Class
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse events of special interest
TESAE	Treatment-emergent serious adverse event
TLF	Table, Listing and Figure
T_{max}	Time to C_{max}
V_z	Volume of distribution during the elimination phase
λ_z	Terminal elimination rate constant
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, randomization and pharmacokinetic parameter calculation are being performed under contract with [redacted], in collaboration with CELLTRION. The bioanalytical lab analysis is being performed under contract with [redacted], in collaboration with CELLTRION. The data management and statistical analyses are being performed by CELLTRION.

2. INTRODUCTION

This Statistical Analysis Plan (SAP) defines the statistical methods to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P59 1.1, entitled as "A Phase 1, Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CT-P59 in Healthy Subjects".

There are two clinical study reports (CSRs) planned for the following time points:

- First CSR: Data up to Day 14 of the last enrolled subject will be included, except for pharmacokinetic (PK) and immunogenicity data, which will include results up to Day 7 of each subject. List of TLFs for the first CSR is presented in Appendix 2.
- Final CSR: All data after completion of the study

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

This SAP covers all specified analyses and is based on the following documents:

- Study Protocol Version 1.3 – 03rd July 2020
- Unique Case Report Form Version 1.0 – 01st July 2020

Table, Listing and Figure (TLF) mock shells will be provided as an addendum to this document.

3. Study Objective

Primary and secondary objectives are described as below.

3.1. Primary Objective

The primary objective is to evaluate the preliminary safety and tolerability of CT-P59 up to Day 14 of the last enrolled subject.

3.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the PK of CT-P59
- To evaluate additional safety of CT-P59 including immunogenicity

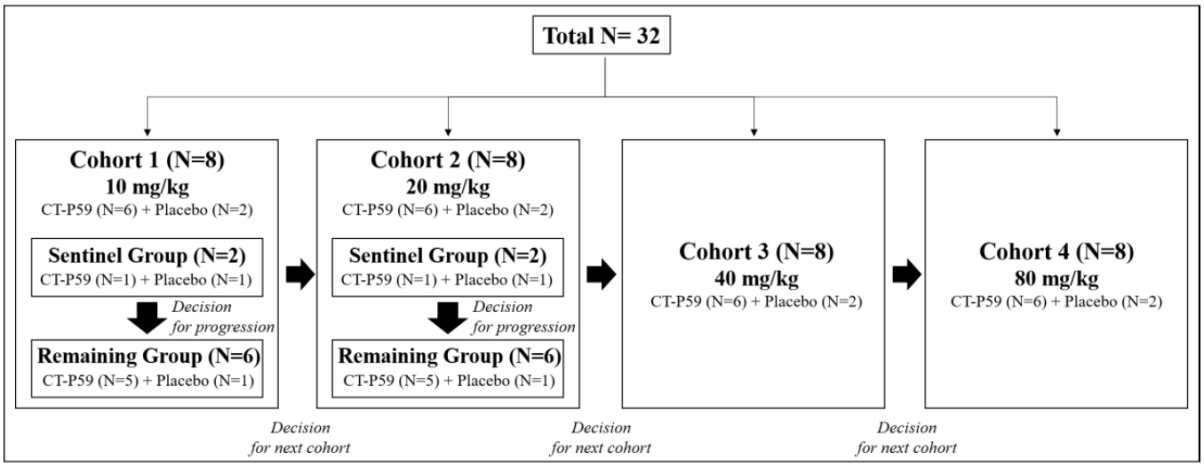
4. INVESTIGATIONAL PLAN

4.1. Study Design and Plan

This study is a randomized, double-blind, placebo-controlled, parallel group, single ascending dose, Phase 1 study to evaluate the safety, tolerability and PK of CT-P59 in healthy subjects. Approximately 32 subjects in 4 cohorts are planned for enrollment and each cohort will consist of 8 subjects, 6 of whom will receive CT-P59 and 2 of whom will receive a placebo. In cohorts 1 and 2, each cohort includes a sentinel group of 2 subjects and a remaining group of 6 subjects. In a sentinel group, 2 subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo. In a remaining group, 6 subjects will be randomized in a 5:1 ratio to receive CT-P59 or placebo. In cohorts 3 and 4, 8 subjects will be randomized in 3:1 ratio to receive CT-P59 or placebo.

The study design overview is presented in Figure 1.

Figure 1: Study Design Overview



This study will be started with the lowest dose that will maximize safety and the dose levels will be escalated to the higher doses. In cohorts 1 and 2, the first study drug administration will be administered as intravenous (IV) infusion to each sentinel group. In cohorts 3 and 4, all subjects in each cohort will randomly receive study drug without group sequence. Dose Escalation Committee (DEC) will review all available safety data after an observation period of 48 hours and will decide whether to proceed dosing of remaining group and escalating dose to next cohort. If any safety concern including predefined stopping rule is raised under decision

of committee, the study will be temporarily stopped and Data and Safety Monitoring Board (DSMB) will review all available data and evaluate the relationship to CT-P59 of the event with unblinded manner and will make a decision on continuation of the study.

This study consists of Screening period (Day -21 to Day -2), Admission (Day -1), Study period (Day 1 to prior to end-of-study visit), and end-of-study (EOS) visit (Day 90). The total duration of this study will be approximately 16 weeks for the individual subject. Subjects will sign the informed consent at screening visit and undergo procedures to determine eligibility. Eligible subjects will have admission visit on Day -1 and under go baseline assessments and recheck eligibility. If subjects are confirmed to be eligible, subjects will be randomized to receive a single dose of CT-P59 or placebo on Day 1. All subjects will be confined to the study center on Day -1 until completion of the 72-hour (Day 4) assessments after the study drug administration and confinement can be extended depending on subjects and study center's availability up to Day 14. The subsequent study visits will be carried out on an out-patient basis. Subjects will return to the study center on Day 90 and undergo predefined End-of-Study (EOS) visit assessments.

The schedule of assessments is presented in Appendix 1.

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: number of subjects (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 regards to the number of decimal places:

- Minimum and maximum will be presented to the same number of decimal places as reported.
- Mean, median, geometric mean and percent coefficient of variation (%CV) will be rounded to one more decimal place than the maximum decimal place of values in the source listing.
- SD will be rounded to one more decimal place than mean.
- Point estimate and confidence intervals (CI) obtained from statistical procedures will be displayed to two decimal places.

Geometric mean will not be reported if the dataset includes zero values and %CV will not be reported if the mean is zero.

Categorical data will be summarized using frequency tables showing numbers and percentages of subjects. Percentages will be rounded to one decimal place and will be suppressed when the count is zero. The denominator for all percentages will be the number of subjects within each treatment group for the set of interest, unless otherwise specified.

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

When combining data from electronic Case Report Form (eCRF) and analytical facilities such as Central Laboratory for pharmacokinetics or immunogenicity, discrepancy will be handled as following:

1) Recorded as sample collected in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date from eCRF;

2) No corresponding records in eCRF for results from analytical facility – listing will display only specimen collection visit/date and results from analytical facility;

3) Discrepancy in sample collection date from eCRF and analytical facility – listing will display results from analytical facility and visit/date from eCRF if not missing; if sample collection date is missing in eCRF then use specimen collection visit/date from analytical facility.

All available results from analytical facilities will be included in the summary table.

This SAP could be updated after the Data Review Meeting (DRM) but prior to database hard lock to document any deviations.

5.1. Software

All statistical analyses will be conducted using [redacted] PK parameters will be computed by noncompartmental methods using appropriate validated software such as [redacted]

5.2. Sample Size

The total sample size of 32 subjects is not based on a formal statistical hypothesis. A sample size justification based on statistical hypotheses is not relevant in this study. The proposed number of 8 subjects (6 subjects for CT-P59 and 2 subjects for placebo) in each cohort is set empirically based on sample sizes in other Phase 1 studies investigating the safety and

tolerability of their study drugs and is considered to be sufficient to achieve the objectives of the study.

5.3. Randomization, Stratification, and Blinding

On Day 1, eligible subjects will be randomly assigned to CT-P59 or placebo. In cohorts 1 and 2, subjects will be randomized in a 1:1 ratio to receive CT-P59 or placebo in sentinel group and in a 5:1 ratio to receive CT-P59 or placebo in remaining group. In cohorts 3 and 4, 8 subjects will be randomized in a 3:1 ratio to receive CT-P59 or placebo.

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

[redacted] will generate the randomization and kit schedules which contain the randomization and kit number, and corresponding treatment group using [redacted]. The unblinded site pharmacist will use both the randomization and kit schedule provided by [redacted] for treatment assignment.

This study will be double-blind until the end of the study. The randomization codes will not be revealed to study subjects, investigator, and study center personnel, except for delegated unblinded site pharmacist who will handle the study drug and predefined unblinded teams in CELLTRION and [redacted] until all final data have been entered into the database and the database is locked and released for analysis.

Under normal circumstances, the blind should not be broken. The blind should only be broken if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the investigator may, in emergency, determine the identity of the study drug by using applicable procedure. The specified envelope, which contains randomization information, should be opened by principal investigator or its designee.

The date, time, and reason for the unblinding must be documented in the "End of Study Participation" page of eCRF and the medical monitor will be informed as soon as possible. All unblinding events will be reported to the medical monitor and CELLTRION. Any subjects for whom the blind is broken may continue in the study at the investigator's discretion.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Day 14 of the last enrolled subject. The unblinded personnel will be predefined and documented before performing the analyses.

5.4. Analysis sets

Analysis set and its definition are described in this section. The analysis set will be identified and included as a subtitle of each TLF.

Subjects could be excluded from analysis set because of major protocol deviation described in Section 5.6.

The following treatment groups will be used for analysis: CT-P59 10mg/kg, CT-P59 20mg/kg, CT-P59 40mg/kg, CT-P59 80mg/kg and Placebo. For placebo group, pooling of placebo subjects within each cohort is considered for analysis.

For ITT set, subjects will be assigned to either "CT-P59 10mg/kg", "CT-P59 20mg/kg", "CT-P59 40mg/kg", "CT-P59 80 mg/kg" or Placebo treatment group according to the treatment they were randomized to. The PK and Safety sets will be analyzed according to actual treatment group. Subjects receiving at least one kit of CT-P59 will be assigned to the actual treatment group of CT-P59 of corresponding cohort, even if the subject is randomized to Placebo group.

The number of subjects in all sets will be tabulated by the treatment group on ITT set. A listing will also be produced displaying data on ITT set.

5.4.1. Intent-to-Treat (ITT) Set

The ITT set is defined as all subjects enrolled and randomly assigned to receive a dose of either of the study drugs, regardless of whether or not any study drug dosing was completed.

5.4.2. Safety Set

The safety set will consist of all subjects who receive a full or partial dose of the study drugs.

5.4.3. Pharmacokinetic Set

The PK set will consist of all subjects who receive a full dose of CT-P59 and have at least 1 evaluable post-treatment PK concentration result.

5.5. Definition of Baseline

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

5.6. Protocol Deviations

Protocol deviation will be categorized as "major" or "minor". A major protocol deviation is one that may affect the interpretation of study results or the subject's rights, safety or welfare,

and will be identified prior to study unblinding. Major protocol deviations include, but are not limited to, the following:

- Mis-randomization (defined as subjects who received treatment other than randomly assigned treatment)
- Non-adherence to Inclusion or Exclusion criteria (to be identified through review of data)
- Significant Good Clinical Practice (GCP) non-compliance

A listing of major protocol deviations for each subject will be provided by treatment group for the ITT set.

5.7. Outliers

Any outliers that are detected during the review of the data will be investigated and discussed during the DRM. In general, outliers will not be excluded.

6. SUBJECT DISPOSITION

The number of subjects 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 number and percentage of subjects who were randomized, initiated study treatment, discontinued from the study and completed the study will also be displayed for the ITT set by treatment group.

Subject disposition will be defined as follows:

- A subject will be considered to have failed the Screening if the subject was considered as not eligible to be enrolled in the study based on the 'Eligibility Criteria' page of eCRF.
- A subject will be considered to be randomized if a randomization ID was allocated to the subject based on the 'Randomization' page of eCRF.
- A subject will be considered to be initiated study if it is recorded that the subject was administered the study drug ('Yes' box checked) on the 'Study Drug Administration' page of eCRF.
- A subject will be considered to have completed the study if it is recorded that the subject completed the study ('Yes' box checked) on the 'End of Study Participation' page of eCRF.

- A subject will be considered to have discontinued the study if it is recorded that the subject was discontinued from the study ('No' box checked) on the 'End of Study Participation' page of eCRF.

The number and percentage of subjects who discontinued the study will be displayed by primary reason for discontinuation based on the "End of Study Participation" page of eCRF and treatment group. In addition, time on study prior to discontinuation will also be displayed using descriptive statistics, for those subjects who initiate the study treatment and discontinue for the ITT set. The study duration in days will be calculated as (study discontinuation date – study drug administration date +1). The study discontinuation date and study drug administration date will be taken as the date on the 'End of Study Participation' page and on the 'Study Drug Administration' page of eCRF, respectively.

Subject randomization and subject disposition data will be listed in separate listings for the ITT set by treatment group. A listing of subjects reported as screening failures will also be provided.

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics

The following demographic measures will be summarized for the ITT set: Age (years); Sex (Male, Female); Fertility Status (Pre-Menarche, Surgically Sterilized, Post-Menopausal, Potentially Able to Bear Children for female subject only); 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); Screening Height (cm), Day -1 Weight (kg) and Screening Body Mass Index (BMI) (kg/m^2).

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

Demographics will be presented for the ITT set by treatment group.

7.2. SARS-CoV-2 Infection Test

A Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection test will be performed at Screening and Day -1 visit to confirm a subject is not infected to SARS-CoV-2. Only subjects who are negative on both screening and Day -1 tests can be enrolled in the study. If the scheduled SARS-CoV-2 infection test seemed unavailable on Day -1, it can be performed on Day -2 or Day -3 instead. All SARS-CoV-2 infection test results will be listed for the ITT set by treatment group.

7.3. Viral Serology Test

At Screening, the following assessments for serologic markers will be performed:

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis C Antibody
- Anti-Human Immunodeficiency Virus (HIV)
- Rapid Plasma Reagin

If any of the test result is positive, the subject cannot be enrolled in the study. All viral serology test results will be listed for the ITT set by treatment group.

7.4. Urine Drug Test

A urine drug tests will be performed at screening and Day -1 visit. The screen for drug abuse includes methamphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol and opiates. The urine test can be repeated once at the discretion of the Investigator. All urine drug test results will be listed for the ITT set by treatment group.

7.5. Chest X-ray

A chest X-ray will be performed on screening visit for baseline data collection purposes. An additional assessment can be performed when the Investigator considers it is clinically necessary. Results for Chest X-ray will be classified as either “Normal”, “Abnormal, Not Clinically Significant” or “Abnormal, Clinically Significant”. All Chest X-ray data will be listed for the ITT set by treatment group.

7.6. Medical History

Medical history is captured at Screening and Day -1 visit, and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 23.0 or the later version). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the ITT set. Medical history will be listed for the ITT set by treatment group.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

All medications used during the study, taken within 30 days before the subject signs the Informed Consent Form (ICF) until the EOS visit will be collected on the eCRF. All medications will be coded according to the World Health Organization drug dictionary (WHO

Drug Dictionary March 2020 or the later version). Medications will be classified as either prior or concomitant.

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

- A medication checked as "Yes" to "If stop date is unknown, was this drug stopped before the study drug administration (Day 1)?" on eCRF or
- A medication having actual stop date of medication before the date of study drug administration.

The prior medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior medications and the number and percentage of subjects with at least one prior medication for the Safety set. The separate tables will be also generated for the concomitant medications by treatment group, drug class (using ATC level 2), and PT along with the total number of concomitant medications and the number and percentage of subjects with at least one concomitant medication for the Safety set. At each level of summarization, a subject is counted only once if the subject reported one or more medications at that level. When ATC Level 2 for drug class is not available, Level 1 will be used instead.

All prior and concomitant medications will be listed separately by treatment group for the Safety set.

8.2. Exposure to Study Drug

The number and percentage of subjects who received the study drug will be summarized by treatment group for the Safety set. The prescribed and actual administered dose (mg) of study drug will also be summarized using descriptive statistics.

A listing will be provided by treatment group for the ITT set showing the details collected on the "Study Drug Administration" page of eCRF.

8.3. Study Restriction Assessment

Subjects who follow or not any of the study restriction will be listed for the Safety set by treatment group, visit and category.

9. PHARMACOKINETIC ANALYSIS

All PK analyses will be conducted on the PK set unless otherwise specified.

9.1. Serum Concentrations

Blood samples for PK analyses will be collected from all subjects at the time points specified in PK Blood Sampling Time Points and acceptable tolerance windows (Table 1). If the PK blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for immunogenicity assessment at same time point can be used for PK assessment.

Descriptive statistics (n, mean, SD, geometric mean, %CV, minimum, median, and maximum) for serum concentrations will be summarized by cohort of CT-P59 groups at each scheduled visit and time point. Individual serum concentrations, collection date/time, and deviations from scheduled time will be listed for the Safety set by cohort of CT-P59 groups, visit and time points.

Below the lower limit of quantification (BLQ) prior to the study drug administration will be treated as zero (0), and all other BLQ values will be treated as to missing for serum PK concentrations and PK parameter estimation. Measurable concentrations after consecutive BLQs during the terminal phase will also be set to missing.

The mean (±SD) serum concentration versus scheduled sample time profiles for the CT-P59 will be presented graphically on both linear and semi-logarithmic scales by cohort of CT-P59 groups. In addition, the spaghetti plot of serum concentrations versus scheduled sample time profiles will be presented graphically on both linear and semi-logarithmic scales by cohort of CT-P59 groups.

Table 1 Blood Sampling Time Points for Pharmacokinetic Assessment

Day	Time point	Window
Day 1	Predose	Predose within the day
	End of infusion	+ 5 minutes
	1 hour after end of infusion	± 15 minutes
	4 hour after end of infusion	
	8 hour after end of infusion	
	12 hour after end of infusion	
Day 2	24 hour after start of infusion	±1 hours
Day 3	48 hour after start of infusion	
Day 5	96 hour after start of infusion	±4 hours
Day 7	144 hour after start of infusion	
Day 10	216 hour after start of infusion	
Day 14	312 hour after start of infusion	±1 day
Day 28	648 hour after start of infusion	±3 days
Day 56	1,320 hour after start of infusion	±5 days
Day 90	2,136 hour after start of infusion	

The first CSR will present PK serum concentration results up to Day 7 of each subject.

9.2. Serum Pharmacokinetic Parameters

The following serum PK parameters will be calculated by noncompartmental methods based on the actual sampling time points using [redacted].

Parameter	Definition
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time zero to infinity, calculated using the linear up and low down trapezoidal rule
$AUC_{0\text{-}inf}$/Dose	Dose normalized $AUC_{0\text{-}inf}$ (normalized to total body dose and dose/body weight)
$AUC_{0\text{-}last}$	Area under the serum concentration-time curve from time zero to the last quantifiable concentration, calculated using the linear up and log down trapezoidal rule
$AUC_{0\text{-}last}$/Dose	Dose normalized $AUC_{0\text{-}last}$ (normalized to total body dose and dose/body weight)
C_{max}	Maximum observed serum concentration
C_{max}/Dose	Dose normalized C_{max} (normalized to total body dose and dose/body weight)
T_{max}	Time to C_{max}
$t_{1/2}$	Terminal elimination half-life, calculated as: $t_{1/2} = \ln 2/\lambda_z$
$\%AUC_{ext}$	Percentage of the area extrapolated for calculation of $AUC_{0\text{-}inf}$.
λ_z	Terminal elimination rate constant estimated from the linear regression of the natural log-transformed concentration over time at the terminal phase. At least 3 time points (excluding C_{max}) and in general, adjusted correlation coefficient (r^2) greater than or equal to 0.85 is needed to calculate and retain λ_z and its associated parameters ($t_{1/2}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}inf}$/Dose, CL, and V_z). Values of adjusted r^2 less than 0.85 will be examined on a case-by-case basis for reliability to calculate and retain λ_z and its associated parameters ($t_{1/2}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}inf}$/Dose, CL, and V_z). Pharmacokinetic parameters that do not meet this criterion will be listed but not summarized
CL	Total body clearance, calculated as: $CL = Dose/AUC_{0\text{-}inf}$ where Dose is the total body dose
V_z	Volume of distribution during the terminal phase, calculated as: $V_z = (CL)/\lambda_z$

Pharmacokinetic parameters will be summarized by cohort of CT-P59 groups using descriptive statistics (n, mean, SD, geometric mean, %CV, minimum, median, and maximum values for all parameters).

All data for the PK parameters will be listed by cohort of CT-P59 groups using the following rules: C_{max} and C_{max}/Dose will be presented to same level of precision as the PK concentration results, T_{max} will be presented to 2 decimal places, and all other PK parameters will be presented to 3 significant digits.

Scatter plots of individual values and geometric mean versus dose (mg/kg) will be presented for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, and the corresponding dose-normalized parameters.

Dose proportionality of the PK parameters, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}, over the administered dose range (mg/kg) will be quantified using the following power model:

log (parameter) = a + b * log (dose)
where 'a' is the intercept and 'b' is the slope.

The power model parameters (slope and intercept) along with the corresponding 90% CIs will be estimated using least-squares (LS) regression or an equivalent method, and will be presented in tabular format and graphically.

The first CSR will present only C_{max} and T_{max} derived from serum concentration up to Day 7 and scatter plots and dose proportionality assessment only for C_{max} using [redacted].

10. SAFETY ANALYSIS

All Safety analyses will be conducted on the Safety set unless otherwise stated.

10.1. Adverse Events

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

A TEAE includes any untoward medical occurrence in a subject after administration of a study drug, which does not necessarily have to have a causal relationship with this the study drug. A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the study drug.

All AEs will be collected from the date subjects signs ICF until EOS visit, and graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and coded to system organ class (SOC) and preferred term (PT) according to MedDRA Version 23.0 or later

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

- Missing day (e.g. XXJUL2020): Assume the last day of the month. (e.g. 31JUL2020)
- Missing day and month (e.g. XXXXX2020): Assume December 31st. (e.g. 31DEC2020)
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as Missing.

In case a subject dies during the study, the stop date will be imputed with the date of death if the imputed stop date is after the date of death.

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

- If the day is missing (e.g. XXJUN2020), the month and year of the incomplete date will be compared to the date of the study drug administration.
    - If the month and year are equal for both dates, the AE start date will be imputed as the earlier of: (i) the date of study drug administration, and (ii) the end 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. 01JUN2020).
- If the day and month are missing (e.g. XXXXX2020), the year of the incomplete date will be compared to the date of the study drug administration.
    - If the years of both dates are equal, start date will be imputed as earlier date of: (i) the date of the study drug administration, and (ii) the end date of the AE.
    - If the year is not equal, start date will be imputed as the 1st of January of the incomplete date year (e.g. 01JAN2020).
- If the AE start date is missing (e.g. XXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the study drug administration, and (ii) the end date of the AE.

All AEs recorded will be presented in a data listing. Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date/time; Time to Occurrence [calculated as (AE start date – date of study drug administration +1)]; TEAE flag; intensity (CTCAE Grade 1 to 5); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); relationship with study drug (unrelated, possible, probable, definite); action taken with study drug (dose not changed, drug interrupted, drug withdrawn, not applicable); any treatment received (no, medication, non-medication treatment, both medication and non-medication treatment); whether the event was serious (yes, no); whether the AE is classified as Infusion Related Reactions (IRR) including Hypersensitivity and Anaphylactic Reactions (yes, no).

In summaries, AEs will be considered to be related if the relationship is possible, probable, or definite. If relationship or intensity is missing, it will be summarized separately under a missing category.

10.1.1. Incidence of Treatment-Emergent Adverse Events

All TEAEs will be summarized by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of subjects with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of subjects with at least one TEAE over all SOCs will also be displayed.

10.1.2. Serious Adverse Events

A serious adverse event (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 and scientific judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment-emergent serious adverse events (TESAEs) will be summarized by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of subjects with at least one TESAE using only the most severe intensity recorded at each level of summarization. The total number of events and number of subjects with at least one TESAE over all SOCs will also be displayed. All SAEs will be listed including serious criteria, SAE description and additional information.

10.1.3. Deaths

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

10.1.4. Treatment-Emergent Adverse Events Leading to Discontinuation

All subjects who have a TEAE with an action taken with study drug of "Drug Withdrawn" will be summarized by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of subjects 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 subjects with at least one TEAE which led to study drug discontinuation will also be displayed.

10.1.5. Treatment-Emergent Adverse Events of Special Interest

The AEs checked as 'Yes' to 'Is Adverse event classified Infusion Related Reactions including Hypersensitivity and Anaphylactic Reactions?' on the 'Adverse Event' page of eCRF will be classified as Infusion Related Reaction (IRR) including Hypersensitivity and Anaphylactic Reaction, and considered as adverse events of special interest (AESI) because AE is related to infusion related reactions (hypersensitivity/anaphylactic reactions).

Treatment emergent adverse events of special interest (TEAESI) will be summarized by treatment group, SOC, PT, relationship and intensity, displaying number and percentage of subjects with at least one TEAESI using only the most severe TEAESI recorded at each levels of summarization. The total number of events and number of subjects with at least one TEAESI over all SOCs will also be displayed. Additionally, table for signs and symptoms of TEAESI

will be provided separately by SOC, PT and intensity. Experienced signs and symptoms of TEAESI will be presented in additional information listing for TEAESI.

10.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory testing (hematology, clinical chemistry, and urinalysis) will be collected at each scheduled visit specified in Appendix 1. The analysis will be performed at the local laboratory. All summaries and listings will be based on the SI (System International) units. The following clinical laboratory assessments will be performed and only the parameters specified will be summarized and listed:

Clinical chemistry:	Total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-myocardial band isoenzyme, troponin I, albumin, sodium, potassium, total calcium, chloride, phosphorus, glucose, lactate dehydrogenase, total cholesterol, gamma-glutamyltransferase, estimated glomerular filtration rate (eGFR), uric acid and C-reactive protein (Direct bilirubin, troponin T, triglyceride and high-density lipoprotein cholesterol will be analyzed when the investigator consider it is clinically necessary)
Hematology:	Red blood cell count, white blood cell count, absolute neutrophil count, eosinophil count, lymphocyte count, monocyte count, basophil count, platelet, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis:	Bilirubin, red blood cell, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination of white blood cell count, red blood cell count, and bacteria

Abnormal numeric clinical laboratory values will be flagged as either “High” or “Low” based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormal clinical laboratory values are clinically significant or not clinically significant.

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 version 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 grades 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 subject does not satisfy any CTCAE grade, it will be classified as “No Grade”.

Actual values and changes from baseline of numeric laboratory parameters except for direct bilirubin, troponin T, triglyceride and high-density lipoprotein cholesterol will be summarized by treatment group, parameter and scheduled visit using descriptive statistics in separate tables by laboratory category. All numeric values recorded BLQ or above the upper limit of qualification are set to the respective limit for all summaries.

The number and percentage of subjects for clinical laboratory test results except for direct bilirubin, troponin T, triglyceride and high-density lipoprotein cholesterol will be summarized by treatment group, parameter and scheduled visit using {"Normal", "Abnormal, Not Clinically Significant", "Abnormal, Clinically Significant"} categories as appropriate, in separate tables by laboratory category in the form of a shift table to detect changes from baseline.

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

All clinical laboratory test results of hematology, clinical chemistry, and urinalysis will be presented in separate listings by laboratory category. For values that are outside the normal range, high and low flags and clinical significance as evaluated by the investigator will be presented if applicable, and CTCAE results will also be presented for applicable parameters.

10.3. Vital Signs and Weight

Vital signs (systolic and diastolic blood pressures, heart rate, respiratory rate and body temperature) and weight measurements will be assessed at the each scheduled visit specified in Appendix 1.

All vital signs will be summarized using descriptive statistics of actual value and change from baseline by treatment group and parameter at each scheduled visit. All vital signs data including weight, except for hypersensitivity monitoring results will be listed for each subject by treatment group, parameter and visit.

10.4. Electrocardiogram

12-lead Electrocardiograms (ECGs) will be performed at each scheduled visit specified in Appendix 1 and if the subject experienced cardiac symptoms during study drug administration. The investigator will interpret the 12-lead ECG and the findings of 12-lead ECG will be classified as either "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant".

The number and percentage of subjects will be summarized by treatment group and scheduled visit, in the form of a shift table to detect changes from baseline. All ECG data will be listed for each subject by treatment group and visit.

10.5. Hypersensitivity Monitoring

For hypersensitivity monitoring, additional vital signs measurements including systolic and

diastolic blood pressure, heart rate, respiratory rate and body temperature will be assessed at the following time points in Table 2.

Table 2 Scheduled of Assessments for Hypersensitivity Monitoring

Day	Time points	Window
Day 1	Predose (prior to dosing on Day 1)	Within 30 minutes
	15 minutes from start of infusion	± 5 minutes
	30 minutes from start of infusion	
	60 minutes from start of infusion	
	End of infusion	
	2 hours from start of infusion	± 15 minutes
	3 hours from start of infusion	
	6 hours from start of infusion	
	12 hours from start of infusion	
Day 2	24 hours from start of infusion	± 30 minutes

The number and percentage of subjects who have clinically notable hypersensitivity result will be summarized in a table by treatment group, scheduled visit, time points and parameter. The criteria for clinically notable results are defined as follows:

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 (°C)	≤ 35.0	≥ 38.0

All vital signs data for hypersensitivity monitoring will be listed for each subject by treatment group, parameter and time point. High and low flags will be presented in the listing to show whether a hypersensitivity reaction result is outside of normal range.

10.6. Physical Examination

A physical examination will be performed on each scheduled visit specified in Appendix 1. The examination will include assessment of general appearance, head and neck, skin, cardiovascular, respiratory, abdominal, neurological, musculoskeletal and lymphatic systems. Findings of physical examination will be classified as either "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant".

The number and percentage of subjects will be summarized by treatment group, scheduled visit and category, in the form of a shift table to detect changes from baseline. All physical examination data will be listed for each subject by treatment group, category and visit.

10.7. Pregnancy Test

Pregnancy tests consist of serum and urine pregnancy tests. Serum pregnancy tests will be performed at Screening and EOS, and urine pregnancy test will be performed on female subjects with childbearing potential on Day -1. The serum and urine pregnancy test samples will be analyzed at the local laboratory. The result of serum test will be either "Negative" or "Positive" and urine test will be "Negative", "Positive" or "Equivocal".

The number and percentage of the results of serum and urine pregnancy test will be summarized by treatment group and scheduled visit. All pregnancy test results will be listed for each subject tested by treatment group and visit

10.8. Immunogenicity

The immunogenicity will be assessed by Anti-Drug Antibody (ADA) and neutralizing antibody (NAb) in validated immunoassay. Blood samples for immunogenicity assessment will be collected at each scheduled visit specified in Appendix 1. If the blood sample for immunogenicity is unable to be analyzed or is missing at certain time point, some blood samples collected for PK assessment at the same time point can be used for immunogenicity assessment. Additional samples for immunogenicity assessment may be collected if a subject experiences immune-related AEs. The analysis will be performed at the central laboratory.

The ADA assay will follow a three-tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. Sample that are "Potential Positive" in the screening assay will undergo further test in the confirmatory assay to determine if subjects are true positive. The test outcome for the overall assay will be either "Positive" or "Negative". For further characterization, the antibody level will be assessed by titration in confirmed positive samples. Samples that are positive in the ADA confirmatory assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening NAb assay will be either "Positive" or "Negative".

The number and percentage of subjects for the results of the final ADA and the screening NAb assay will be summarized by treatment group and test at each scheduled visit. The descriptive statistics of ADA titration results for each treatment group will also be presented by scheduled visit. All immunogenicity data will be listed for each subject by treatment group, test and scheduled visit.

The first CSR will present only results of ADA screening and confirmatory assay up to Day 7 of each subject.

11. Reference List

International Council for Harmonisation (ICH) Assembly. ICH E9: Statistical principles for clinical trials – Step 5. 01 September 1998.

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

12. APPENDIX

Appendix 1: Schedule of Assessments

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

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

1. If screening visit date and the admission date (Day -1) are same, all assessments scheduled for the screening and Day -1 visit will be performed only once on the date.
2. End-of-study visit assessments will be performed on Day 90 (± 5 days). If a subject withdraws prematurely after study drug administration, the subject will be asked to return to the study center for the safety assessments predefined on EOS visit. If deemed necessary by the Investigator, the subject will be asked to return for the scheduled EOS visit.
3. Inclusion and exclusion criteria will be confirmed at screening and will be rechecked on Day -1.
4. Height will be measured only once at screening visit. BMI will be measured once at screening for eligibility check.
5. Drug abuse testing includes drugs specified in Section 6.1.2.3 (in protocol V1.3). The urine test for drugs of abuse will be performed at screening and Day -1 visit. The urine test can be repeated once at the Investigator's discretion.
6. For female subjects with childbearing potential, a serum pregnancy test will be performed at screening and EOS visits, and urine pregnancy test will be performed on Day -1. Only subjects who are confirmed as nonpregnant by both serum pregnancy test at screening and urine pregnancy test on Day -1 can be enrolled in the study. A urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive or equivocal throughout the study.
7. Viral serology test including HBsAg, HBcAb, hepatitis C antibody, RPR, and anti-HIV test must be assessed in all subjects (mandatory). If any of the test result is positive, the subject cannot be enrolled in the study.
8. Chest X-ray will be performed at screening visit to collect baseline data. Additional chest X-ray assessments can be performed when the Investigator consider it is clinically necessary.
9. These assessments should be performed on Day 1 prior to the study drug administration.
10. Study drug will be administered as an IV infusion for 90 minutes (±15 minutes) on Day 1. When calculating total volume of study drug to be administered, the body weight of each subject measured on Day -1 will be used.
11. Additional vital sign assessments will be evaluated for hypersensitivity monitoring purpose at the time point specified in Table 6-1 (in protocol V1.3). Any type of ECG will be performed if a subject experiences cardiac symptoms. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (inhalational therapy, oxygen and/or artificial ventilator) must be available.
12. Hematology, clinical chemistry, and urinalysis will be performed and detail analyses are listed in Section 6.1.9 (in protocol V1.3).
13. All scheduled 12-lead ECG assessments must be performed after the subject has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the Investigator's discretion.
14. Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 6-2 (in protocol V1.3). Analysis will be performed at the central laboratory.
15. In addition to sampling time point specified, serum samples for immunogenicity testing may be collected if a subject experiences immune-related AEs. Analysis will be performed at the central laboratory.
16. Prior and/or concomitant medication use will be recorded within 30 days before the signed date of ICF (inclusive of the applicable periods for prohibited medications as defined in Section 5.7 (in protocol V1.3)) until the EOS visit.
17. Adverse events will be assessed from the date the ICF is signed until up to EOS visit, regardless of the relationship to the study drug.
18. If the scheduled SARS-CoV-2 infection test seemed unavailable on Day -1, it can be performed on Day -2 or Day -3 instead.

Appendix 2: Tables, Listings, and Figures in the Initial Analysis (For first CSR)

Output Number	Title	Analysis set
Listings:		
Listing 16.2.1.1	Subject Disposition	ITT set
Listing 16.2.2.1	Analysis Sets	ITT set
Listing 16.2.2.2	Major Protocol Deviations	ITT set
Listing 16.2.2.3	Screening Failures	
Listing 16.2.4.1	Demographics	ITT set
Listing 16.2.4.6	Medical History	ITT set
Listing 16.2.4.7	Prior Medication	Safety set
Listing 16.2.4.8	Concomitant Medication	Safety set
Listing 16.2.5.1	Study Drug Administration	Safety set
Listing 16.2.6.1	Individual Serum Concentration (Unit)	Safety set
Listing 16.2.6.2	Individual Serum Pharmacokinetic Parameters	PK set
Listing 16.2.7.1	Adverse Events	Safety set
Listing 14.3.2.1	Deaths	Safety set
Listing 14.3.2.2	Serious Adverse Events: Additional Information	Safety set
Listing 14.3.2.3	Infusion Related Reaction including hypersensitivity/anaphylactic reactions: Additional Information	Safety set
Listing 16.2.8.1	Hematology	Safety set
Listing 16.2.8.2	Clinical Chemistry	Safety set
Listing 16.2.8.3	Urinalysis	Safety set
Listing 16.2.9.1	Vital Signs and Weight	Safety set
Listing 16.2.9.2	Vital Signs for Hypersensitivity Monitoring	Safety set
Listing 16.2.9.3	Electrocardiograms	Safety set
Listing 16.2.9.4	Physical Examinations	Safety set
Listing 16.2.9.6	Immunogenicity Results	Safety set
Tables:		
Table 14.1.1	Summary of Subject Disposition	ITT set

Table 14.1.2	Analysis Sets	ITT set
Table 14.1.3	Summary of Demographics	ITT set
Table 14.1.7	Study Drug Administration	Safety set
Table 14.2.1.1	Summary of Serum Concentration	PK set
Table 14.2.1.2	Summary of Serum Pharmacokinetic Parameters	PK set
Table 14.2.1.3	Statistical Analysis to Assess Dose Proportionality	PK set
Table 14.3.1.1	Treatment-Emergent Adverse Events by Intensity	Safety set
Table 14.3.1.2	Treatment-Emergent Serious Adverse Events by Intensity	Safety set
Table 14.3.1.4	Treatment-Emergent Adverse Events classified as Infusion related reaction including hypersensitivity/anaphylactic reactions	Safety set
Table 14.3.1.5	Signs and Symptoms of Treatment-Emergent Adverse Events Classified as Infusion Related Reaction including hypersensitivity/anaphylactic reactions	Safety set
Table 14.3.6.6	Summary of Immunogenicity	Safety set
Figures:		
Figure 14.2.1.1	Mean (+/- SD) Serum Concentration of CT-P59 (unit)	PK set
Figure 14.2.1.2	Individual Serum Concentration of CT-P59 (unit)	PK set
Figure 14.2.1.3	Scatter plot of PK Parameter versus Dose	PK set

Appendix 3: CTCAE v5.0 for Clinical Laboratory Test Results

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
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
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	-
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	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
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
Blood bilirubin increased	Total Bilirubin	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
Leukocytosis	White Blood Cells	High	-	-	>100,000/mm^3	-
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L
Creatinine increased [1)]	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
Eosinophilia	Eosinophils (Absolute Ct)	High	>ULN and >Baseline	-	-	-
GGT increased	Gamma Glutamyl Transferase (GGT)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline	>20.0 x ULN if baseline was normal; >20.0 x baseline if

			baseline was abnormal	if baseline was abnormal	if baseline was abnormal	baseline was abnormal
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
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 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Hemoglobin increased	Hemoglobin	High	Increase in >0 – 2 g/dL from ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL from ULN or above baseline if baseline is above ULN	Increase in >4 g/dL from ULN or above baseline if baseline is above ULN	-
Blood lactate dehydrogenase increased	Lactate Dehydrogenase (LDH)	High	>ULN	-	-	-
Lymphocyte count decreased	WBC Differential, Lymphocytes	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$/L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	WBC Differential, Lymphocytes	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 $10e^9$ /L	<75,000-50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000-25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm3; <25.0 x $10e^9$ /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		<3.0 - 2.5 mmol/L	<2.5 mmol/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 regardless of symptoms	<120 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
Neutrophil count decreased	WBC Differential, Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /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

LLN = lower limit of normal, ULN = upper limit of normal.
1) The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.
Note: In case both clinical input and numeric value for grading can be used for grading (e.g. Hypokalemia), CTCAE grade which includes numeric value will only be applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.
@ indicates that calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 – serum albumin [g/dL]), where 4.0 represents the average albumin level.