CELLTRION, Inc.

CT-P17 1.1

A Phase 1, Randomized, Double-blind, Three-arm, Parallel group, Single-dose Study to Compare the Pharmacokinetics and Safety of CT-P17 and Humira (US-licensed Humira and EU-approved Humira) in Healthy Subjects

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Final Statistical Analysis Plan

Version 2.0

Prepared by:

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List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance model
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from zero to infinity
$AUC_{0\text{-last}}$	area under the concentration-time curve from zero to the last quantifiable concentration
$\%AUC_{extrap}$	percentage of the area extrapolated for calculation of area under the serum concentration-time curve from time zero to infinity
BLQ	below the lower limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CK-MB	creatine kinase–myocardial band isoenzyme
CL/F	apparent total body clearance
C_{max}	maximum serum concentration
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DRM	data review meeting
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EU	European Union

Abbreviation	Term
GGT	gamma glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HCAb	hepatitis C antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonization
IGRA	interferon-γ release assay
ISR	injection site reaction
ITT	intent-to-treat
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
λ_z	terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NYHA	New York Heart Association
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PT	preferred term
PVG	pharmacovigilance
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SI units	International System of Units
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life

Abbreviation	Term
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time to C_{max}
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
V_z/F	apparent volume of distribution during the terminal phase after non-intravenous administration
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1. Administrative Structure

This study is being conducted under the sponsorship of CELLTRION, Inc. The clinical monitoring, data management, medical writing and statistical analysis are being performed under contract with [redacted], in collaboration with CELLTRION, Inc.

2. Introduction

This document outlines the statistical methods to be implemented and data presentations to be used during the analyses of data collected within the scope of CELLTRION, Inc., protocol CT-P17 1.1 (A Phase 1, Randomized, Double-blind, Three-arm, Parallel group, Single-dose Study to Compare the Pharmacokinetics and Safety of CT-P17 and Humira [United States (US)-licensed Humira and European Union (EU)-approved Humira] in Healthy Subjects), Version 2.1 dated 08 January 2019 and electronic case report form (eCRF) Version 6.0 dated 06 November 2019. The purpose of this plan is to provide specific guidelines for which the analyses will proceed.

The clinical study report (CSR) will be generated after completion of all visits of all subjects to report the pharmacokinetics (PK), safety and immunogenicity.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as 'Post-hoc' on the outputs and identified in the CSR.

3. Objectives

The primary objective of this study is to demonstrate the PK similarity in terms of area under the concentration-time curve from zero to the infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum serum concentration (C_{max}) of CT-P17, US-licensed Humira, and EU-approved Humira in healthy subjects (CT-P17 to US-licensed Humira, CT-P17 to EU-approved Humira, and US-licensed Humira to EU-approved Humira).

The secondary objective of this study is to evaluate the additional PK parameters, safety, and immunogenicity of CT-P17, US-licensed Humira, and EU-approved Humira in healthy subjects.

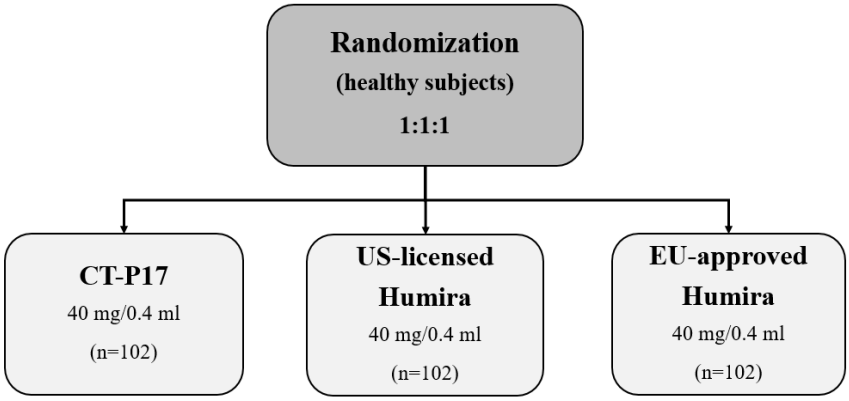
4. Overall Study Design and Plan

4.1. Overview

CT-P17 is being developed as a proposed biosimilar of Humira (adalimumab). This study is a phase 1, randomized, multicenter, double-blind, three-arm, parallel group, single-dose, active comparator study, which is designed to demonstrate equivalence in PK of CT-P17 to US-licensed Humira and EU-approved Humira in healthy subjects. Approximately 306 subjects will be enrolled and randomly assigned to one of the three treatment arms in a 1:1:1 ratio. In each treatment arm,

all subjects will receive a single dose (40 mg) of either CT-P17, US-licensed Humira, or EU-approved Humira by subcutaneous (SC) injection via pre-filled syringe (PFS) on Day 1 followed by 10 weeks during which PK, safety, and immunogenicity measurements will be made. The randomization to treatment assignment will be stratified by body weight (≥80 kg vs. <80 kg) as measured on Day -1, gender (male vs. female) and study center. A schematic of the study design is presented in Figure 4-1.

Figure 4−1 Study Design Overview



The study drugs in this document are referred to CT-P17, US-licensed Humira, and EU-approved Humira.

This study will be composed of 4 study phases, including a Screening period, Admission, Study period, and End-of-Study (EOS) visit.

Screening Period (Day −28 to Day −2):

Subjects will sign and date the informed consent form (ICF) and undergo procedures to determine eligibility. If necessary, a prescreening process may be carried out according to the standard operating procedures of the study center.

During the screening period, retest for screening is permitted only once by the investigator's judgement. If the repeated test result is again not suitable or indeterminate for inclusion, the subject will be screen failed.

Admission (Day -1):

Eligible subjects will undergo baseline assessments: recheck of inclusion and exclusion criteria, medical history, adverse events (AEs), prior and concomitant medications, clinical signs and symptoms of tuberculosis (TB), clinical laboratory tests, vital signs, body weight, physical examination, check for drug abuse, nicotine and alcohol and urine pregnancy test in women of childbearing potential.

Subjects will be admitted to the study center, and will be randomized to receive either CT-P17, US-licensed Humira, or EU-approved Humira once all pertaining tests have been concluded to confirm the eligibility during Screening period and Day -1 (if it is concluded that the subject is not eligible in Day -1 assessments, the subject will be considered as screening failure even if they passed the screening).

Study Period (Day 1 to Day 71):

The study drug will be administered on the subject's lower abdomen except for the 5 cm around the subject's navel.

Subjects will be confined to the study center until completion of the 48-hour assessments after the administration of the study drug (Day 1) and admission can be extended depending on the subject's and study center's availability, up to Day 7. The consecutive study visits will be carried out on an out-patient basis.

Clinical laboratory testing and vital sign measurements, will be obtained during the study period. For hypersensitivity monitoring, vital sign measurements will be performed before the start of the study drug administration (within 15 minutes) and at 3, 6, 12, and 24 hours after the administration of the study drug on Day 1. The tolerance window for hypersensitivity monitoring is ±30 minutes for 3 and 6 hours, and ±60 minutes for 12 and 24 hours after the administration. Either 3-lead or 12-lead electrocardiogram (ECG) can be used for hypersensitivity monitoring at 3 hours (±30 minutes) after the administration of the study drug on Day 1, and additional ECGs can be performed throughout the study if the subject experiences cardiac symptoms. Local site pain using 100 mm visual analogue scale (VAS) will be assessed immediately (within 15 minutes) after study drug administration (Day 1) and injection site reactions will be assessed 30 minutes (±10 minutes) after study drug administration. A physical examination will be performed on Day 3. Immunogenicity samples will be obtained prior to the administration of the study drug on Day 1, and on Day 15, 29, 57 and 71. Adverse events, concomitant medications, and clinical signs and symptoms of TB will be monitored throughout the study. Blood samples for PK analysis will be collected from all subjects at the predefined time points in Table 4.1.

Table 4.1 PK Sampling Time Points

PK sampling time points
Day 1 Pre-dose (within 60 minutes prior to administration of the study drug)
Day 1 (6 hours after the administration of the study drug); ±15 minutes
Day 1 (12 hours after the administration of the study drug); ±1 hour
Day 2 (24 hours after the administration of the study drug); ±2 hours
Day 3, 4, 5, 5.5, 6, 6.5, 7, 8, and 9 (48, 72, 96, 108, 120, 132, 144, 168, and 192 hours, respectively, after the administration of the study drug); ±2 hours
Day 15 and 22 (336 and 504 hours, respectively, after the administration of the study drug); ±4 hours
Day 29, 43, 57, and 71 (i.e., EOS) after the administration of the study drug; ±1 day

End-of-Study Visit (Day 71):

The EOS visit will be performed on Day 71. Subjects will return to the study center and undergo the following PK and safety assessments: PK and immunogenicity sampling for CT-P17, US-licensed Humira, and EU-approved Humira; collection of information related to AEs and concomitant medications; serum pregnancy tests in women of childbearing potential; TB monitoring and interferon-γ release assay (IGRA); vital signs; body weight; 12-lead ECG; clinical laboratory tests; and physical examination. The acceptable tolerance window for PK, safety, and immunogenicity assessments is ±1 day for EOS (Day 71) assessments.

The schedule of study procedures is presented in Appendix 14.1.

4.2. Study Endpoints

4.2.1. Primary Endpoints

Pharmacokinetics

- Area under the concentration-time curve from zero to infinity ($AUC_{0\text{-inf}}$)
- Area under the concentration-time curve from zero to the last quantifiable concentration ($AUC_{0\text{-last}}$)
- Maximum serum concentration (C_{max})

4.2.2. Secondary Endpoints

Pharmacokinetics

- Percentage of the area extrapolated for calculation of area under the serum concentration-time curve from time zero to infinity ($\%AUC_{extrap}$)
- Time to C_{max} (T_{max})
- Apparent volume of distribution during the terminal phase after non-intravenous administration (V_z/F)
- Terminal elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent total body clearance (CL/F)

Safety and Immunogenicity

- Adverse events
- Serious AEs (SAEs)
- Adverse events of special interest (AESIs) (injection site reactions [ISRs], hypersensitivity/allergic reactions, infections, and malignancies)
- Immunogenicity
- Hypersensitivity/allergic reaction assessments by additional ECG and vital sign monitoring (including systolic and diastolic blood pressure (BP), heart rate, respiratory rate, and body temperature)

- Vital sign and weight measurement
- Electrocardiogram (ECG)
- Physical examination
- Interferon-γ release assay (IGRA)
- Chest X-ray
- Pregnancy testing
- Clinical laboratory testing (including hematology, serum chemistry, and urinalysis)
- Local site pain using 100 mm VAS
- Signs and symptoms of TB
- Prior and concomitant medications monitored throughout the study

5. General Statistical Considerations

All statistical analyses will be performed using [redacted].

For categorical variables, the number and percentage of subjects will be presented. Percentages will be suppressed when the count is zero and will be presented to one decimal place. The denominator for all percentages will be the number of subjects within the treatment arm for the population of interest, unless otherwise specified. A row denoted "Missing" will be included in count tabulations where necessary to account for missing values.

Continuous variables will be summarized using descriptive statistics: number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum, unless otherwise specified. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data. If the geometric mean is to be presented, it will be set to the same precision as the mean. If the minimum value from the data is zero, then the geometric mean will not be calculated. Point estimates and confidence intervals (CIs) obtained from statistical procedures will be displayed to two decimal places.

For safety laboratory evaluations, 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.

Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies by treatment arms or overall (as appropriate), and all data listings will be sorted by treatment arm, subject number, and assessment date or visit date if applicable. In cases where more additional sorting is required, other variables will be included in the sort order as applicable.

Unless otherwise specified, all data collected on the eCRF will be presented in data listings by treatment arm and subject number where applicable.

If there are repeated measurements at a time point, the initial scheduled measurement at that time point will be used in the summary tables. If the initial scheduled measurement at that time point is missing, the next available repeated measurement will be used in the summary tables. The repeated measurements will be listed with indicator. Unscheduled visit results will not be included in the summaries except for determining baseline, but will be presented in data listings.

Unscheduled visits will be slotted to the proceeding scheduled visits by comparing the assessment date (and time if it is available) with the scheduled visit start date (and time) as follows: if the assessment date (and time) is on or after the start date (and time) of scheduled visit 'n', but prior to the start date (and time) of scheduled visit 'n+1', then the unscheduled visit will be slotted to scheduled visit 'n' with unscheduled indicator presented.

When combining data from eCRF and analytical facilities, any discrepancies will be handled as follows:

- If data is recorded as collecting sample in eCRF but there're no corresponding results from analytical facility - listing will display only sample collection visit, date, and time from eCRF;
- If there are no corresponding records in eCRF for results from analytical facility - listing will display only specimen collection visit, date, time, and results from analytical facility;
- If there is a discrepancy in sample collection date (or time) from eCRF and analytical facility - listing will display results from analytical facility and visit, date, and time from eCRF if they are not missing; if sample collection date and time are missing in eCRF then listing will display specimen collection visit and date from analytical facility.
- Unless otherwise specified, all available results from analytical facilities will be included in the summary table.

5.1. Sample Size

A sample size of 91 subjects from each arm will provide at least 90% power to show similarity in PK; CT-P17 vs. US-licensed Humira, CT-P17 vs. EU-approved Humira and US-licensed Humira vs. EU-approved Humira using 90% CI approach based on 80% to 125% equivalence margin, expected geometric mean ratio of 1.0 and coefficient of variation (CV) of 48%, which is assumed based upon historical PK data in healthy subjects.

The sample size is calculated from a two one-sided alpha level of 0.05. Approximately 306 enrolled subjects (102 in each arm) are expected to yield at least 273 evaluable subjects (91 in each arm) with a 10% drop-out rate. By assuming that the primary PK parameters are highly correlated, the Type I/II error adjustment for multiplicity correction is not considered.

5.2. Definition of Baseline

Unless stated otherwise, Baseline will be defined as the last non-missing measurement (including repeated and unscheduled assessments) before the administration of the study drug. Post-baseline will be considered as all measurements collected after the administration of the study drug.

5.3. Study Day Calculation

Study Day is calculated as (Date - Dose Date + 1) when Date is on or after Dose Date, and (Date - Dose Date) otherwise.

5.4. Randomization, Stratification, and Blinding

Interactive web response system (IWRS) will be used for the randomization. On Day -1, subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned in a 1:1:1 ratio into one of three treatment arms.

- Treatment Arm 1: CT-P17 (test), 40 mg/0.4 mL (100 mg/mL) administered as a single SC injection via PFS
- Treatment Arm 2: US-licensed Humira (reference), 40 mg/0.4 mL (100 mg/mL) administered as a single SC injection via PFS
- Treatment Arm 3: EU-approved Humira (reference), 40 mg/0.4 mL (100 mg/mL) administered as a single SC injection via PFS

As it is known that the body weight and gender are potential impact factors on PK profile, the randomization to treatment assignment will be stratified by body weight (≥80 kg vs. <80 kg) as measured on Day –1 and gender (male vs. female) and study center, considering that it is a multi-center study. Subjects withdrawn after randomization will not be replaced.

All stratums will be dynamically allocated by the [redacted] IWRS system using permuted blocks.

[redacted] will generate the randomization schedule which contains the randomization number and corresponding treatment arm using [redacted]. An external vendor selected by CELLTRION, Inc. will provide the kit schedule which contains the kit number and corresponding treatment arm. Both randomization schedule and kit schedule are provided to the [redacted] IWRS team for treatment assignment.

This is a double-blinded study. 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. In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and the medical monitor and/or the sponsor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and/or the sponsor. Any subjects for whom the blind is broken may continue in the study. [redacted] will have access to the randomization code, if suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities, if required.

The overall randomization code will be broken for reporting purposes after all subjects have completed the study and the database has been finalized for study completion. The randomization code will not be revealed to study subjects, study center personnel, or investigators.

5.5. Analysis Population

5.5.1. Intent-to-treat (ITT) Population

The intent-to-treat (ITT) population is defined as all subjects enrolled and randomly assigned to receive a dose of any study drug, regardless of whether or not any study drug dosing was completed. Subjects will be assigned to treatment arms based on randomization; in an event there is a discrepancy between the actual treatment received and the randomized treatment, subjects in the ITT population will be analyzed according to the treatment to which they were randomized.

All study population analyses, including disposition of subjects, protocol deviations, and analysis populations as well as demographic and background characteristics will be analyzed using the ITT population.

5.5.2. Pharmacokinetic Population

The PK population is defined as all randomly assigned subjects who receive a complete dose of study drug and provide at least 1 post-treatment serum concentration above the lower limit of quantification for adalimumab. A subject will be considered to have received a complete dose of study drug if the subject is recorded as 'YES' for "Was whole volume of study drug administered successfully?" on the exposure-injection page in the eCRF. If terminal elimination rate constant cannot be estimated as not having at least 3 time points following C_{max}, subjects will be excluded from the PK population. Subjects in this population will be used in all PK analyses. Subjects in the PK population will be analyzed according to the treatment they actually received.

A subject with major protocol(s) deviation that may affect the interpretation of study results of PK will be excluded from PK population. Final determinations of the PK population will be made at the DRM held in accordance with International Council for Harmonization (ICH) harmonized tripartite guideline E9. Drop-out and withdrawal of subjects should be fully documented. If available, concentration data and PK parameters from such subjects should be presented in the individual listings but should not be included in the summary statistics.

There were no major protocol deviations identified during the DRM.

5.5.3. Safety Population

The safety population is defined as all randomly assigned subjects who receive a complete or partial dose of study drug. Subjects will be assigned to treatment arms based on treatment actually received. A subject will be considered to have received a study drug if the subject is recorded as treatment data available or if a date of administration is recorded on the "exposure-injection" page of the eCRF.

5.6. 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 unless they are considered to be erroneous values. Sensitivity analyses and exploratory analyses may be conducted using imputation or excluding outliers to ensure robustness of study conclusions. Details of outliers detected will be presented in the footnotes of the relevant outputs.

There were no outliers identified during the DRM.

6. Subject Disposition

6.1. Disposition

A summary table reflecting the number of subjects who were screened, who were randomized, who were administered study drug, who completed the study, who discontinued from the study prior to study drug administration, and who discontinued from the study after study drug administration will be summarized for the ITT population. This table will also present the number of subjects who were screen failed according to primary screen failure reason, who did not complete the study according to reasons for discontinuation from the study, and descriptive statistics (n, mean, SD, minimum, median, and maximum) of time on study prior to discontinuation for subjects who discontinued study after study drug administration. The time on study in days will be calculated as (Last Visit Date – Dose Date + 1).

A summary table reflecting the number and percentage of subjects who comprised the ITT, safety and PK populations, and anti-drug antibodies (ADA) status within the PK population will be summarized by treatment arm and overall for the ITT population.

Subject randomization and subject disposition will be presented in separate listings for the ITT population. A listing of subjects reported as screening failures will be provided.

6.2. Inclusion and Exclusion Criteria

All recorded inclusion/exclusion criteria status and deviations for subjects who passed Screening will be presented in a data listing.

6.3. Protocol Deviations

A major protocol deviation is a subset of protocol deviations defined as follows:

- Protocol deviations that may affect the interpretation of study results or the subject's rights, safety, or welfare.
- Protocol deviations thought to interfere with the absorption, distribution, metabolism, and excretion of the compound to be measured.

Major protocol deviations will be summarized by treatment arm and overall for the ITT population. Major protocol deviations leading to exclusion from PK population will be counted in the same table. All major protocol deviations will be presented in a data listing for the ITT population.

There were no major protocol deviations identified during the DRM.

7. Demographics and Baseline Characteristics

7.1. Demographics

Demographics and baseline characteristics will be summarized for the ITT and Safety populations by treatment arm and overall. The demographic characteristics will consist of age (years), gender (male, and female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown), and race (American Indian or Alaska Native, Asian, Black or African American, White, Other, and Multi-racial). Subjects who are from multiple races will be only counted in "Multi-racial" category and will not be counted in each specific race category. The baseline characteristics consist of whether New York Heart Association (NYHA) Functional Classification assessment was performed (yes or no), whether subject had any cardiac disease which can be classified by NYHA Functional Classification (yes or no), NYHA class (NYHA Class I, NYHA Class II, NYHA Class III, and NYHA Class IV), height (cm), weight (kg), and body mass index (BMI) (kg/m^2) which are measured at Screening, and weight category (body weight <80 kg and body weight ≥80 kg) which is measured on Day -1. For female subjects, female fertility status (surgically sterilized, post-menopausal, potentially able to bear children) will be presented.

Subject demographic and baseline characteristics will be presented in a data listing for the ITT population. The NYHA Functional Classification performed at Screening will be provided in a separate listing for the ITT population.

7.2. General Medical History

General medical history information is collected at the Screening visit and will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0 or higher. General medical history will be summarized by treatment arm and overall, system organ class (SOC), and preferred term (PT) using the number and percentage of subjects with at least one medical history for the ITT and Safety populations. The total number of medical history and the number and percentage of subjects with at least one medical history will also be presented in the table. At each level of subject summarization, a subject is counted once if the subject reported one or more findings. A listing of general medical history will also be provided for the ITT population.

7.3. Urine Drug Screen, Alcohol and Cotinine Check

Urine drug screen (tetrahydrocannabinol, opiates, cocaine, methamphetamine, barbiturates, and benzodiazepines) and history check by the investigator will be performed for alcohol, and cotinine check at Screening and Day –1.

The urine drug screen results will be presented in a data listing for the ITT population. History check results will be presented in a separate listing. Subjects may undergo an alcohol breath test at the discretion of the investigator, and it will be presented in a seperate listing.

7.4. Serology

Serology tests (anti-HIV [HIV-1 and HIV-2] antibodies, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody [total or IgG], HBV DNA, hepatitis C antibody, nontreponemal test [e.g., Rapid Plasma Reagin]) will be performed at Screening. The results will be presented in a data listing for the ITT population. A summary table will be presented for serology test results by treatment arm and overall for the ITT and Safety populations.

8. Treatments and Medications

8.1. Prior and Concomitant Medications

Information about prior medications taken by the subject within the 30 days before the administration of study drug (Day 1) will be recorded in the subject's eCRF.

Concomitant medication use will be recorded for medications taken by the subject from the time the subject signs the ICF until the EOS visit. Concomitant medication use is permitted if indicated by the investigator for treatment of an AE.

Prohibited medications during the study include the following:

- Monoclonal antibody or fusion protein or other a biologic agent (including but not limited to tumor necrosis factor-α blockers)
- Any other investigational drug except for the study drug during this study
- Live or live-attenuated vaccine during the study and until 6 months after the study drug administration (Day 1)
- Over-the-counter medications, prescription medications (excluding hormonal birth control), dietary supplements, or herbal remedies excluding the premedications or treatment of AEs.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD), Version March 2019 or later. It is the investigator's responsibility to ensure that details regarding the medication are adequately recorded in the eCRF.

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 on eCRF 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: Assume that the medication is continuing;

  - In the case of the death of a subject, and if the imputed end date is after the date of death, the end 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 end date will be used instead of reported end date:
  - Missing day: Assume the first day of the month;
    However, if the partial date and the date of study drug administration (defined as the earliest date recorded on the "Exposure - Injection" page of eCRF) 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 it's 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: UNJUN2019
  Medication end: 20OCT2019
  Date of administration: 16OCT2019
  Medication start imputed: 01JUN2019
- Example 2:
  Medication start: UNOCT2019
  Medication end: 20OCT2019
  Date of administration: 16OCT2019
  Medication start imputed: 16OCT2019
- Example 3:
  Medication start: UNOCT2019
  Medication end: 20OCT2019
  Date of administration: 24OCT2019
  Medication start imputed: 20OCT2019

Relative start day or end day with respect to the dose date of study drug will not be calculated if the medication start date or end date is incomplete.

A prior medication is defined as any medication where the start and stop dates or imputed start and stop dates are before the date of study drug administration or checked as 'Yes' for the questionnaire 'If end date is unknown, was this drug stopped before the administration of study drug?' in eCRF. A concomitant medication is defined as any medication that has an actual or imputed stop date on or after the date of study drug administration, marked as ongoing or missing or checked as 'No' for the questionnaire 'If end date is unknown, was this drug stopped before the administration of study drug?' in eCRF.

The total number of prior or concomitant medications and the number and percentages of subjects with at least one prior or concomitant medication will be summarized for the safety population. Prior and concomitant medication data will be presented separately by drug class (using Anatomical Therapeutic Chemical [ATC] Level 2), PT, and treatment arm. 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 presented in data listings for the safety population.

8.2. Study Treatments

The number and percentage of subjects who administered study drug will be presented. The planned dose amount of study drug administration data for CT-P17, US-licensed Humira, and EU-approved Humira will be presented in a summary table using descriptive statistics (n, mean, SD, minimum, median, and maximum) by treatment arm for the safety population. In addition, the number and percentage of subjects who did and did not have whole volume of study drug administered successfully will be presented.

Study drug administration data for CT-P17, US-licensed Humira and EU-approved Humira will be presented in a data listing for the safety population.

9. Pharmacokinetic Analysis

All PK analyses will be performed on the PK population unless otherwise specified.

9.1. Serum Concentrations

Blood samples will be collected from each subject during this study for the determination of the PK of adalimumab administered as CT-P17 or US-licensed Humira or EU-approved Humira. Blood samples for PK analysis of adalimumab will be drawn according to the following schedule and acceptable tolerance window:

- Pre-dose (Day 1, within 60 minutes prior to administration of the study drug)
- 6 hours after the start of administration of the study drug (Day 1, ±15 minutes)
- 12 hours after the start of administration of the study drug (Day 1, ±1 hour)
- 24 hours after the start of administration of the study drug (Day 2, ±2 hours)
- 48, 72, 96, 108, 120, 132, 144, 168, and 192 hours after the start of administration of the study drug (Days 3, 4, 5, 5.5, 6, 6.5, 7, 8, and 9, respectively, ±2 hours)
- 336 and 504 hours after the start of administration of the study drug (Days 15 and 22, respectively, ±4 hours)
- 672, 1008, 1344, and 1680 hours after the start of administration of the study drug (Days 29, 43, 57, and 71 (i.e. EOS), respectively, ±1 day)

Even if an assessment takes place using the given tolerance window, the consecutive assessment will be performed from the baseline time point (prior to start of study drug administration for assessments to be performed before the injection, and after study drug administration for assessments to be performed after the injection).

Serum samples will be analyzed to determine the concentrations of adalimumab using a validated immunoassay.

Serum adalimumab concentrations, collection times, and collection time deviations will be listed for the safety population by actual treatment arm. Serum adalimumab concentrations will be summarized for the PK population by treatment and time point, using descriptive statistics (n, arithmetic mean, SD, %CV, geometric mean, minimum, median, and maximum).

Serum adalimumab concentrations will also be summarized for the PK population by treatment, time point, and ADA status. Based on the immunogenicity data (Section 10.10) subjects will be assigned either a positive or negative ADA status, if they meet the following criteria:

- Positive ADA status: At least one "Positive" post-treatment result (including unscheduled visit and EOS visit). Subjects will still be assigned a "Positive" ADA status where missing ADA post-treatment results exist alongside a positive result.
- Negative ADA status: All "Negative" post-treatment result (including unscheduled visit and EOS visit). Subjects will still be assigned a "Negative" ADA status where missing ADA post-treatment results exist alongside a negative result.

Individual serum concentration versus time profiles for adalimumab will be presented graphically on both linear and semi-logarithmic scales by treatment and subject using actual sampling times. An overlay plot (Spaghetti plot) of subjects within each treatment will be presented graphically on both linear and semi-logarithmic scales for each treatment using actual sampling times. The mean (±SD) serum concentration versus time profiles for adalimumab will be presented graphically on both linear and semi-logarithmic scales by treatment, and also by treatment and ADA status. For ease of presentation, scheduled sampling times will be used to present results for the mean figures.

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

9.2. Serum Pharmacokinetic Parameters

The following serum PK parameters will be calculated for adalimumab administered as CT-P17, US-licensed Humira, or EU-approved Humira by non-compartmental method using [redacted], with the following guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.

Parameter	Definition
Primary	
$AUC_{0\text{-inf}}$	Area under the serum concentration-time curve from time zero to infinity, calculated using the linear trapezoidal (linear interpolation) rule
$AUC_{0\text{-last}}$	Area under the serum concentration-time curve from time zero to the last quantifiable concentration, calculated using the linear trapezoidal (linear interpolation) rule
C_{max}	Maximum serum concentration
Secondary	
T_{max}	Time to C_{max}
$t_{1/2}$	Terminal elimination half-life, calculated as: $t_{1/2} = \ln 2/\lambda_z$
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 ($t_{1/2}$, $AUC_{0\text{-inf}}$, CL/F, and V_z/F). Values of adjusted r^2 <0.85 will be examined on a case-by-case basis for reliability to calculate and retain λ_z and its associated parameters. Pharmacokinetic parameters that do not meet this criterion will be listed but not summarized or included in the statistical analysis.
$\%AUC_{extrap}$	percentage of the area extrapolated for calculation of area under the serum concentration-time curve from time zero to infinity. Percent extrapolation ≤ 20% will be required to retain $AUC_{0\text{-inf}}$ and its associated parameters (λ_z, $t_{1/2}$, CL/F, and V_z/F). Pharmacokinetic parameters that do not meet this criterion will be listed but not summarized or included in the statistical analysis.
CL/F	Apparent total body clearance, calculated as: $CL/F = Dose/AUC_{0\text{-inf}}$
V_z/F	Apparent volume of distribution during the terminal phase after non-intravenous administration, calculated as: $V_z/F = (CL/F)/\lambda_z$

All PK analyses will be conducted by the [redacted].

Pharmacokinetic parameters will be presented in data listings and summarized in tables by treatment arm, using descriptive statistics (n, arithmetic mean, SD, %CV, geometric mean, minimum, median, and maximum). Additionally, primary PK parameters will be summarized by treatment and ADA status.

For $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, the results will be rounded to integer in listing presentations; summary statistics for minimum and maximum will be rounded to integer; arithmetic mean, median, and geometric mean will be rounded to 1 decimal place; SD and %CV will be rounded to 2 decimal places. For T_{max}, the results will be rounded to 2 decimal places in listing presentations; summary statistics for minimum and maximum will be rounded to 2 decimal places; arithmetic mean,

median, and geometric mean will be rounded to 3 decimal places; SD and %CV will be rounded to 4 decimal places. For all PK concentrations and other PK parameters, the results will be reported to 3 significant figures in listing presentations; summary statistics for minimum and maximum will be reported to 3 significant figures; arithmetic mean, median, and geometric mean will be reported to 4 significant figures; SD and %CV will be reported to 5 significant figures.

9.3. Statistical Analysis of Pharmacokinetic Data

The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) will be based on an analysis of covariance model (ANCOVA) with treatment as a fixed effect and body weight as measured on baseline (Day −1), gender (male vs. female) and study center as covariates. The similarity of PK between; CT-P17 vs. US-licensed Humira, CT-P17 vs. EU-approved Humira, and US-licensed Humira vs. EU-approved Humira will be concluded if the 90% CIs for percent ratios of geometric LS means of each comparison are entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}.

Statistical analysis will also be done by ADA status for both positive and negative subjects. If subjects for one of the ADA status category is missing or too small to conduct ANCOVA analysis, then the analysis will not be reported.

10. Safety and Immunogenicity Analyses

All safety and immunogenicity analyses will be based on the safety population unless otherwise stated.

10.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after the ICF was signed if any symptoms develop.

All AEs will be collected from the date the ICF is signed and until the end of the subject's participation in the study, and will be coded by PT and SOC using MedDRA, Version 22.0 or higher. All AEs will be presented in a data listing for the safety population.

Relationship to study drug (unrelated, possible, probable, or definite) will be summarized and events will be considered to be related if relationship is possible, probable, or definite. Adverse events with no relationship or intensity will be summarized separately under a missing category.

Adverse drug reaction is defined as any treatment-emergent adverse event (TEAE) which has causal relationship with study drug at least a reasonable possibility, i.e., a TEAE which is considered as related.

All AEs will be graded for intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A TEAE is defined as any event not present before study drug administration or any event already present that worsens in intensity or frequency after study drug administration. Treatment-emergent AEs will be flagged in listings and all AE summaries will be restricted to TEAEs except the overall summary of AEs. All TEAE summary tables will include the number and percentage of subjects experiencing TEAEs by MedDRA SOC and PT, relationship, and intensity, by treatment arm and overall, and the total number of events overall, unless otherwise specified. Additionally, TEAEs, TESAEs, and TEAEs leading to study discontinuation will be summarized by treatment group, SOC, PT and intensity, regardless of relationship, displaying the number and percentage of subjects experiencing at least one TEAE. Summaries that are displayed by SOC and PT will be ordered by alphabetical order of SOC and PT. A subject with 2 or more TEAEs within the same SOC, PT, and relationship will be counted only once using the most severe intensity recorded in that level. Percentages will be based on the number of subjects in the safety population who received each treatment arm and overall.

For the purpose of inclusion in TEAE tables, the eCRF question "Did this AE start before administration of study drug?" on "Adverse Events" page will be used to determine TEAEs if the AE onset date is incomplete. If the answer is not available, incomplete AE onset and end 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., XXFEB2019): Assume the last day of the month (e.g., 28FEB2019).
    - Missing day and month (e.g., XXXXX2019): Assume December 31st (e.g., 31DEC2019).
    - Missing day, month, and year (e.g., XXXXXXXXX): 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 AE is missing (e.g., XXFEB2019), the month and year of the partial 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 date of: (i) the date of the 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., 01FEB2019).
    - If the day and month are missing (e.g., XXXXX2019), the year of the partial 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 the 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 partial date year (e.g., 01JAN2019).

- 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.

Relative start day or end day with respect to the dose date of study drug will not be calculated if the event start date or end date is incomplete.

The duration of the AE will be calculated using the below formula.

- For events with start time and end time collected: duration = adverse event stop datetime – adverse event start datetime

    - Present in minutes if duration is less than (<) 1 hour (60 minutes)
    - Present in hours with 1 decimal place if the duration is more than or equal to (≥) 1 hour (60 minutes) but less than (<) 24 hours (1440 minutes)
    - Present in days with 2 decimal places if duration is more than or equal to (≥) 24 hours (1440 minutes)

- For events without start time or end time collected: duration in days = adverse event stop date – adverse event start date + 1

All AEs recorded will be presented in a data listing for the safety population.

10.1.1. Incidence of Adverse Events

A summary table of overall AEs will be presented by treatment arm and overall for the safety population, including total number of AEs, total number of SAEs, total number of TEAEs, number and percentage of subjects with at least one AE, with at least one SAE, with at least one TEAE, with at least one treatment-emergent SAE (TESAE), with at least one TEAE leading to study discontinuation, with at least one TEAE leading to death, with at least one TEAE of hypersensitivity/allergic reaction, with at least one TEAE of ISR, with at least one TEAE of infection, and with at least one TEAE of malignancy.

10.1.2. Serious Adverse Events and Deaths

A SAE is defined as any untoward medical occurrence that at any dose meets any of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize

the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Unless otherwise specified, treatment-emergent SAEs will be summarized by treatment arm, overall and by relationship, intensity, SOC and PT 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 TESAEs will also be displayed.

All SAEs, including deaths, will be presented in a data listing for the safety population. All subjects who have a SAE with serious criteria of "death" will be presented in a data listing for the safety population.

10.1.3. Treatment-Emergent Adverse Events Leading to Study Discontinuation

The AE leading to study discontinuation will be determined based on question "Did the adverse event cause the subject to be discontinued from the study?" on "Adverse Events" page of eCRF. Unless otherwise specified, the TEAEs leading to study discontinuation will be summarized by treatment arm, overall and by relationship, intensity, SOC and PT displaying the number and percentage of subjects with at least one TEAE leading to study discontinuation. The total number of TEAEs leading to study discontinuation will also be displayed.

All AEs that lead to study discontinuation will be presented in a data listing for the safety population.

10.1.4. Treatment-Emergent Adverse Events of Special Interest

Treatment-emergent AEs of special interest (hypersensitivity/allergic reactions, ISRs, infections, and malignancy) will be determined as follows:

- **Hypersensitivity/allergic reactions:** Treatment-emergent AEs classified as hypersensitivity/allergic reactions are determined if the eCRF question "Is Adverse event classified as a Hypersensitivity/Allergic Reactions?" is answered as "Yes". Signs and symptoms of hypersensitivity/allergic reactions will be captured on separate eCRF pages. Signs and symptoms of hypersensitivity/allergic reactions will be coded using MedDRA Version 22.0 or higher.
- **Injection site reactions:** Treatment-emergent AEs classified as ISRs are determined if the eCRF question "Is Adverse event classified as an injection site reaction (ISR)?" is answered as "Yes". Signs and symptoms of ISRs will be captured on separate eCRF pages. Signs and symptoms of ISRs will be coded using MedDRA Version 22.0 or higher.
- **Infection:** Treatment-emergent AEs classified as infections are determined by SOC if the SOC is "Infections and Infestations".
- **Malignancy:** Treatment-emergent AEs classified as malignancy are determined by SOC if the SOC is "Neoplasms benign, malignant and unspecified (incl cysts and polyps)", excluding

events where any of the High Level Group Term, High Level Term, PT, and Lowest Level Term contains "benign". And it will be determined to be included by medical review.

The TEAEs which are classified as hypersensitivity/allergic reaction, ISR, infection, and malignancy will be summarized by treatment arm, overall and by relationship, intensity, SOC and PT in separate tables. The total number of events and number of subjects with at least one TEAE classified as hypersensitivity/allergic reaction, or with at least one TEAE classified as ISR, or with at least one TEAE classified as infection, or with at least one TEAE classified as malignancy will also be displayed in corresponding table.

Signs and symptoms of hypersensitivity/allergic reactions and ISRs are summarized by SOC, PT, treatment arms and overall, and intensity for the safety population, respectively.

All TEAEs classified as hypersensitivity/allergic reactions, ISRs, infection, and malignancy will be presented in separate data listings for the safety population.

10.2. Clinical Laboratory Evaluations

Blood and urine samples will be performed by the local laboratory. All laboratory test results will be presented in the International System of Units (SI units). If the local unit provided by the laboratory is not consistent with the SI unit, the local unit will be converted to the SI unit. The conversion factors will be provided to CELLTRION, Inc. for review and approval before the DRM.

The following clinical laboratory assessments will be performed:

Hematology:	Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, absolute neutrophil count, platelets
Serum Chemistry:	Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), Aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, total cholesterol, creatine phosphokinase (CPK), creatinine, creatine kinase–myocardial band isoenzyme (CK-MB), creatinine clearance (CrCl) [estimated by Modification of Diet in Renal Disease formula][1], C-reactive protein (CRP), gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total bilirubin, total protein, uric acid, direct bilirubin, triglycerides, inorganic phosphorus, high-density lipoprotein (HDL) cholesterol, Troponin I
Urinalysis:	Color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination[2]

[1] Creatinine clearance (CrCl) will be calculated using serum creatinine level only at Screening and recorded on source document and eCRF
[2] Only the parameters including squamous cells, white and red blood cell will be presented in the listings.

Clinical laboratory testing (hematology, serum chemistry, and urinalysis) will be performed at Screening, on Day -1, and on Days 3, 8, 15, 29, 43, and 57, and at EOS.

Only the parameters specified in the protocol will be included in summary tables by laboratory categories: hematology, serum chemistry, and urinalysis. All parameters collected from the

laboratory will be included in the raw data and Study Data Tabulation Model, but only protocol-specified laboratory parameters and Troponin T (if it's performed) will be presented in the listings.

Abnormal clinical laboratory values will be flagged as either high or low or abnormal based on the reference ranges provided by the local laboratories for each laboratory parameter. The investigator will determine whether any of the abnormal clinical laboratory values are clinically significant or not clinically significant.

Clinical laboratory test results will be labeled with a CTCAE term, and grading will be applied to post-baseline values for numeric parameters based on CTCAE v5.0 where applicable. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only; lower grade will be used if different grades share the same criteria. The criteria are listed in Appendix 14.2. Unit conversion will be performed if the clinical laboratory unit is not consistent with unit in CTCAE v5.0, however it will be the CTCAE criteria unit that is converted as all laboratory findings will be reported in the SI units.

Actual values and changes from Baseline for quantitative clinical laboratory test results (hematology, serum chemistry, and urinalysis) will be summarized by treatment arm and overall at each time point using descriptive statistics (n, mean, SD, minimum, median, and maximum) for the safety population. Shift tables from baseline to each schedule post-baseline visit, will be generated for clinical laboratory test results (hematology, serum chemistry, and urinalysis) using normal; abnormal, clinically significant; abnormal, not clinically significant categories as appropriate, by treatment arm and overall for the safety population.

The number and percentage of subjects will be summarized by CTCAE term, CTCAE grade, and treatment arms and overall for the safety population, where this summary includes only the most severe case during the overall visits. The CTCAE terms and ranges for applicable parameters are listed in Appendix 14.2. 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 a subject's most severe result does not satisfy any CTCAE criteria, this subject will be summarized as "No Grade".

Absolute lymphocyte and absolute eosinophil will be calculated as follows:

- Absolute lymphocyte count (10^9/L) = [WBC (10^9/L) * Lymphocytes (Proportion of 1.0)].
- Absolute eosinophil count (10^9/L) = [WBC (10^9/L) * Eosinophil (Proportion of 1.0)].

Absolute lymphocyte count and absolute eosinophil count will be presented in the listing and summarized in the CTCAE grading table, but will not be included in the hematology summary tables.

Individual clinical laboratory test results will be presented in data listings for the safety population.

10.3. Vital Sign Measurements and Body Weight

Vital sign measurements will be performed at Screening, on Day –1, on Day 1 prior to the start of study drug administration (within 30 minutes), on Days 2 (at 24 hours after injection), 3, 8, 15, 29, 43, and 57, and at EOS.

Vital signs measurements will include systolic and diastolic BPs, heart rate, respiratory rate, and body temperature. Blood pressure and heart rate measurements will be performed after the subject has been resting for at least 5 minutes.

Actual values and change from Baseline for systolic and diastolic BPs, heart rate, respiratory rate, and body temperature will be summarized by treatment arm and overall at each time point using descriptive statistics (n, mean, SD, minimum, median, and maximum) for the safety population.

Individual vital sign measurements (including repeated and unscheduled measurements) will be presented in a data listing for the safety population.

Body weight will be measured at Screening, on Day –1, and at EOS. All body weight data will be presented in a data listing for the safety population.

10.4. Electrocardiogram

Single 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes at Screening and at EOS.

The investigator will determine whether any of the 12-lead ECG results are clinically significant or not clinically significant. Findings of 12-lead ECG will be classified as either “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”.

The shift from baseline of categorical investigator interpretation will be summarized at each visit by treatment arm and overall for the safety population.

The investigator’s interpretation, including hypersensitivity/allergic reactions monitoring, will be presented in a data listing for the safety population.

10.5. Hypersensitivity/Allergic Reactions Monitoring

Hypersensitivity/allergic reactions will be assessed by additional ECG and vital sign monitoring (including systolic and diastolic BP, heart rate, respiratory rate, and body temperature).

Vital sign measurements for hypersensitivity/allergic reactions monitoring will be performed on Day 1 (prior to start of study drug administration [within 15 minutes], at 3 hours [±30 minutes], 6 hours [±30 minutes], and 12 hours [±60 minutes] after injection) and on Day 2 at 24 hours (±60 minutes) after injection. On Day 1 (pre-dose) and Day 2, the vital signs measurement may be considered as a part of hypersensitivity monitoring and only either one will be recorded in the eCRF.

Electrocardiograms for hypersensitivity/allergic reactions monitoring will be performed at 3 hours (±30 minutes) after the administration of study drug and additional ECGs can be performed if the subject experiences cardiac symptoms.

In addition, hypersensitivity/allergic reactions will be monitored by routine continuous clinical monitoring. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation, will be available and an ECG can be performed.

Actual values and changes from Baseline for hypersensitivity/allergic reactions monitoring will be summarized separately for vital sign measurements by treatment arm and overall at each time point using descriptive statistics (n, mean, SD, minimum, median, and maximum) for the safety population.

The number and percentage of subjects who have clinically notable hypersensitivity/allergic reactions vital sign measurements will be summarized in a table by treatment arm and overall, time point, and parameter for the safety population. The criteria for clinically notable results are defined as below.

Parameter	**Low**	**High**
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Heart rate (beats per minute)	≤ 50	≥ 100
Body temperature (°C)	≤ 35.0	≥ 38.0

A shift table comparing the categorical investigator interpretation of ECGs at 3 hours after the administration of study drug on Day 1 with those at Baseline will be summarized by treatment arm and overall for the safety population.

Hypersensitivity/allergic reactions monitoring for vital sign measurements (including repeated assessment) will be listed in a data listing for the safety population. High and low flags will be included to show whether a hypersensitivity/allergic reaction result is outside of the clinically notable ranges.

Hypersensitivity/allergic reactions monitoring for ECG assessments will be listed within ECG listing as described in Section 10.4.

10.6. Physical Examination

A standard physical examination will be performed at Screening, on Day -1, on Day 3, and at EOS. The examination will include an assessment of general appearance and a review of systems.

All physical examination findings will be presented in a data listing for the safety population. A shift table comparing the categorical results at each scheduled post-baseline visit with those at Baseline will be summarized by treatment arm and overall for the safety population.

10.7. Tuberculosis Assessments

A chest X-ray (both posterior–anterior and lateral views), IGRA, and signs and symptoms of TB clinical monitoring will be performed at Screening. Subjects will be monitored for the clinical signs and symptoms of TB throughout the study and until the EOS. Additional chest X-ray and IGRA testing will be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring throughout the study and until the EOS. Only IGRA will be performed at the EOS visit.

Results of IGRA will be summarized in a table by treatment arm and overall for the safety population.

Chest X-ray, TB monitoring, and IGRA test results will be presented in data listings for the safety population.

10.8. Pregnancy Test

A serum pregnancy test will be performed at Screening and the EOS visit. A urine pregnancy test will be performed in women of childbearing potential on Day -1. Throughout the study, a urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive.

The pregnancy test results will be summarized for female subjects of childbearing potential in the safety population. All pregnancy test results will be presented in a data listing.

10.9. Local Site Pain

Local site pain will be assessed immediately (within 15 minutes) after study drug administration (Day 1) using 100 mm VAS. Subjects will be asked to indicate their current level of pain intensity by drawing a single vertical line on the 100 mm VAS labeled "no pain" (0 mm) as the left anchor and "most severe pain" (100 mm) as the right anchor. The length of the line will be measured from the left (in mm) and the value (in mm) will be recorded in the eCRF.

Individual VAS results will be presented in a data listing for the safety population. The VAS results will be summarized by treatment arm and overall for the safety population.

10.10. Immunogenicity Testing

Immunogenicity of CT-P17, US-licensed Humira and EU-approved Humira will be assessed prior to study drug administration on Day 1, and on Days 15, 29, and 57, and at EOS.

The ADA assay will follow a three-tiered approach consisting of (i) screening assay, (ii) specificity/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 undergo further testing in the specificity/confirmatory assay to determine if the subject is a true positive. The test outcome for the specificity/confirmatory assay will be "Reactive", "Negative", and "Not applicable (N/A)". "Reactive" indicates a true positive test outcome and will be labeled as "Positive" in the outputs; "Negative" is considered negative; "N/A" indicates the assay was negative at the screening phase of the process. Subjects with a "Negative" test outcome for either screening or specificity/confirmatory assays will be considered 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". Samples with mean replicate response above the assay cut point will be reported as negative. Samples with mean replicate response equal to or below the assay cut point will be considered NAb positive and progressed to titration analysis.

The results of the final ADA and the screening NAb assay will be summarized. The number and percentage of the subjects will be presented by treatment arm and overall and test at each scheduled visit for the safety population. The number and percentage of subjects with at least one positive ADA status after study drug administration (including unscheduled visit and EOS visit) will also be presented in the table. A listing showing immunogenicity test results for each subject will be provided by treatment arm and visit for the safety population.

11. Initial Analysis

No formal interim analyses are planned.

12. Changes in the Planned Analysis

Synopsis and Section 6.1 of the protocol states that $\%AUC_{extrap}$ is defined as $AUC_{0\text{-}inf}$ as a percentage of total AUC. Definition of $\%AUC_{extrap}$ is modified in the SAP Section 4.2.2 for clarification.

In the primary PK analysis, the body weight as measured on Day -1 will be included in covariates instead of the stratification level of body weight (≥80 kg vs. <80 kg).

13. References

eCRF: A Phase 1, Randomized, Double-blind, Three-arm, Parallel group, Single-dose Study to Compare the Pharmacokinetics and Safety of CT-P17 and Humira (US-licensed Humira and EU-approved Humira) in Healthy Subjects, Version 6.0, 06 November 2019.

Protocol: A Phase 1, Randomized, Double-blind, Three-arm, Parallel group, Single-dose Study to Compare the Pharmacokinetics and Safety of CT-P17 and Humira (US-licensed Humira and EU-approved Humira) in Healthy Subjects, Version 2.1 08 January 2019.

14. Appendices

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14.1. Schedule of Study Procedures

	Screening[1]	Study Period[2]																	EOS[3]
Study day (Visit windows)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**5.5**	**6**	**6.5**	**7**	**8**	**9**	**15**	**22**	**29 (±1)**	**43 (±1)**	**57 (±1)**	**71 (±1)**
Procedure																			
Informed consent	X																		
Medical history	X	X																	
Demographics	X																		
Inclusion / exclusion criteria[4]	X	X																	
Body weight & height[5]	X	X																	X
Physical examination	X	X			X														X
Hepatitis B/C, HIV and syphilis test[6]	X																		
TB screening (chest X-ray and IGRA)[7]	X																		(X)
Serum pregnancy test[8]	X																		X
Urine pregnancy test[8]		X																	
Urine drug abuse / alcohol / cotinine check[9]	X	X																	
Randomization		X																	
Clinical laboratory tests[10]	X	X			X							X		X		X	X	X	X
Vital signs[11]	X	X	X	X	X							X		X		X	X	X	X
12-Lead ECG	X																		X
Administration of study drug[12]			X																
Pharmacokinetic sampling[13]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling[14]			X											X		X		X	X
Hypersensitivity monitoring[15]			X	X															
Injection site reaction[16]			X																
VAS local site pain[17]			X																
Prior, concomitant medications[18]	X																		
Adverse events[19]	X																		
TB clinical monitoring[7]	X																		

Abbreviations: ECG, electrocardiogram; EOS, End-of-Study; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; TB, tuberculosis; VAS, visual analogue scale.

1. During the screening period, retest for screening is permitted only once by the Investigator's judgment. If the repeated test result is again not suitable or indeterminate for inclusion, the subject will be screen failed.
2. Subjects will be confined to the study center until completion of the 48-hour assessments after the administration of the study drug (Day 1) and admission can be extended depending on the subject's and study center's availability, up to Day 7. The consecutive study visits will be carried out on an out-patient basis.
3. All EOS assessments will be performed on Day 71, for all subjects including those who discontinued prematurely.
4. Inclusion and exclusion criteria should be confirmed before Day -1. On the Day -1, recheck process will be performed.
5. Height will be measured at Screening only.
6. Serology tests will be performed at the Screening visit for anti-HIV (HIV-1 and HIV-2) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb [total or IgG]), HBV DNA (if subject has HBsAg negative, HBsAb negative or positive, and HBcAb positive), hepatitis C antibody (HCAb), and nontreponemal (e.g., Rapid Plasma Reagin) tests.
7. At Screening, a chest X-ray, an IGRA, and signs and symptoms of TB clinical monitoring will be performed. If the result of IGRA is indeterminate at Screening, a retest will be allowed only once during the Screening period. Additional IGRA test and chest X-ray will be performed if symptoms raise a suspicion of TB upon the judgement of the investigator during the study and until the EOS. Only IGRA will be performed at the EOS visit; signs and symptoms of TB clinical monitoring will be performed throughout the study and until the EOS.
8. A serum pregnancy test on women of childbearing potential will be performed at Screening and the EOS visit. A urine pregnancy test will be performed in women of childbearing potential on Day -1. Throughout the study, a urine pregnancy test will be performed when there is any possibility of pregnancy, and a confirmatory serum pregnancy test will be performed if a urine pregnancy test result is positive.
9. Urine drug screen (tetrahydrocannabinol, opiates, cocaine, methamphetamine, barbiturates and benzodiazepines) and history check by the investigator will be performed for drug abuse, alcohol, and cotinine check in Screening and Day -1.
10. Clinical laboratory tests will be carried out: **Hematology** (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, platelets), **Serum chemistry** (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, total cholesterol, creatine phosphokinase, creatinine, creatine kinase–myocardial band isoenzyme [CK-MB], creatinine clearance [estimated by Modification of Diet in Renal Disease formula], C-reactive protein, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, potassium, sodium, total bilirubin, total protein, uric acid, direct bilirubin, triglycerides, inorganic phosphorus, high-density lipoprotein cholesterol, Troponin I), **Urinalysis** (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination). Creatinine clearance will be calculated using serum creatinine level only at screening for inclusion.
11. Vital sign measurement on Day 1 will be performed before the start of the study drug administration (within 30 minutes). Additional vital signs will be measured after the study drug administration. On Day 1 (pre-dose) and Day 2, the vital signs measurement may be considered as a part of hypersensitivity monitoring and only either one will be recorded in the eCRF.
12. The study drug will be administered on the subject's lower abdomen except for the 5 cm around the subject's navel.
13. Samples for pharmacokinetic analysis will be obtained at the following time points:

PK sampling time points
Day 1 Pre-dose (within 60 minutes prior to administration of the study drug)
Day 1 (6 hours after the administration of the study drug); ±15 minutes
Day 1 (12 hours after the administration of the study drug); ±1 hour
Day 2 (24 hours after the administration of the study drug); ±2 hours

Day 3, 4, 5, 5.5, 6, 6.5, 7, 8, and 9 (48, 72, 96, 108, 120, 132, 144, 168, and 192 hours, respectively, after the administration of the study drug); ±2 hours
Day 15 and 22 (336 and 504 hours, respectively, after the administration of the study drug); ±4 hours
Day 29, 43, 57, and 71 (i.e., EOS) after the administration of the study drug; ±1 day

14. Sample for immunogenicity analysis on Day 1 will be performed prior to the study drug administration.
15. For hypersensitivity monitoring, vital sign measurements will be performed before the start of the study drug administration (within 15 minutes) and at 3, 6, 12, and 24 hours after injection on Day 1. The tolerance window is ±30 minutes for 3 and 6 hours, and ±60 minutes for 12 and 24 hours after the administration. Either 3-lead or 12-lead ECG can be used for hypersensitivity monitoring at 3 hours (±30 minutes) after the administration of the study drug on Day 1 and additional ECG will be performed if a subject experiences cardiac symptoms. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (inhalational therapy, oxygen and artificial ventilator) must be available.
16. Injection site reaction will be assessed 30 minutes (±10 minutes) after the study drug administration.
17. Local site pain will be observed using VAS immediately (within 15 minutes) after the study drug administration.
18. Use of all prior and concomitant medications, from within 30 days prior to the administration of the study drug (Day 1) until the last assessment date or EOS visit, will be recorded.
19. Adverse events (and serious adverse events) should be reported until the end of the subject's participation in the study, regardless of the relationship to the study drug.

14.2. CTCAE v5.0 for Clinical Laboratory Test Results

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L; <LLN – 6.2 mmol/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	-
Alanine aminotransferase increased	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
Alkaline phosphatase increased	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	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
Blood lactate dehydrogenase increased	LDH	High	>ULN			
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

CPK increased	CPK	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
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
Eosinophilia	Eosinophils	High	>ULN and >Baseline			
GGT increased	GGT	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
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	Magnesium	High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L		>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 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 – 1,000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1,000 mg/dL; >11.4 mmol/L
Hyperuricemia	Uric acid	High	>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	-
Hypoglycemia	Glucose	Low	<LLN-55mg/dL;<LLN-3.0 mmol / L	< 55 -40mg/dL;< 3.0 – 2.2 mmol / L	< 40 -30mg/dL;< - 2.2 – 1.7 mmol / L	<30mg/dL; <1.7mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L		<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hypomagnesemia	Magnesium	Low	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L

Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L regardless of symptoms	<120 mmol/L
Leukocytosis	Blood WBC	High			>100,000/mm^3	
Lymphocyte count decreased	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	Lymphocytes	High	-	>4,000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Neutrophil count decreased	Total Neutrophils	Low	<LLN – 1,500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 – 1,000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1,000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L
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/mm^3; <25.0 x $10e^9$ /L
White blood cell decreased	Blood WBC	Low	<LLN – 3,000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3,000 – 2,000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2,000 – 1,000/mm^3; <2.0 - 1.0 x $10e^9$ /L	<1,000/mm^3; <1.0 x $10e^9$ /L

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 local laboratory. Semicolon (;) indicates "or".

CTCAE = Common Terminology Criteria for Adverse Events, ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase, CPK = creatine phosphokinase, GGT = gamma glutamyl transferase, WBC= white blood cell.

In case of numeric value for grading is identical such as Hypokalemia and Hyperuricemia, CTCAE grade which includes numeric value only was applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.