CLINICAL STUDY 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

Protocol Number CT-P17 1.1

Sponsor: 

Sponsor Contact: 

SAE Reporting and Data Center: 

Version and Date of Protocol: Protocol Version 2.1, 08 Jan 2019

CONFIDENTIAL

Protocol Approval

Study Title:	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
Protocol Number:	CT-P17 1.1
Protocol Date:	Protocol Version 2.1, 08 Jan 2019

Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "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" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.1, dated 08 Jan 2019, the International Council for Harmonisation harmonised tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without institutional review board approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: CT-P17 1.1

Title: 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

Study Phase: Phase 1

Study Center(s): [redacted]

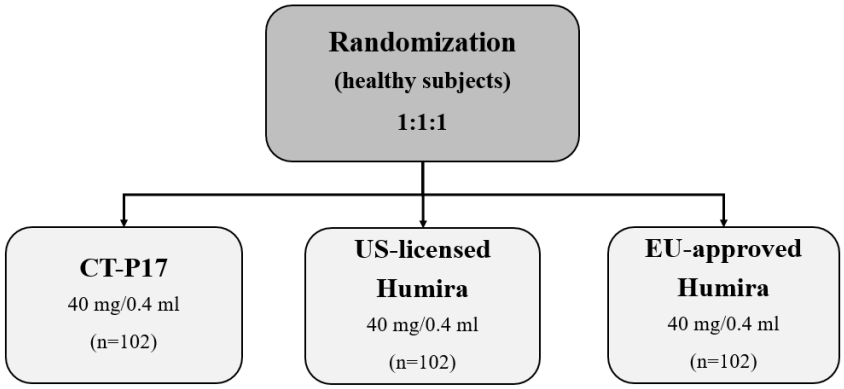
Test Drug, Dose and Route of Administration:
CT-P17, 40 mg/0.4 ml (100 mg/mL), a single subcutaneous (SC) injection via pre-filled syringe (PFS)

Reference Drug, Doses and Routes of Administration:
United States (US)-licensed Humira, 40 mg/0.4 ml (100 mg/mL), a single SC injection via PFS
European Union (EU)-approved Humira, 40 mg/0.4 ml (100 mg/mL), a single SC injection via PFS

Study Design and Rationale:
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 pharmacokinetics (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 SC injection via 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 baseline (Day -1), gender (male vs. female) and study center.

A schematic of the study design is presented in Figure S1.

Figure S1 Study Design Overview



Objectives:

Primary objective

- To demonstrate the PK similarity in terms of area under the concentration-time curve (AUC) from zero to infinity ($AUC_{0\text{-}inf}$), AUC 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).

Secondary objective

- To evaluate the additional PK parameters, safety, and immunogenicity of CT-P17, US-licensed Humira, and EU-approved Humira in healthy subjects.

Number of Subjects:
Approximately 306 subjects will be enrolled and randomly assigned (1:1:1) into one of three treatment arms as follows:

- Treatment Arm 1 (n=102) CT-P17
- Treatment Arm 2 (n=102) US-licensed Humira
- Treatment Arm 3 (n=102) EU-approved Humira

Study Population: Healthy male or female subjects 19 to 55 years of age, both inclusive, with a body mass index (BMI) between 18.0 and 29.9 kg/m^2, both inclusive, are planned for enrollment.

Inclusion Criteria:
Subjects who meet all of the following criteria will be considered eligible to participate in the clinical study:

1. Healthy male or female subjects, between the ages of 19 and 55 years, both inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and heart rate measurement, 12-lead electrocardiogram [ECG], and clinical laboratory tests prior to the administration of the study drug).
2. Subject with C-reactive protein ≤1.5 times the upper limit of normal (ULN).
3. Subject has adequate liver function as determined by following results:
   - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 × ULN and
   - Total bilirubin ≤1.5 × ULN.
4. Subject is informed and able to understand the full nature and purpose of the study, including possible risks and side effects, and is given ample time and opportunity to read and understand this information. The subject has the ability and agrees to cooperate with the investigator and must sign and date the written informed consent prior to performing any of the screening procedures.
5. BMI between 18.0 and 29.9 kg/m^2, both inclusive, when rounded to the nearest tenth.
6. Subject and their partner of childbearing potential must agree to use a highly effective method of contraception as specified in Section 5.8.2, throughout the study and for 5 months after the administration of assigned treatment. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active. Male and female subjects and their partners who have been surgically sterilized for less than 24 weeks prior to the date of informed consent must agree to use any medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential.

Exclusion Criteria:
Subjects who meet any of the following criteria will not be considered eligible to participate in the clinical study:

1. Subject has a medical history and/or condition including one or more of the following disease(s):
   - History and/or current presence of clinically significant atopy (e.g., allergic asthma, eczematous dermatitis), known or suspected clinically relevant hypersensitivity or allergic reactions to any of the excipients of study drug, other murine and human proteins or immunoglobulin products.
   - Known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, human immunodeficiency virus (HIV) or syphilis. However, a subject with history of hepatitis B virus is allowed if resolved.
   - History of invasive systemic fungal infections (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, etc.) or other opportunistic infections judged by the investigator, including local fungal infections or a history of herpes zoster.
   - History of and/or current cardiac (including New York Heart Association class III/IV heart failure), gastrointestinal, renal, endocrine, neurologic, autoimmune, hepatic, hematological (including pancytopenia, aplastic anemia or blood dyscrasia, etc.), metabolic (including diabetes mellitus), or pulmonary disease classed as significant by the investigator.
   - History of any malignancy.

- History of systemic or local infection, a known risk for developing sepsis, and/or known active inflammatory process or evidence of an infection requiring in-patient hospitalization or intravenous antibiotics within 24 weeks prior to the administration of the study drug (Day 1).

2. Subject is considered to have a significant abnormal cardiac function in investigator's discretion determined by the laboratory results.
3. Subject underwent surgical intervention or an operation within 4 weeks prior to the administration of the study drug (Day 1) or plans to have a surgical procedure during the study period.
4. Subject has active tuberculosis (TB), latent TB (defined as a positive result for interferon-γ release assay [IGRA] with no active lesion in examination of chest X-ray without any sign or symptom of TB), a history of TB, or had close contact with a person with active TB within 8 weeks prior to the administration of the study drug (Day 1). If the result of IGRA is indeterminate at Screening, retest will be allowed only once during the Screening period. If the repeated IGRA result is again indeterminate or positive, the subject will be excluded from the study. If the repeated IGRA result is negative, the subject may be included in the study.
5. Female subject is pregnant or lactating or planning to be pregnant or to breastfeed before, during, or within 5 months after the administration of the study drug (Day 1).
6. Male subject is planning to father a child or donate sperm within 5 months after the administration of the study drug (Day 1).
7. Subject has received a monoclonal antibody or fusion protein, or current use of a biologic (including but not limited to tumor necrosis factor [TNF] - α blockers).
8. Subject used prescription (excluding hormonal birth control), over-the-counter drugs, dietary supplements, or herbal remedies that could affect the outcome of the study within 2 weeks prior to the administration of the study drug (Day 1).
9. Subject has undergone treatment with an investigational drug or participated in another clinical trial for healthy subject or bioequivalence test within 90 days or 5 half-lives (whichever is longer) prior to the administration of the study drug (Day 1) or plan to do so during the study.
10. Subject received a live or live-attenuated vaccine within 4 weeks prior to the administration of the study drug (Day 1) or plan to do so until the 6 months after Day 1.
11. Subject has donated or lost 450 mL or more of whole blood within 8 weeks, or donated blood components within 4 weeks prior to the administration of the study drug (Day 1).
12. Subject shows reasonable evidence of drug abuse (positive result for drug urine test and/or the opinion of the investigator).
13. Subject has a history or presence of regular consumption exceeding an average weekly intake of >21 units of alcohol in recent 12 weeks prior to the Screening visit. One unit is equivalent to a half-pint (285 mL) of beer/lager, one measure (25 mL) of spirits, or one small glass (125 mL) of wine. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications, or beverages within 24 hours prior to admission (Day -1), and each study visit until completion of the study.
14. Subject has smoked 10 or more cigarettes per day in the recent 12 weeks prior to the administration of the study drug (Day 1) and/or is unable to refrain from smoking up to 24 hours after the administration of the study drug.
15. In the opinion of the investigator, the subject is not eligible for the study participation for any reason (including clinical laboratory results) or; shows evidence of a condition (e.g., psychological or emotional problem, any disorder or resultant therapy) that is likely to invalidate an informed consent or limit the ability of the subject to comply with the protocol requirements. Subject is unable to understand the protocol requirements, instructions, study-related restrictions, or the nature, scope, and possible consequences of the clinical study; or is unable to give written informed consent or to comply fully with the protocol.
16. Subject is vulnerable (e.g., employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).

Study Procedures:

The study will include a Screening period, Admission, Study period, and End-of-Study (EOS) visit. All study procedures will be performed at the time points specified in the schedule of assessments (Table 10-1).

Screening Period (Day -28 to Day -2):
Subjects will sign and date the informed consent form and undergo procedures to determine eligibility.

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 TB, clinical laboratory tests, vital signs, body weight, physical examination, check for history of 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 signs** will be measured and **either 3-lead or 12-lead ECG** can be used. **Local site pain** using 100 mm visual analogue scale (VAS) and **injection site reactions** will be assessed after study drug administration. A **physical examination** will be performed. **Immunogenicity samples** will be obtained and **AEs**, **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 the following table:

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
Days 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
Days 15 and 22 (336 and 504 hours, respectively, after the administration of the study drug); ±4 hours
Days 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 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.

Pharmacokinetic Assessments

Primary endpoints:

- 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})

Secondary endpoints:

- Area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC (%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 Assessments

Adverse events, serious AEs, AEs of special interest (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), immunogenicity, hypersensitivity/allergic reaction assessments by additional ECG and vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), vital sign and weight measurement, ECG, physical examination, IGRA, chest X-ray, pregnancy testing, clinical laboratory testing (including hematology, chemistry, and urinalysis), local site pain using 100 mm VAS, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, HIV (HIV-1 and HIV-2) status and syphilis will be tested for the subject's eligibility determination.

Sample Size:

A sample size of 91 subjects from each arm will provide at least 90% power to show similarity in PK of the followings; CT-P17 vs. US-licensed Humira, CT-P17 vs. EU-approved Humira and US-licensed Humira vs. EU-approved Humira using 90% confidence interval (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 for PK parameters is not considered.

Statistical Analyses:

Pharmacokinetic analysis: 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 with covariate(s). 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 ratios of geometric means of each comparison are entirely contained within 80% to 125% for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}. The PK endpoints will be calculated using non-compartmental methods. The PK analysis will be conducted based on the PK population.

Pharmacokinetic parameters will be presented in data listings and summarized in tables. The tables will display the following descriptive statistics: number of subjects, mean, standard deviation, median, minimum, maximum, geometric mean, and CV.

For secondary endpoints, following PK parameters will be assessed: $\%AUC_{extrap}$, T_{max}, V_z/F, λ_z, $t_{1/2}$, and CL/F.

Additional PK analyses may be performed as detailed in the statistical analysis plan.

Safety and immunogenicity analysis: All safety and immunogenicity analyses will be conducted based on the safety population, and listed and summarized by treatment arm. The number and percentage of subject experienced AEs will be summarized by treatment arm using system organ class and preferred term. Adverse events will be summarized by severity and relationship to study drug. Serious adverse events will be listed separately. Adverse events will be recorded according to the Common Terminology Criteria for Adverse Events v5.0 and will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities. Prior and concomitant medications will be coded using the WHO Drug Dictionary. These medications will be tabulated by drug class and preferred term.

List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AS	axial spondylitis
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
$\%AUC_{extrap}$	Area under the concentration-time curve extrapolated from zero to infinity as a percentage of total AUC
BMI	body mass index
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximumserum concentration
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EOS	end-of-study
EU	European Union
FDA	Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HCAb	hepatitis C antibody
HIV	human immunodeficiency virus
IB	investigator’s brochure
ICF	informed consent form

Abbreviation	Term
ICH	International Council for Harmonisation
IgG1	immunoglobulin G1
IGRA	interferon-γ release assay
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
λ_z	terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PT	preferred term
PVG	pharmacovigilance
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

Abbreviation	Term
VAS	visual analogue scale
V_z/F	apparent volume of distribution during the terminal phase after non-intravenous administration

1 Introduction

1.1 Background

Tumor necrosis factor (TNF)-α, a proinflammatory cytokine, is a key mediator of inflammation shown to be a central factor in inflammatory immune response (*Harriman et al 1999*; *Hsia et al 2006*). In general, TNF-α is produced mainly by macrophages, but also by a broad variety of other cell types. It has a wide spectrum of activities including coordinating host immune and inflammatory response to infectious, malignant, and autoimmune conditions. There are 2 types of TNF receptors, p55 and p75, part of a large family of structurally related cell-surface receptors (*Bazzoni and Beutler 1996*). There is evidence that the p75 receptor stimulates T cells proliferation and suppresses TNF-α-mediated inflammatory responses, whereas the p55 receptor appears to be critical in triggering host defense and inflammatory responses (*Tartaglia et al 1993*; *Peschon et al 1998*).

Large amounts of TNF-α are released in response to lipopolysaccharide, other bacterial products, and interleukin-1. Tumor necrosis factor-alpha induces proinflammatory cytokines such as interleukin-1 and interleukin-6, enhances leukocyte migration, activates neutrophil and eosinophil functional activity, and induces acute phase reactants, other liver proteins, and tissue-degrading enzymes. Although there is a benefit to TNF-α expression in response to infection or injury, there are increased concentrations associated with a variety of inflammatory conditions such as rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, uveitis, ankylosing spondylitis (AS), psoriatic arthritis, and psoriasis.

Greater understanding of the role of inflammatory mediators has produced effective biologic treatments for inflammatory conditions, including Humira (adalimumab), a fully humanized anti-TNF-α monoclonal antibody. Adalimumab is structurally and functionally analogous to naturally occurring human immunoglobulin G1 (IgG1) and demonstrates a high specificity and affinity for TNF. Adalimumab binds to TNF-α and blocks its interaction with the cell surface TNF receptors, p55 and p75 (*Humira SmPC 2018*). It does not bind other cytokines such as lymphotoxin. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement (*Humira USPI 2018*).

1.2 CT-P17 Product Description

CT-P17, containing the active ingredient adalimumab, is a recombinant humanized monoclonal antibody that is being developed as a similar biological medicinal product to the reference product, Humira. The reference product was originally approved in the United States (US) in December of 2002 and in the European Union (EU) in September of 2003

(*FDA 2002*, *EMA EPAR for Humira 2017*, *Humira SmPC 2018*). In the EU, Humira is indicated for the following conditions: RA, juvenile idiopathic arthritis, axial spondyloarthritis (AS, axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, uveitis and pediatric uveitis; in the US, Humira is indicated for the same conditions except axial spondyloarthritis without radiographic evidence of AS, pediatric plaque psoriasis, and pediatric uveitis (*Humira USPI 2018*, *Humira SmPC 2018*).

The reference product, Humira, is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous (SC) administration (*Humira SmPC 2018*). Humira is supplied in two strengths: 50 mg/mL (40 mg/0.8 mL) and 100 mg/mL (40 mg/0.4 mL).

CT-P17 is manufactured using a Chinese Hamster Ovary cell line by fed-batch cell culture, followed by harvest, purification, formulation, and subsequent fill-finish operations. The primary amino acid sequences of adalimumab in CT-P17 are identical to those of Humira. CT-P17 will be supplied in a pre-filled syringe (PFS) at a concentration of 100 mg/mL (40 mg/0.4 mL) as a clear to opalescent, colorless to brown liquid for subcutaneous administration. The CT-P17 drug product will have the same pharmaceutical form and strength as Humira and is intended to have a highly similar quality profile to Humira.

CELLTRION, Inc. plans to seek approval for all indications for which the reference product has been approved by demonstrating similarity of CT-P17 with the reference product through an extensive array of quality, nonclinical and clinical comparability assessments.

1.3 Nonclinical Studies

Detailed information regarding the nonclinical pharmacology and toxicology of CT-P17 can be found in the investigator's brochure (IB).

1.4 Clinical Studies

No clinical studies of CT-P17 have been performed. The safety, tolerability, and pharmacokinetics (PK) of Humira (adalimumab) in healthy subjects were evaluated in a series of phase 1 studies.

Study DE024 was a single center, double-blind, randomized, placebo-controlled, parallel-group, ascending single-dose study in healthy male subjects. A total of 80 subjects (60 active and 20 placebo) participated in the study. Active subjects received a single intravenous (IV) dose of 1 mg/kg Humira over 2 to 3 minutes or 0.1, 0.3, and 1 mg/kg Humira via SC injection. Results demonstrated that following SC administration of Humira the mean

maximum observed serum concentration (C_{max}) and area under the concentration-time curve (AUC) from zero to infinity ($AUC_{0\text{-}inf}$) increased with increasing dose, with dose proportional increases noted at the 0.3 and 1 mg/kg SC doses only. The time to C_{max} (T_{max}) ranged from 48 to 336 hours and the mean half-lives ranged from 284 to 433 hours across doses.

Study DE015 was an open-label, randomized, parallel-group, single-dose study to assess the absolute and relative bioavailability of three injectable formulations of human anti-TNF antibody D2E7 in healthy male and female subjects. Subjects received 40 mg D2E7 as three different formulations via IV (50 mg/mL D2E7, with Tween-80) or SC injection (25 mg/mL D2E7, without Tween-80; 50 mg/mL D2E7, with Tween-80; and 50 mg/mL D2E7, without Tween-80). The results indicated that the mean C_{max} and T_{max} for the three SC formulations of D2E7 were comparable. The overview and results of Studies DE024 and DE015 can be found in *Clinical Pharmacology and Biopharmaceutics Review(s), FDA*.

Study M10-867 was a phase 1, single-dose, parallel-arm, single-blind, randomized study in healthy adult subjects. A total of 300 subjects were administered two formulations of Humira (40 mg/0.8 mL [50 mg/mL], reference vs. 40 mg/0.4 mL [100 mg/mL], test). The 90% CIs for the ratio of C_{max} central values (101.9 – 115.2) and the ratio of AUC from time zero to 1344 hours ($AUC_{0\text{-}1344}$) central values (107.2 – 124.9) demonstrated comparable bioavailability of the two formulations. The overview and results of Study M10-867 can be found in the Product Monograph of Humira (*HUMIRA Product Monograph 2018*).

An overview of the safety profile of Humira, including undesirable effects, can be found in the Humira Summary of Product Characteristics (SmPC), European Public Assessment Report (EPAR) for Humira, and United States Prescribing Information (USPI) for US-licensed Humira (*Humira SmPC 2018*; *EMA EPAR for Humira 2017*; *Humira USPI 2018*).

1.5 Rationale for Study

The introduction of biosimilar (follow-on) medicinal products is desirable as they will enhance patient access by expanding the field of competing biotechnological treatments. The purpose of this study is to compare the PK, safety, and immunogenicity of the biosimilar test product (CT-P17) and the reference products (US-licensed Humira and EU-approved Humira) after a single SC injection of 40 mg of each product to healthy subjects following the recommendations of the guidance for industry, “Scientific Considerations in Demonstrating Biosimilarity with a Reference Product” (*DHHS 2015*).

The dose of Humira (40 mg) selected for this study is in line with the approved labeling for Humira (*Humira SmPC 2018*; *Humira USPI 2018*).

The study will be conducted in healthy subjects to avoid potentially high variability of the exposure of adalimumab if administered to patients with underlying and/or concomitant disease and concomitant medications. Due to the long half-life of adalimumab (approximately 2 weeks), a parallel-group design will be used in this study.

1.6 Risk–Benefit Assessment

Information about the risk following the administration of adalimumab was taken from the prescribing information for US-licensed Humira (*Humira USPI 2018*) and Humira SmPC for EU-approved Humira (*Humira SmPC 2018*). In view of the structural, biological, and toxicological similarity to Humira, CT-P17 is expected to display a similar safety profile.

The proposed safety screening and monitoring assessments are deemed to be sufficient to monitor potential risks of CT-P17 administration. Since adalimumab will be administered only once at the approved dosage of 40 mg, the overall risk of the study for healthy subjects is considered to be acceptable. No therapeutic benefit from adalimumab treatment is intended for the healthy subjects in this study.

2 Study Objectives

2.1 Primary Objective

- To demonstrate the PK similarity in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and 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)

2.2 Secondary Objective

- To evaluate the additional PK parameters, safety, and immunogenicity of CT-P17, US-licensed Humira, and EU-approved Humira in healthy subjects

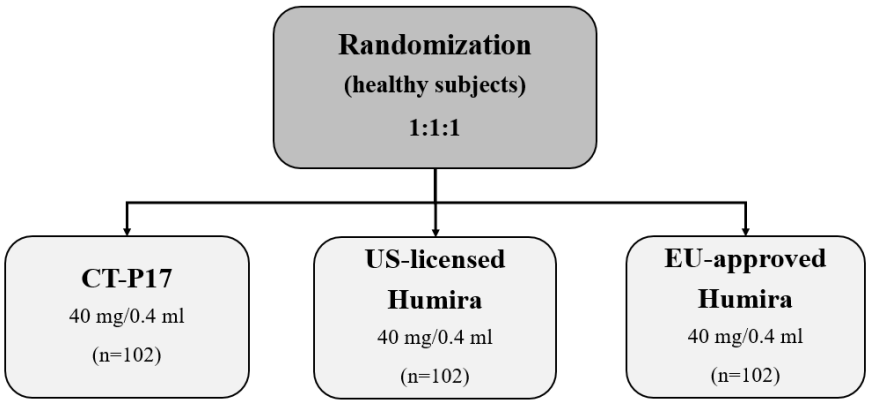
3 Investigational Plan

3.1 Study Design

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 SC injection via 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 3−1. Refer to Section 3.2 for the study overview, including procedures to be performed during the study.

Figure 3−1 Study Design Overview



3.2 Study Overview

The study will include a Screening period, Admission, Study period, and End-of-Study (EOS) visit. All study procedures will be performed at the time points specified in the schedule of assessments (Table 10-1).

3.2.1 Screening Period (Day -28 to Day -2)

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

3.2.2 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 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.

Subject 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).

3.2.3 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 in 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 the following table:

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

3.2.4 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.

4 Study Population Selection and Withdrawal Criteria

Healthy male or female subjects 19 to 55 years of age, both inclusive, with a body mass index (BMI) between 18.0 and 29.9 kg/m^2, both inclusive, will be enrolled. Approximately 306 subjects (102 subjects in each arm) are planned to achieve at least 273 evaluable subjects (91 subjects in each arm).

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be considered eligible to participate in the clinical study:

1. Healthy male or female subjects, between the ages of 19 and 55 years, both inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and heart rate measurement, 12-lead ECG, and clinical laboratory tests prior to the administration of the study drug).

2. Subject with C-reactive protein ≤1.5 times the upper limit of normal (ULN).

3. Subject has adequate liver function as determined by the following results:

   - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 × ULN and,

   - Total bilirubin ≤1.5 × ULN.

4. Subject is informed and able to understand the full nature and purpose of the study, including possible risks and side effects, and is given ample time and opportunity to read and understand this information. The subject has the ability and agrees to cooperate with the investigator and must sign and date the written informed consent prior to performing any of the screening procedures.

5. BMI between 18.0 and 29.9 kg/m^2, both inclusive, when rounded to the nearest tenth

6. Subject and their partner of childbearing potential must agree to use a highly effective method of contraception as specified in Section 5.8.2, throughout the study and for 5 months after the administration of assigned treatment. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active. Male and female subjects and their partners who have been surgically sterilized for less than 24 weeks prior to the date of informed consent must agree to use any medically acceptable methods of contraception. Menopausal

females must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be considered eligible to participate in the clinical study:

1. Subject has a medical history and/or condition including one or more of the following disease(s):

    - History and/or current presence of clinically significant atopy (e.g., allergic asthma, eczematous dermatitis), known or suspected clinically relevant hypersensitivity or allergic reactions to any of the excipients of study drug, other murine and human proteins or immunoglobulin products.

    - Known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, human immunodeficiency virus (HIV) or syphilis. However, a subject with history of hepatitis B virus is allowed if resolved.

    - History of invasive systemic fungal infections (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, etc.) or other opportunistic infections judged by the investigator, including local fungal infections or a history of herpes zoster.

    - History of and/or current cardiac (including New York Heart Association class III/IV heart failure), gastrointestinal, renal, endocrine, neurologic, autoimmune, hepatic, hematological (including pancytopenia, aplastic anemia or blood dyscrasia, etc.), metabolic (including diabetes mellitus), or pulmonary disease classed as significant by the investigator.

    - History of any malignancy.

    - History of systemic or local infection, a known risk for developing sepsis, and/or known active inflammatory process or evidence of an infection requiring in-patient hospitalization or IV antibiotics within 24 weeks prior to the administration of the study drug (Day 1).

2. Subject is considered to have a significant abnormal cardiac function in investigator's discretion determined by the laboratory results.

3. Subject underwent surgical intervention or an operation within 4 weeks prior to the administration of the study drug (Day 1) or plans to have a surgical procedure during the study period.

4. Subject has active TB, latent TB (defined as a positive result for IGRA with no active lesion in examination of chest X-ray without any sign or symptom of TB), a history of TB, or had close contact with a person with active TB within 8 weeks prior to the administration of the study drug (Day 1). If the result of IGRA is indeterminate at Screening, retest will be allowed only once during the Screening period. If the repeated IGRA result is again indeterminate or positive, the subject will be excluded from the study. If the repeated IGRA result is negative, the subject may be included in the study.

5. Female subject is pregnant or lactating or planning to be pregnant or to breastfeed before, during, or within 5 months after the administration of the study drug (Day 1).

6. Male subject is planning to father a child or donate sperm within 5 months after the administration of the study drug (Day 1).

7. Subject has received a monoclonal antibody or fusion protein, or current use of a biologic (including but not limited to TNF- α blockers).

8. Subject used prescription (excluding hormonal birth control) or over-the-counter (OTC) drugs, dietary supplements, or herbal remedies that could affect the outcome of the study within 2 weeks prior to the administration of the study drug (Day 1).

9. Subject has undergone treatment with an investigational drug or participated in another clinical trial for healthy subject or bioequivalence within 90 days or 5 half-lives (whichever is longer) prior to the administration of the study drug (Day 1) or plan to do so during the study.

10. Subject received a live or live-attenuated vaccine within 4 weeks prior to the administration of the study drug (Day 1) or plan to do so until the 6 months after Day 1.

11. Subject has donated or lost 450 mL or more of whole blood within 8 weeks, or donated blood components within 4 weeks prior to the administration of the study drug (Day 1).

12. Subject shows reasonable evidence of drug abuse (positive result for drug urine test and/or the opinion of the investigator).

13. Subject has a history or presence of regular consumption exceeding an average weekly intake of >21 units of alcohol in recent 12 weeks prior to the Screening visit. One unit is equivalent to a half-pint (285 mL) of beer/lager, one measure (25 mL) of spirits, or one small glass (125 mL) of wine. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications, or beverages, within 24 hours prior to the admission (Day -1), and each study visit until completion of the study.

14. Subject has smoked 10 or more cigarettes per day in the recent 12 weeks prior to the administration of the study drug (Day 1) and/or is unable to refrain from smoking up to 24 hours after the administration of the study drug.

15. In the opinion of the investigator, the subject is not eligible for the study participation for any reason (including clinical laboratory results) or; shows evidence of a condition (e.g., psychological or emotional problem, any disorder or resultant therapy) that is likely to invalidate an informed consent or limit the ability of the subject to comply with the protocol requirements. Subject is unable to understand the protocol requirements, instructions, study-related restrictions, or the nature, scope, and possible consequences of the clinical study; or is unable to give written informed consent or to comply fully with the protocol.

16. Subject is vulnerable (e.g., employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).

4.3 Subject Withdrawal/Discontinuation and Replacement

Subjects will be withdrawn from the study prematurely for the following reasons:

- Withdrawal of consent: Subjects have the right to withdraw from the study at any time for any reason.

- Protocol deviation of concern: The subject may be withdrawn by the investigator after discussion with the sponsor:

  – If protocol deviations that may affect study objectives occur, or

  – If it is discovered that the subject has entered the study in violation of the protocol.

- Adverse event: If a subject reports symptoms that are considered unacceptable by the investigator and/or sponsor, he or she will be withdrawn from the study.

- Subject dies.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator in both the source documents and electronic case report form (eCRF).

If a subject withdraws prematurely after dosing, the subject will be asked to return to the study center and will undergo all EOS (i.e., Day 71) assessments. All subjects who withdraw from the study because of an AE or clinical laboratory abnormality will be followed-up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure resolution or stabilization of the event. The subsequent outcomes of these events will be recorded in the both the source documents and eCRF.

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

For screen failed subjects, rescreen will be allowed only once after receiving informed consent form (ICF) again with new screening ID; however, subjects withdrawn (after randomization) will not be replaced.

4.4 Premature Termination of the Clinical Trial

The sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is terminated prematurely by the sponsor, all subjects will be kept fully informed and an appropriate follow-up examination of the subjects will be arranged. The investigator will inform the institutional review board (IRB) of any premature termination or suspension of the study, where applicable.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Arms

An interactive voice response system (IVRS) or an interactive web response system (IWRS) will be used for the randomization. Enrolled 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. Randomization numbers will be assigned before administration of the study drug on Day -1. As it is known that the body weight and gender are potential impact factors on pharmacokinetic profile, 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, considering that it is a multi-center study.

5.2 Treatment Administered

On Day 1, subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to one of three treatment arms according to the randomization scheme. The treatments arms are as follows:

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

All subjects will fast overnight (nothing to eat or drink except water) for at least 8 hours prior to study drug administration. Subjects will remain fasted for 4 hours after study drug administration. Water is permitted as desired except for the period 1 hour before and 1 hour after study drug administration.

The study drug will be administered on the subject's lower abdomen except for the 5 cm around the subject's navel. Immediately after the study drug administration, a cotton ball or gauze pad will be pressed over the injection site and held it for 10 seconds without rubbing. The time of dose administration will be called "0" hour.

5.3 Identity of Investigational Products

The study drugs that will be used in this study are outlined in Table 5-1.

Table 5-1 Identity of Study Drugs

Product	Supplied as:
CT-P17	Pre-filled syringe containing 100 mg/mL (40 mg/0.4 mL) of CT-P17
US-licensed Humira	Pre-filled syringe containing 100 mg/mL (40 mg/0.4 mL) adalimumab
EU-approved Humira	Pre-filled syringe containing 100 mg/mL (40 mg/0.4 mL) adalimumab

Dosing instruction described in the Humira prescribing information will be followed (*Humira USPI 2018*, *Humira SmPC 2018*).

CT-P17, containing the active ingredient adalimumab, is a recombinant humanized monoclonal antibody that is being developed as a similar biological medicinal product to the reference product, Humira.

The company code of the product is CT-P17. The International Nonproprietary Name of the commercially available reference product (Humira) is adalimumab and the Anatomical Therapeutic Chemical Classification System code is L04AB04. CT-P17 is a full-length IgG1 kappa isotype antibody with a total molecular weight of 148 kDa.

The reference products, US-licensed Humira and EU-approved Humira, are supplied as a sterile, preservative-free solution of adalimumab for SC administration. Humira is a clear and colorless solution, with a pH of approximately 5.2 (*Humira USPI 2018*, *Humira SmPC 2018*).

CELLTRION, Inc. will provide adequate supplies of CT-P17 and Humira for distribution to the study centers.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging, Labeling, and Storage

CELLTRION, Inc. will provide the investigator and study centers with adequate quantities of CT-P17, US-licensed Humira, and EU-approved Humira. A label will be attached to the outside of each subject kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Subject number/study center number

- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator's name
- Storage instructions
- Caution statement (for study use only)
- CELLTRION, Inc.'s contact name and address
- Expiry date

All study drug supplies will be stored in a secured area (e.g., a locked cabinet), protected from light. CT-P17, US-licensed Humira, and EU-approved Humira must be kept at a controlled refrigerated temperature between 2°C and 8°C and it will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study drug from light. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

5.4.2 Study Drug Accountability, Dispensing and Destruction

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen will also be recorded.

The investigator agrees not to supply the study drug to any person other than sub-investigators, designated staff, and the subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects unless approved by CELLTRION, Inc.

During the study, unused study drug syringes should be returned to the depot of origin. Accountability of the product must be completed at the site level and discrepancies, if any, need to be resolved prior to return. Only if it is written in SOPs or documentation in place, the used syringes can be destroyed locally. The list of destroyed syringes must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc.

Details in study drugs accountability and destruction will be followed according to the pharmacy manual.

5.5 Treatment Compliance

Study drug will be administered at the study center and a designated personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug administration and the completion of dosing will be recorded in both the source documents and eCRF. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.6 Blinding

The study will be performed in a double-blind manner.

The randomization codes will not be revealed to study subjects, investigators, or study center personnel.

5.6.1 Breaking the Blind

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 or IVRS (see study manual, which is provided as a separate document).

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 or IVRS to the medical monitor and/or the sponsor. Any subjects for whom the blind is broken may continue in the study. [redacted] pharmacovigilance (PVG) 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.

5.7 Prior, Concomitant, and Prohibited Medications

Information (e.g., drug name, date[s] of administration, etc) about prior medications taken by the subject within 30 days before he or she signs the ICF (inclusive of the applicable periods for prohibited medications as defined in Section 4.2) will be recorded in both the source documents and eCRF.

Concomitant medication use will be recorded 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 biologic agent (including but not limited to TNF- α blockers)
- Any other investigational drug except for the study drug used during this study
- Live or live-attenuated vaccine during the study and 6 months after the study drug administration (Day 1).
- OTC medications, prescription medications (excluding hormonal birth control), dietary supplements, or herbal remedies excluding the premedications or treatment of AEs.

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

5.8 Subject Restrictions During the Study

5.8.1 Food, Fluid, and Activity

- Alcohol consumption will be avoided from 24 hours before any study visit and while subjects are confined to the study center. Subjects will abstain from alcohol-containing products for 24 hours prior to each PK sample time point. Subjects may undergo an alcohol breath test at the discretion of the investigator. Subjects will not exceed an alcohol consumption of 7 units per week during the study from time of signing the ICF through the EOS visit. One unit is equivalent to a half-pint (285 mL) of beer/lager, one measure (25 mL) of spirits, or one small glass (125 mL) of wine.
- Subjects will not be permitted to drink caffeine-containing products (e.g., coffee, black tea, cola) or use caffeine or xanthine-containing products for 48 hours prior to the

administration of the study drug and 24 hours prior to each PK sample time point. Subjects will not be permitted to use nicotine-containing products up to 24 hours after the study drug administration. At all times during the study, subjects will not consume more than 10 cigarettes per day (24 hours), or equivalent.

- Strenuous activity (e.g., heavy lifting, weight training, calisthenics, and aerobics) is prohibited from 72 hours prior to Day -1 and 72 hours prior to each PK sample time point. Mild physical activity may be resumed after Day 7.

- All subjects will fast (nothing to eat or drink except water) for at least 8 hours prior to study drug administration (Day 1). Subjects will remain fasted for 4 hours after study drug administration. Water is permitted as desired except for the period 1 hour before and 1 hour after study drug administration. No outside food or drink is permitted at the study center. All meals and snacks while the subjects are confined will be provided by the study center.

5.8.2 Contraception

- Subject and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 5 months after the administration of assigned treatment. Examples include the following:

    - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation

    - Intrauterine devices

    - True abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

- A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active. Male and female subjects and their partners who have been surgically sterilized for less than 24 weeks prior to the date of informed consent must agree to use any medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential.

- Male subjects are not permitted to donate sperm or father a child within 5 months after administration of study drug.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign and date an ICF. The investigator will address all questions raised by the subject before the subject signs the ICF. The investigator will also sign and date the ICF. Subjects will undergo study procedures at the time points specified in the schedule of assessments (Table 10-1).

6.1 Pharmacokinetic Assessments

Blood samples for PK assessments of CT-P17 and adalimumab will be collected from all subjects at the time points specified in the schedule of assessments (Table 10-1). Analysis of the samples will be performed at the central laboratory.

The following serum PK parameters will be calculated for CT-P17 and adalimumab using actual sampling times rather than scheduled sampling times.

Primary endpoints:

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

Secondary endpoints:

- Area under the concentration-time curve extrapolated from time zero to infinity as a percentage of total AUC ($\%AUC_{extrap}$)
- 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)

6.2 Safety Assessments

Safety assessments will be performed on AEs (including serious AEs [SAEs]), AEs of special interest (AESI) (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), immunogenicity, hypersensitivity/allergic reaction assessments by additional ECG and vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), vital sign and weight measurement, ECG, physical examination, IGRA, chest X-ray, pregnancy testing, clinical laboratory testing (including hematology, chemistry, and urinalysis), local site pain using 100 mm VAS, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, HIV status and syphilis will be tested for the subject's eligibility determination.

6.2.1 Adverse Events

6.2.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

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.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

Medical interventions such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as

treatment(s) of the AEs. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.2.1.1.1 Adverse Events of Special Interest

The following AESIs will be reported using the same process as for AEs:

Injection site reactions

Injection site reactions will be observed after study drug administration and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AEs related to injection site reaction including erythema, itching, hemorrhage, pain, and swelling will be reported.

Hypersensitivity/allergic reactions

All AEs related to hypersensitivity and allergic reactions occurring within 24 hours after the study drug administration will be reported.

Infection

All AEs related to infection including TB, sepsis, and other opportunistic infections will be reported.

Malignancy

All AEs related to malignancy including but not limited to the following: hepatosplenic T-cell lymphoma, leukemia, lymphoma, melanoma, and Merkel cell carcinoma.

6.2.1.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- 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.

6.2.1.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., IB) for an unapproved investigational product or the label (e.g., package insert, SmPC, or prescribing information) for an approved product. Assessment of expectedness will be made with the use of the IB and the SmPC. Therefore, if a treatment-related SAE occurs and it was not mentioned in the applicable product information, then it will be reported as a SUSAR (Suspected Unexpected Serious Adverse Reaction).

6.2.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the ICF is signed and until the end of the subject's participation in the study. All AEs will be followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Adverse events of special interest (e.g., injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies) will be closely monitored.

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

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

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded in both the source documents and on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, action taken with study drug, investigator-specified assessment of

severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states will also be reported. Adverse events will be recorded according CTCAE v5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

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

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

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 6.2.1.5 and 6.2.1.6, respectively.

Adverse events (and SAEs) should be reported until the EOS visit regardless of the relationship to the study drug. After the EOS visit, serious adverse drug reactions will be reported to CELLTRION, Inc. or its designee.

6.2.1.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.2.1.1.2) must be reported to [redacted] PVG and the sponsor immediately (within 24 hours after the study center staff first notices about the event).

The following contact information is to be used for SAE reporting:

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax (or e-mail) it

to [redacted] PVG within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the subject is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be faxed (or e-mailed) to [redacted] PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or sub-investigator.

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

CELLTRION, Inc. or its designee is responsible for reporting fatal or life-threatening SUSARs, (expedited reports) to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

Adverse events associated with hospitalization or prolongations of hospitalization are considered as SAEs. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a TB unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)

- Hospitalization for observation without a medical AE
- Hospitalization purely for convenience (e.g., for easier performance of study assessments)
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual subject

6.2.1.5 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The severity of the AE will be graded based on the CTCAE v5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance)

Grade 2: Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])

Grade 3: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, or sepsis; life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy, or operation)

Grade 5: Death related to AE

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an AE upgrades in severity or, changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in severity, it should not be reported as a new AE. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.1.6 Assessment of Causality

As discussed in Section 6.2.1.3, the investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not

reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P17 or Humira in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.2.2 Other Safety Assessments

6.2.2.1 Immunogenicity Assessment

Immunogenicity of CT-P17, US-licensed Humira, and EU-approved Humira will be assessed at the time points indicated in the schedule of assessments (Table 10-1).

The immunogenicity of CT-P17 and reference drugs will be assessed at baseline and post-treatment serum measures by a validated immunoassay.

Samples will be drawn before dosing of study drug, at the same time as the clinical laboratory tests, where applicable. If the blood sample was unable to be analyzed or was missing, some blood samples collected for PK assessment at the same time point could be used for

immunogenicity assessment. Analysis of the samples will be performed at the central laboratory.

6.2.2.2 Injection Site Reaction

Injection site reactions will be assessed 30 minutes (±10 minutes) after study drug administration, as specified in the schedule of assessments (Table 10-1).

Details will be recorded in both the source documents and the eCRF.

6.2.2.3 Hypersensitivity/Allergic Reactions Monitoring

Hypersensitivity/allergic reactions will be assessed by additional ECG and vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), to monitor for possible hypersensitivity/allergic reactions, at the time points indicated in the schedule of assessments (Table 10-1).

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.

6.2.2.4 Vital Signs, Weight, and Height

Vital signs will be measured at the time points indicated in the schedule of assessments (Table 10-1). The following vital signs will be measured: systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C). Blood pressure and heart rate measurements will be performed after the subject has been resting for at least 5 minutes. All measurements will be documented at each visit. Details will be recorded in both the source documents and the eCRF.

Vital sign measurements will also be monitored before and after study drug administration as part of the hypersensitivity monitoring (Section 6.2.2.2).

Body weight and height will be measured according to the schedule of assessments (Table 10-1).

6.2.2.5 Electrocardiogram

Single 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes at the time points indicated in the schedule of assessments (Table 10-1).

Electrocardiograms for hypersensitivity 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. Either 3-lead or 12-lead ECGs can be used for hypersensitivity monitoring. If, following ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the subject will be referred to a cardiologist and the event will be recorded in the source documents and the eCRF. Regardless of the ECG result, further evaluation with a cardiologist can be performed depending on the investigator's discretion.

6.2.2.6 Physical Examinations

A standard physical examination will be performed at the time points indicated in the schedule of assessments (Table 10-1).

The physical examination includes an assessment of general appearance and a review of systems. Investigators will evaluate subjects for any indication of infections and injection site reactions in accordance with the investigator's medical judgment.

Information about the physical examinations will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents and eCRF.

6.2.2.7 Tuberculosis Assessments

At Screening, subjects with active TB, latent TB (defined as a positive result for IGRA with no active lesion in examination of chest X-ray without any sign or symptom of TB), a history of TB, or had close contact with a person with active TB within 8 weeks prior to administration of the study drug (Day 1) will not be enrolled in the study.

Subjects will be monitored for the clinical signs and symptoms of TB throughout the study and until the EOS, as specified in the schedule of assessments (Table 10-1); IGRA and chest X-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.

6.2.2.7.1 Chest X-ray

A chest X-ray (both posterior–anterior and lateral views) will be performed at Screening as indicated in the schedule of assessments (Table 10-1). The results will be read by a qualified radiologist to specifically look for evidence of current or previous active or latent TB. The findings will be recorded in both the source documents and eCRF.

Radiographic findings suggestive of healed TB or active TB may include, but are not limited to, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations, and pleural effusions. The chest X-ray will be available to the investigator for review and any abnormal findings will be discussed with the medical monitor and sponsor before the administration of the study drug (Day 1).

6.2.2.7.2 Interferon-γ Release Assay

An IGRA will be performed at Screening and at the EOS indicated in the schedule of assessments (Table 10-1).

If the result of IGRA is indeterminate at Screening, retest will be allowed only once during the Screening period. If the repeated IGRA result is again indeterminate or positive, the subject will be excluded from the study. If the repeated IGRA result is negative, the subject may be included in the study.

If the result of the IGRA is indeterminate after administration of the study drug, one retest will be possible. If the repeated IGRA test result is again indeterminate, the investigator will discuss and agree with the sponsor or its designee the next action to be taken.

If the result of the IGRA is positive during the study, subjects will be referred to the clinicians immediately to be investigated for the presence of active TB based on medical history and any clinical signs and symptoms including chest X-ray result.

The analysis will be performed at the local laboratory.

6.2.2.8 Pregnancy

A serum pregnancy test (β-human chorionic gonadotropin) will be performed on women of childbearing potential at Screening and EOS, as indicated in the schedule of assessments (Table 10-1). A urine pregnancy test will be performed on women of childbearing potential on Day -1. Only subjects with negative results for both serum pregnancy test at Screening and urine pregnancy test on Day -1 can be enrolled in the study.

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

In an event of unexpected pregnancy during study participation and for 5 months after administration of the study drug, the subjects will be counselled to inform the investigator. If a female subject or the partner of a male subject becomes pregnant, the pregnancy must be

reported to CELLTRION, Inc. and [redacted] PVG within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. The study center must complete the supplied pregnancy form (female subject or partner of a male subject) and return it to CELLTRION, Inc. and [redacted] PVG within 24 hours after acquisition of the consent for the pregnancy form.

Pregnant subjects or the pregnant partners of male subjects will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. Pregnancy alone will not be regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be handled as AEs, unless they are therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered as SAE. Any SAE that occurs during pregnancy (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.2.1.4).

6.2.3 Hepatitis B, Hepatitis C, Human Immunodeficiency Virus and Nontreponemal Test

At Screening, HBsAg, HBsAb, and HBcAb (total or IgG) will be assessed in all subjects (mandatory) as specified in the Table 6-1. If a subject has HBsAg negative, HBsAb negative or positive, and HBcAb (IgG or total) positive, a hepatitis B virus (HBV) DNA test will be performed at Screening and its result will be used to determine the eligibility.

Table 6-1 Eligibility Based on Serology Markers for Hepatitis B Infection

Test results				Eligibility
HBsAg	**HBsAb**	**HBcAb**	**HBV DNA**	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
			-	Eligible
–	+/–	–	Not applicable	Eligible

Abbreviations: HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

As specified in Table 6-1, the subject enrollment will be based on the test results.

Hepatitis C antibody (HCAb) test, HIV (HIV-1 and HIV-2) tests and nontreponemal test will be performed at Screening in all subjects (mandatory). If any of those test results is positive, the subject will be excluded from the study.

6.2.4 Clinical Laboratory Testing

Blood and urine samples for clinical laboratory assessments will be collected at the time points indicated in the schedule of assessments (Table 10-1) and will be prepared using standard procedures. The analysis will be performed at the local laboratory.

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], C-reactive protein , 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
Serology:	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, hepatitis C antibody (HCAb), nontreponemal (e.g., Rapid Plasma Reagin) tests
Urine drug, alcohol, and nicotine:	Tetrahydrocannabinol (THC) (or other metabolite to screen cannabis), opiates (OPI), cocaine (COC), methamphetamine (MET), barbiturates (BAR), and benzodiazepines (BZO). The history of drug abuse, alcohol and nicotine will be checked by medical history taking by the Investigator during the Screening period and Baseline (Day -1).

Creatinine clearance will be calculated using serum creatinine level only at screening for inclusion. The result will be considered for inclusion by the discretion of the investigator, and it will be recorded on source document and eCRF.

Any value outside the normal range will be flagged for the attention of the investigator or the sponsor at the study center. The investigator will indicate whether or not the value is clinically significant. If the result of the screening is indicated as clinically significant abnormal value, the subject will NOT be allowed into the study without permission of the sponsor. However, retest is permitted only once during screening period by the Investigator's judgment. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality defined as per Section 6.2.1 is found in the samples taken after dosing, during the study, and/or at the EOS visit, it should be recorded as an AE and the study subject will be followed up until the test(s) has (have) normalized or stabilized.

6.2.5 Local Site Pain

Local site pain will be assessed using 100 mm VAS immediately (within 15 minutes) after study drug administration (Day 1) according to the schedule of assessments (Table 10-1). Subjects will be asked to indicate their current level of pain intensity by drawing a single vertical line (|) on the 100 mm line (Appendix 10.2).

6.3 Sample Collections, Storage and Shipment

6.3.1 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

6.3.1.1 Pharmacokinetic Sampling

Blood will be collected per blood sampling time points for PK assessment sample at the time points specified in the schedule of assessments (Table 10-1). All samples will be collected as close as possible to the scheduled time point, and the actual sampling time will be recorded. Explanation will be provided in the eCRF for missed or mishandled samples and for samples collected outside the specified time windows.

Samples should be stored and shipped as detailed in the laboratory manual.

6.3.1.2 Interferon-γ Release Assay

Blood samples for IGRA will be obtained at the time points specified in the schedule of assessments (Table 10-1).

6.3.1.3 Clinical Laboratory Testing

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Table 10-1).

An additional blood for hepatitis B and C, HIV (HIV-1, HIV-2) and nontreponemal tests will also be required at Screening. A serum pregnancy test sample will be required at Screening and at the EOS visit for women of childbearing potential who have not been surgically sterilized.

6.3.1.4 Immunogenicity Sampling

Blood samples for immunogenicity assessments will be obtained at the time points specified in the schedule of assessments (Table 10-1).

Samples should be stored and shipped as detailed in the laboratory manual.

6.4 Labeling, Storage, and Transportation of Samples

6.4.1 Sample Labeling

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

6.4.2 Sample Storage and Shipment

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

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK and immunogenicity should be retained at the central laboratory as a backup for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK and immunogenicity is not required, the samples will be stored at CELLTRION, Inc. or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by CELLTRION, Inc. to destroy the sample. Additional tests can be conducted at CELLTRION, Inc. or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Analysis Plan

The statistical analysis will be performed using [redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized before locking of the database. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final clinical study report (CSR).

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum).

7.1 Study Population

7.1.1 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented by treatment arm.

The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.1.2 Protocol Deviations

Deviations from the protocol, including deviations of inclusion/exclusion criteria, will be defined as “minor” or “major” before overall code breaking.

7.1.3 Analysis Populations

Intent-to-treat (ITT) Population: The 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.

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.

Pharmacokinetic Population: The PK population will include subjects who receive a complete dose of study drug and provide at least 1 post-treatment serum concentration with a concentration above the lower limit of quantification. Subjects in the PK population will be analyzed according to the treatment they received.

Safety Population: The safety population will include all randomized subjects who receive a complete or partial dose of study drug. Subjects will be assigned to treatment arms based on treatment actually received.

7.2 Pharmacokinetic Analyses

All PK analyses will be conducted based on the PK population. The primary and secondary PK parameters of CT-P17 and adalimumab will be analyzed using non-compartmental methods based on the actual sampling time points. All parameters will be calculated using [redacted]

7.2.1 Primary Pharmacokinetic Analyses

The primary PK parameters, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}, will be presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects, mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV). Additionally, primary PK parameters will be summarized by treatment and anti-drug antibody status.

For primary endpoints, 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 with treatment as a fixed effect and body weight (≥80 kg vs. <80 kg) 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 ratios of geometric means of each comparison are entirely contained within 80% to 125% for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}.

7.2.2 Secondary Pharmacokinetic Analyses

Serum concentration data will be presented in data listings and summarized by time point for each treatment using the following descriptive statistics: number of subjects, mean, SD, median, minimum, maximum, geometric mean, and CV.

The secondary PK parameters, $\%AUC_{extrap}$, T_{max}, V_z/F, λ_z, $t_{1/2}$, and CL/F, will be also presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects, mean, SD, median, minimum, maximum, geometric mean, and CV.

Additional PK analyses may be performed as detailed in the SAP.

7.3 Safety Analyses

7.3.1 Demographic, Baseline, and Background Characteristics

Baseline demographic and background variables will be summarized by treatment arm using the ITT population.

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

7.3.2 Adverse Events

Adverse events will be recorded according to the CTCAE v5.0 and will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. A TEAE is defined as described in Section 6.2.1.1. The following AE summaries will be reported by SOC, PT, and treatment arm, as appropriate:

- Number and percentage of subjects reporting at least 1 TEAE
- Number and percentage of subjects reporting at least 1 treatment-emergent SAE
- Number and percentage of subjects discontinuing the study drug due to a TEAE
- Number and percentage of subjects with AESIs (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies)

All AE data will be presented in the data listings, and additional TEAE analyses may be performed as detailed in the SAP.

7.3.3 Immunogenicity Analysis

Immunogenicity test results will be summarized by treatment arm and presented in a data listing.

7.3.4 Clinical Laboratory Test

Actual values and changes from Baseline for clinical laboratory test results will be summarized by treatment arm at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results.

Individual clinical laboratory test results will be presented in data listings.

7.3.5 Electrocardiogram, Physical Examination, and Vital Signs

Actual values and change from Baseline for vital sign measurements will be summarized by treatment arm at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

Shift tables comparing the categorical investigator interpretation of 12-lead ECGs and physical examinations at each scheduled post-baseline time point with those at Baseline will be summarized by treatment arm.

Individual 12-lead ECG results and the investigator's interpretation, physical examination findings, and vital sign measurements (including hypersensitivity monitoring) will be presented in data listings.

7.3.6 Tuberculosis Assessments

Results from TB screening and monitoring will be summarized by treatment arm and presented in data listings.

7.3.7 Local Site Pain

Individual local site pain (VAS) results will be summarized by treatment arm after the study drug administration using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

Individual local site pain (VAS) results will be presented in a data listing.

7.3.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD). All prior and concomitant medications data will be listed and summarized by treatment arm as appropriate.

7.4 Sample Size Calculations

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 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.

7.5 Interim Analyses

No formal interim analyses will be performed in this study.

7.6 Data Quality Assurance

This study will be conducted according to the ICH E6 (R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice guidelines on quality and risk management.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff before the study, periodic monitoring visits by CELLTRION, Inc. or its designee, and direct transmission of data from a central laboratory into the clinical database. The eCRFs will be reviewed for accuracy and completeness by the monitor during on-site monitoring visits and after their return to CELLTRION, Inc. or its designee; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from CELLTRION, Inc. or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for

inspection and comparison with the eCRF. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should immediately notify CELLTRION, Inc. or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authority(ies), or the IRB.

The investigator, all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Institutional Review Board

Regulatory authority regulations and the ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6 (R2): Good Clinical Practice guidelines will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals will be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.3 Subject Information and Consent

Written informed consent in compliance with local regulatory authority requirements shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent will be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign and date the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject.

8.4 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under local regulations. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

8.5 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 (R2) 8.2 and local regulations by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,

- Curriculum vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current,

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under local regulations. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,

- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians, and

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with local regulations.

8.6 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6 (R2): Good Clinical Practice, the protocol, and all national, state, and local laws or regulations.

8.7 Data Collection

8.7.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain source documentation (e.g., laboratory reports), enter subject data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc.

The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

The eCRFs are accessed through the appropriate system, which allows for on-site data entry and data management. Study center users can read from and write to the sponsor’s database

where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon and password that allow for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

8.8 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R2) and all applicable guidelines and regulations.

8.9 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. If required by applicable local regulations, the investigator shall promptly notify the relevant IRB (in addition to the sponsor) of any SAE (including follow-up SAEs) and SUSARs that occurred at his/her site. He/she shall verify that the IRB acknowledges receipt of the information. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

8.10 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, will inform the institution; the investigator/institution will provide the IRB with a summary of the study's outcome, and the sponsor and regulatory authority(ies) with any reports required.

8.11 Records Retention

All correspondence (e.g., with sponsor, IRB, or clinical research associates) relating to this clinical study will be kept in appropriate file folders. Records of subjects, source documents, eCRFs, and drug inventory sheets pertaining to the study must be kept on file.

Essential documents will be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the

sponsor. It is the sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer is recommended to be made and agreed upon by the sponsor.

8.12 Subject Identification Register

The investigator agrees to complete a subject identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed by the investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify subjects by assigned number only.

8.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and may work with the investigators to determine how the manuscript is written and edited, the number and order of authors based on SOPs of CELLTRON, Inc., the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9 Study Management

9.1 Monitoring

9.1.1 Data and Safety Monitoring Board

An independent data and safety monitoring board will not be used for this study.

9.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6 (R2) guidelines and SOPs.

9.1.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or regulatory agency access to all study records.

The investigator will promptly notify the sponsor and study center(s) of any audits scheduled by any regulatory authorities.

9.2 Management of Protocol Amendments and Deviations

9.2.1 Modification of the Protocol

Before the beginning of the study, the clinical study protocol and other relevant documents will be approved by the IRB, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol must be followed exactly. To change the protocol, amendments must be written, which must be released by the responsible staff and receive IRB approval prior to implementation as appropriate.

9.2.2 Protocol Deviations

The investigator or designee will document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant and additional risk to the subject's rights, safety and well-being. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to a regulatory agency's regulations or ICH Good Clinical Practice guidelines, and will lead to the subject being withdrawn from the study (Section 4.3).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB will be notified of all protocol deviations, if appropriate, in a timely manner.

9.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the final database is locked.

9.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that one CSR will be prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

10 Appendices

10.1 Appendix: Schedule of Assessments

Table 10-1 Schedule of Assessments

	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), **Clinical 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:

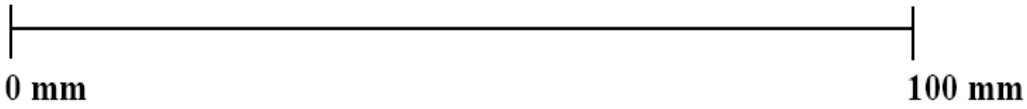
PK sampling time points
Day 1 Pre-dose (within 60 minutes prior to administration of the study drug)
Day 1 (6 hours after the administration of the study drug); ±15 minutes
Day 1 (12 hours after the administration of the study drug); ±1 hour
Day 2 (24 hours after the administration of the study drug);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

10.2 Appendix: VAS Subject's Assessment of Pain

Subject assessment of local site pain is measured by the subject indicating the extent of their pain by marking one line (|) through the 100 mm line (0 mm equals no pain and 100 mm equals most severe pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the subject's eCRF.



No pain Most severe pain

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