CLINICAL STUDY PROTOCOL

A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of CT-P17 with Humira when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis

Protocol Number CT-P17 3.1

EudraCT Number: 2018-001690-25

Sponsor: [redacted]

Sponsor Contact: [redacted]

SAE Reporting and Data Centre: [redacted]

Version and Date of Protocol: Protocol Version 3.0, 06 Aug 2018

Protocol Approval

Study Title	A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of CT-P17 with Humira when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis
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Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of CT-P17 with Humira when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis" 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 3.0, dated 06 Aug 2018, 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 independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients 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. Patient 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 3.1

Title: A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of CT-P17 with Humira when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis

Study Phase: Phase 3

Study Centers: Approximately 60 study centers in approximately 8 countries

Test Drug, Dose and Regimen: CT-P17, 40 mg (100 mg/mL) by subcutaneous (SC) injection via pre-filled syringe (PFS) every other week (EOW), co-administered with methotrexate (MTX) between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral dose (dose and route must be maintained from beginning to end of the study) and folic acid (≥5 mg/week, oral dose)

Reference Drug, Dose and Regimen: EU-approved Humira, 40 mg (100 mg/mL) by SC injection via PFS EOW, co-administered with MTX between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral dose (dose and route must be maintained from beginning to end of the study) and folic acid (≥5 mg/week, oral dose)

Objectives:

Primary Objective

- To demonstrate that CT-P17 is equivalent to Humira, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20) at Week 24.

Secondary Objectives

- To evaluate additional efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and overall safety, including immunogenicity and biomarker.

Main selection criteria: Male or female patient with moderate to severe active rheumatoid arthritis (RA) diagnosed according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (*Aletaha et al., 2010*), despite previous treatment with MTX over at least 12 weeks, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 75 years old, both inclusive.
2. Patient has had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (*Aletaha et al., 2010*) for at least 24 weeks prior to the first administration of the study drug (Day 1).
3. Patient who has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed), 6 or more tender joints (of 68 assessed) and either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a serum C-reactive protein (CRP) concentration >1.0 mg/dL (>10 mg/L) at Screening.
4. Patient who has been receiving oral or parenteral MTX at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and who has been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1).
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
    - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)

- Serum alanine aminotransferase ≤3.0 × ULN
- Serum aspartate aminotransferase ≤3.0 × ULN
- Serum total bilirubin ≤1.5 × ULN

6. Patient has the following hematology laboratory test results at Screening:
   - Hemoglobin >8.0 g/dL (SI units: >80 g/L or 4.96 mmol/L)
   - Absolute neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
   - Platelet count ≥75 × 10^3 cells/μL (SI units: ≥75 × 10^9 cells/L)
7. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, has the ability to cooperate with the investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form with date prior to participation in the study.
8. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 6 months after the last dose of assigned treatment. Examples include the following:
   - Hormonal contraceptives (combined or progestogen-only) associated with inhibition of ovulation.
   - Intrauterine devices.
   - Sexual abstinence (not periodically, but for the entire period of risk).

   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 patients 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.
9. Patient must be able and willing to self-administer SC injections or designate a qualified person(s) to administer SC injection.

Exclusion Criteria:

A patient meeting any of the following criteria will be excluded from the study:

1. Patient who has previously received investigational or licensed product; biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or a tumor necrosis factor (TNF) α inhibitor for any purposes.
2. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
3. Patient who currently has, or has a history of, any of the following infections:
   - A known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved.
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1)
   - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.

- Other serious infections within 24 weeks prior to the first administration of the study drug (Day 1)

4. Patient who currently has, or has a history of, any of the following tuberculosis (TB):
   - Patient who has a history of TB or a current diagnosis of TB. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.
   - Patient who has had exposure to a person with active TB such as first-degree family members or co-workers.
   - Patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest X-ray) at Screening. A patient who has a previous diagnosis of latent TB cannot be enrolled despite sufficient documentation of prophylaxis. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.
5. Patient who has a medical condition including one or more of the following:
   - Classified as Class II or III obese by WHO classification (body mass index [BMI] ≥35 kg/m^2)
   - Uncontrolled diabetes mellitus, even after insulin treatment
   - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)
   - Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, that may confound the evaluation of the effect of the study drug
   - Significant systemic RA involvement (e.g., Sjogren's syndrome, vasculitis, pulmonary fibrosis), which would put the patient at risk if they are enrolled
   - A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
   - New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 24 weeks prior to the first administration of the study drug (Day 1)
   - History of organ transplantation, including corneal graft/transplantation
   - Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion
   - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome
   - Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) if it could interfere with the investigator's assessment on disease activity scores including joint counts
   - Any other serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results
   - History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion
6. Patient who has received or plans to receive any of the following prohibited medications or treatment:

- Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and non-steroidal anti-inflammatory drug, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose must be maintained until the primary endpoint assessment at Week 24. In addition, a patient is permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.
- Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1)
- Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer
- Alkylating agents within 1 year prior to the first administration of the study drug (Day 1)
- Herbal products within 2 weeks prior to the first administration of the study drug (Day 1)
- Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1), or any planned live or live-attenuated vaccination during the study period
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1) or planned within 24 weeks after the first administration of the study drug (Day 1)

7. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV [*Hochberg et al., 1992*], or who cannot benefit from medication)
8. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed within 6 months of the last dose of study drug.
9. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 2 years from Screening.
10. Patient who, in the opinion of their general practitioner or the investigator, should not participate in the study.

Study Design:

This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, PD, overall safety including immunogenicity and biomarker of multiple single-dose (40 mg) of either CT-P17 or Humira administered by SC injection via PFS EOW in combination with MTX (between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral [intramuscular or SC] dose) and folic acid (≥5 mg/week, oral dose). The MTX dose and route must be maintained from beginning to end of the study. Approximately 564 male and female patients with moderate to severe active RA will be enrolled in a 1:1 ratio (approximately 282 patients per treatment group) into the CT-P17 or Humira treatment groups.

The randomization to treatment assignment will be stratified by the following:

- Country
- Disease activity by Simplified Disease Activity Index (SDAI) at Screening; high (SDAI >26) vs. not high (SDAI ≤26)

Patients will receive CT-P17 or Humira EOW up to Week 24. Prior to dosing at Week 26, patients in the Humira treatment group will be randomly assigned in a ratio of 1:1 to either continue Humira (Cohort 2) or

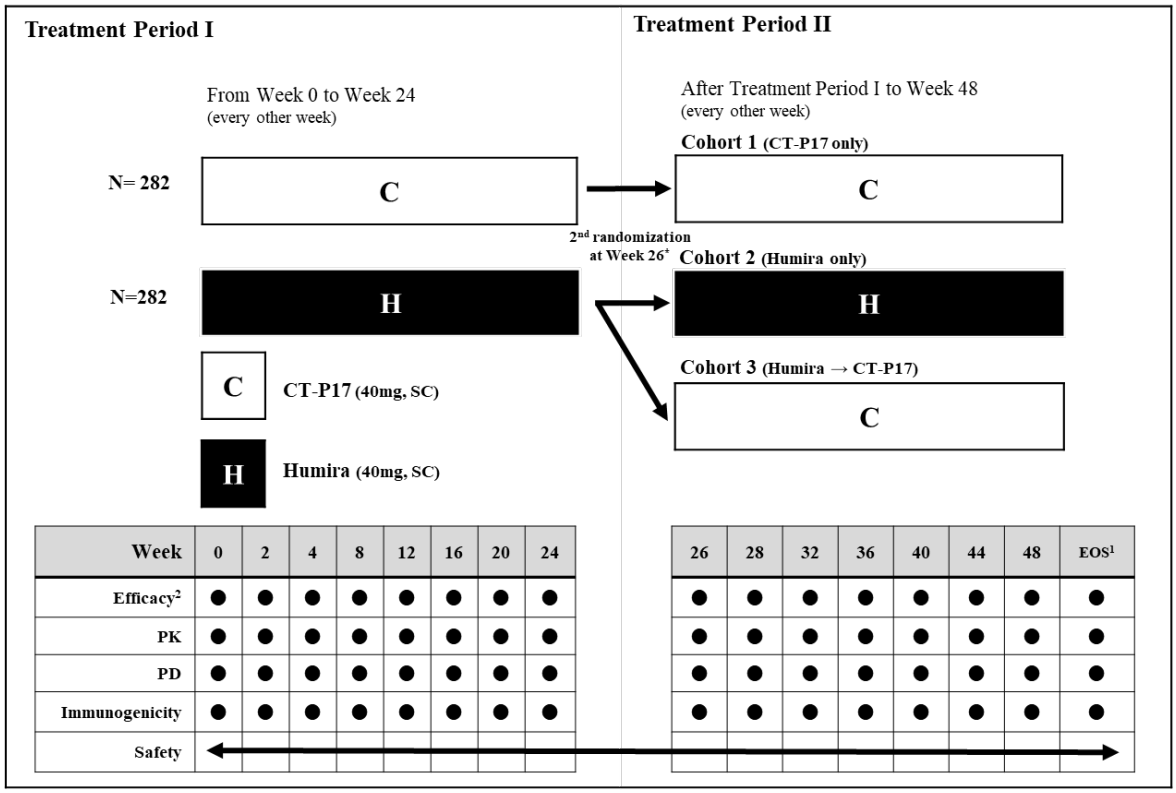
undergo transition to CT-P17 (Cohort 3) from Week 26. All patients who were initially randomly assigned to CT-P17 at Day 1 (Week 0) will continue their treatment with CT-P17 (Cohort 1) until the end of the study. Second randomization process will also be conducted in Cohort 1 at Week 26 to maintain the study blind.

The second randomization to Cohorts 2 or 3 will be stratified by the following:

- Disease activity by SDAI at Week 24; remission (SDAI ≤3.3) vs. non-remission (SDAI >3.3)

The study design and patient assessment overview is presented in Figure S1.

Figure S1 Study Design Overview



Abbreviations: C, CT-P17; EOS, end-of-study; EOW, every other week; H, Humira; N, number of patients; PK, pharmacokinetics; PD, pharmacodynamics; SC, subcutaneous.

* Prior to dosing at Week 26, all patients will undergo a second randomization process. Patients who were initially randomized to Humira will be randomized again in a ratio of 1:1 to either continue Humira or undergo transition to CT-P17. Patients who are randomized to CT-P17 or Humira will receive assigned study drug EOW from Week 26 and thereafter up to Week 48. Only the study center visit is presented in this figure.

[1] The EOS assessments will be performed at Week 52 for all patients who completed or discontinued study treatment. The patients who early discontinued from the study treatment will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiate RA medication changes (including those prohibited by the protocol).

[2] An independent joint count assessor assigned to each study center will assess joint counts. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period.

After database lock for data up to Week 24 for all patients, the study will be unblinded for reporting purposes and efficacy, PK, PD, immunogenicity, and safety endpoints will be evaluated by the pre-defined unblinded Sponsor and Contract Research Operation (CRO) teams. The investigators, patients, and other Sponsor and CRO teams will remain blinded until the end of the study.

Study Schedule: There will be 3 study periods in the study, which are the following: Screening Period, Treatment Period (I and II), and End-of-Study (EOS) visit.

Screening Period (Day –42 [6 weeks] to Day –1):
Screening will take place between Day –42 and Day –1 (6 weeks), prior to the first study drug administration.

Treatment Period (Week 0 to Week 48):

- Treatment Period I (from Week 0 to Week 24)
- Treatment Period II (after Treatment Period I and prior to EOS visit)

On Day 1, Week 0, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned to receive either CT-P17 or Humira prior to treatment. The patient will receive either CT-P17 or Humira, as per first and second randomization, by SC injection EOW, co-administered with MTX between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral dose (intramuscular [IM] or SC; dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose). Patients will comply with all appropriate visits and assessments.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. At each visit, the patient will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

End-of-Study (Week 52) visit:
An EOS visit will occur at Week 52 for all patients who completed or discontinued study treatment. The patients who early discontinued from the study treatment will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiate RA medication changes (including those prohibited by the protocol).

Efficacy Assessments:
Primary Endpoint

- Proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 24.

Secondary Endpoints
The following secondary efficacy endpoints will be assessed up to Week 52:

- ACR20 (except for Week 24), ACR50 and ACR70
- Individual components of the ACR
- Hybrid ACR response
- DAS28 (CRP) and DAS28 (ESR)
- Individual components of the DAS28
- EULAR response
- Simplified disease activity index (SDAI) and clinical disease activity index (CDAI)
- 36-item short form health survey (SF-36)

- Joint damage progression based on radiographic evaluations

Pharmacokinetic Assessment:

Secondary Endpoint

The following PK endpoint will be assessed up to Week 52:

- C_{trough} Trough concentration (concentration prior to the next study drug administration)

Pharmacodynamic Assessments:

Secondary Endpoints

The following PD endpoints will be assessed up to Week 52:

- CRP
- ESR
- Rheumatoid factor (RF)
- Anti-cyclic citrullinated peptide (anti-CCP)

Safety Assessments:

Safety assessments will be performed on AEs (including serious AEs), AEs of special interest (AESI) (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), immunogenicity, hypersensitivity monitoring (via monitoring of vital signs, includes BP, heart and respiratory rates, and body temperature), vital sign and weight measurement, ECGs, physical examination findings, IGRA, chest X-ray, hepatitis B and hepatitis C and HIV status, pregnancy testing, clinical laboratory analyses, local site pain by visual analogue scale (VAS), signs and symptoms of TB, and prior and concomitant medications monitored throughout the study. Adverse events will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Biomarker Assessments (Optional):

For patients who sign a separate informed consent form for the biomarker assessment, a blood sample for evaluation of genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected prior to dosing on Week 0.

Sample Size:

A sample size of 450 patients (225 patients in each treatment group of CT-P17 and Humira) leads to 83% statistical power for the demonstration of similarity of ACR20 at Week 24 based on the expected ACR20 rate of 64% with an equivalence margin of –15% to 15% using a two one-sided 2.5% significance level of an equivalence test. The drop-out rate has been hypothesized at 20%; therefore, approximately 564 patients (282 patients in each treatment group of CT-P17 and Humira) will be randomized.

Statistical Analysis:

[redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. The data documented in this study and the clinical parameters measured will be described using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables.

Efficacy Analysis

The proportion of patients achieving clinical response according to ACR20 criteria at Week 24 will be analyzed. The 95% confidence interval (CI) for the difference in proportion between the 2 treatment groups (CT-P17 and Humira) will be produced. Therapeutic equivalence of clinical response according to ACR20 criteria will be concluded if the 95% CIs for the treatment difference is entirely within –15% to 15% at Week 24. A sensitivity analysis considering covariates will also be performed.

The primary population of primary endpoint (ACR20 at Week 24) is intent-to-treat (ITT) population. All efficacy endpoints will be analyzed using the ITT and PP populations.

- ITT Population is defined as all patients enrolled and randomly assigned to receive a dose of either of the study drugs, regardless of whether or not any study drug dosing was completed. Patients will be assigned to treatment groups based on randomization.
- PP Population is defined as all randomly assigned patients who have received all doses of study drug up to Week 22 (total 12 injections) and have an ACR assessment at Week 24. A major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will be excluded from PP population. Final determinations of the PP population will be made at the blinded data review meeting (DRM) held in accordance with International Council for Harmonization (ICH) harmonised tripartite guideline E9. Patients will be assigned to treatment groups based on randomization.

Pharmacokinetic Analysis

The PK population will consist of all patients who receive at least 1 dose (full) of either of the study drugs and have at least 1 post treatment PK concentration data. The PK population will be the primary population for the summary of PK data. If any patients are found to be non-compliant with respect to dosing, a decision will be made on a case-by-case basis at the blinded DRM prior to code breaking.

Serum concentrations will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation [CV%], as appropriate). Pharmacokinetic parameter will also be summarized using quantitative descriptive statistics (including geometric mean and CV%, as appropriate).

Pharmacodynamic Analysis

The PD population will consist of all patients who receive at least 1 dose (full) of either of study drugs and have at least 1 post treatment PD result. The PD population will be the primary population for the summary of PD data. The PD endpoints (CRP, ESR, RF, and anti-CCP) will be summarized using descriptive statistics (including geometric mean and CV%, as appropriate).

Safety Analysis

The safety population will consist of all patients who receive at least 1 dose (full or partial) of either of the study drugs. Patients will be assigned to treatment groups based on treatment actually received. The safety population will be the primary population for the summary of safety data.

Adverse events will be recorded according to the CTCAE v5.0 and will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the WHO Drug Dictionary.

Biomarker Analysis

Analyses will be performed on genotypes (FcγRIIa, IIIa, and/or any necessary genotypes) in the ITT population.

List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement
ACR50	American College of Rheumatology 50% improvement
ACR70	American College of Rheumatology 70% improvement
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
AS	ankylosing spondylitis
BMI	body mass index
BP	blood pressure
CDAI	clinical disease activity index
CFR	Code of Federal Regulations
CI	confidence interval
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CV	curriculum vitae
CV%	coefficient of variation
DAS28	Disease Activity Score 28
DMARD(s)	disease-modifying antirheumatic drug(s)
DRM	data review meeting
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end-of-study
EOW	every other week
EPAR	European Public Assessment Report
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire

Abbreviation	Definition
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFU	instructions for use
IGRA	interferon-γ release assays
IM	intramuscular
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NRI	non-responder imputation
NSAID(s)	non-steroidal anti-inflammatory drug(s)
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
PVG	pharmacovigilance
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDAI	simplified disease activity index
SI	Système International d'Unités
SJC	swollen joint count
SOC	system organ class
SOPs	standard operating procedures

Abbreviation	Definition
SUSAR(s)	suspected unexpected serious adverse reaction(s)
TB	tuberculosis
TEAE(s)	treatment-emergent adverse event(s)
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WHO	World Health Organizations

1 Introduction

1.1 Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, occurring in approximately 0.8% of the global population (*Kim et al., 2007, Singh et al., 2015*). It is characterized by a progressive inflammatory synovitis of the joints, which may result in irreversible joint erosion within as early as 6 months of disease onset (*van der Heijde et al., 2010*). It has a significant negative impact on the ability to perform daily activities and health-related quality of life, and it increases mortality (*Singh et al., 2016*). Therefore, early identification and appropriate treatment should be the primary focus when managing patients with RA to reduce disease progression and loss of function.

Standard antirheumatic therapy for RA usually consists of traditional/conventional disease-modifying antirheumatic drug (DMARD), low dose corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics (*Furst et al., 2003*). Methotrexate (MTX), a DMARD, has been shown to improve the signs and symptoms of RA and slow the progression of joint destruction in some patients; however, many patients fail to achieve an adequate or sustained response to MTX therapy or even when the patients respond to MTX therapy, patients experience less than 50% improvement (*Weinblatt et al., 2003, Keystone et al., 2004, Kim et al., 2007*).

The proinflammatory cytokine tumor necrosis factor (TNF) α plays a critical role in the pathogenesis of RA and, as such, is a key target for directed biologic therapy (*Furst et al., 2003*). Among its diverse pathologic effects, TNFα induces the production of other proinflammatory cytokines; stimulates endothelial cells to express adhesion molecules that attract leukocytes into affected joints; increases the rate of synthesis of metalloproteinases by synovial macrophages, fibroblasts, osteoclasts, and chondrocytes; and inhibits the synthesis of proteoglycans in cartilage (*Weinblatt et al., 2003*). In recent years, TNF inhibitor biologic agents like adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab and non-TNF biologic agents like abatacept, rituximab, or tocilizumab have been developed for use in RA. Biological DMARDs, such as TNF inhibitors, are recommended when disease activity remains moderate or high despite DMARD monotherapy (*Singh et al., 2016*).

Adalimumab, a novel biologic DMARD and the first fully humanized anti-TNF-α monoclonal antibody for RA treatment, has been shown to be effective in the treatment of

RA. Adalimumab is structurally and functionally analogous to naturally occurring human immunoglobulin G1 and demonstrates a high specificity and affinity for TNF. It does not bind other cytokines such as lymphotoxin (*Keystone et al., 2004*). Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement (*Humira USPI 2017*). It is superior to MTX alone in reducing disease activity, arresting structural damage, and decreasing disability over 2 years in patients with RA (*Chen et al., 2009*).

1.2 CT-P17

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 European Union, Humira is indicated for the following conditions: RA, juvenile idiopathic arthritis, axial spondyloarthritis (ankylosing spondylitis [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, and uveitis; in the United States, Humira is indicated for the same conditions except axial spondyloarthritis without radiographic evidence of AS, pediatric uveitis and pediatric plaque psoriasis (*Humira USPI 2017*, *Humira SmPC 2018*).

The reference product, Humira, is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous (SC) administration (*Humira USPI 2017*). Humira is supplied in 2 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 that of Humira. Like Humira, CT-P17 will be supplied in a single syringe at a concentration of 100 mg/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 as Humira.

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

1.3 Pre-clinical Studies

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

1.4 Clinical Studies

The efficacy and safety of adalimumab in RA was assessed in 4 multicenter, randomized, double-blind pivotal Phase 3 studies.

The Safety Trial of Adalimumab in RA by *Furst et al (2003)* evaluated the safety and efficacy of adalimumab in 636 patients with RA, who were randomly assigned to receive adalimumab 40 mg SC every other week (EOW) or placebo while continuing standard antirheumatic therapy. The study demonstrated that addition of adalimumab 40 mg given SC EOW to concomitant standard antirheumatic therapy, including one or more traditional DMARDs, corticosteroids, NSAIDs, and/or analgesics, is well tolerated and provides significant improvements in signs and symptoms of RA. The results also indicated that adalimumab is a safe and effective therapeutic option in patients with active RA who have an inadequate response to standard antirheumatic therapy.

A similar study by *Weinblatt et al (2003)*, the ARMADA trial, showed that addition of adalimumab at a dose of 20 mg, 40 mg, or 80 mg administered subcutaneously EOW to long-term MTX therapy in patients with active RA provided significant, rapid, and sustained improvement in disease activity over 24 weeks compared with MTX plus placebo.

In the 52-week study of *Keystone et al (2004)*, 619 patients with active RA who had an inadequate response to MTX were randomly assigned to receive adalimumab 40 mg subcutaneously EOW, adalimumab 20 mg subcutaneously every week, or placebo plus concomitant MTX. The study demonstrated that adalimumab was more effective than placebo at inhibiting the progression of structural joint damage, reducing the signs and symptoms, and improving physical function in patients with active RA who had demonstrated an incomplete response to MTX.

Likewise, the efficacy and safety of monotherapy with adalimumab in patients with RA for whom previous DMARD treatment has failed was assessed in 544 patients in the study of *van de Putte et al (2004)*. The patients were randomized to monotherapy with adalimumab 20 mg EOW, 20 mg weekly, 40 mg EOW, 40 mg weekly, or placebo and the study showed that after 26 weeks, patients treated with adalimumab (any dose) had significantly better response rates and achieved better improvements in mean Disability Index of the Health Assessment Questionnaire than those treated with placebo. In addition, the study also found no significant differences between adalimumab and placebo treated patients for serious AE(SAE)s, serious infections, or malignancies.

1.5 Study Rationale

CT-P17 is currently being developed by CELLTRION, Inc., and is intended to be developed as a biosimilar to Humira. For a biosimilar to be approved, it must be shown that there are no clinically meaningful differences between the two products. The stepwise 'totality of evidence' approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis. However, statistically proven equivalence between biosimilar and reference product in both pharmacokinetics (PK) and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. Therefore, the PK profile of CT-P17, EU-approved Humira, and US-licensed Humira will be compared to demonstrate PK equivalence in a Phase 1 study in healthy volunteers. An additional assessment of the similarity in efficacy, PK, safety, and immunogenicity will be carried out in this proposed comparative clinical trial (Study CT-P17 3.1) in patients with moderate to severe active rheumatoid arthritis. CELLTRION, Inc. considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence of CT-P17 (Study CT-P17 1.1 PK similarity healthy volunteer study) and therapeutic equivalence and safety (Study CT-P17 3.1 comparative clinical similarity) to the reference product. In addition, the pilot study (Study CT-P17 1.2) will be conducted to evaluate safety to provide the first human data of CT-P17 in comparison to adalimumab.

1.5.1 Choice of Study Population

International regulations (*WHO 2009*, *EMA 2010*, *FDA 2015*) suggest that proposed biosimilars should be tested in a population representative of approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the biosimilar and the reference product.

Consequently, RA has been selected as indication for the comparative clinical trial, due to the relatively high magnitude of the treatment effect and immunogenicity rates observed in the Humira clinical studies in this indication; thus, facilitating the detection of potential differences between CT-P17 and the Humira.

The study population in the proposed Study CT-P17 3.1 was selected in order to be a representative of the original placebo controlled studies supporting the development of the reference product and to align with the indications approved for the reference product.

1.6 Benefit and Risk Assessment

The CT-P17 drug product will have the same pharmaceutical form and strength as the EU-approved Humira (40 mg/0.4 mL). The proposed dosing regimen is in line with the approved labeling for Humira (*Humira USPI 2017*, *Humira SmPC 2018*).

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P17 administration. In view of the structural, biological, and toxicological similarity to Humira, CT-P17 is expected to display a similar safety profile. Humira has been studied extensively and has been shown to be effective at reducing symptoms in patients with inflammatory conditions (*EMA EPAR for Humira 2017*, *Humira USPI 2017*).

Based upon the clinical evidence (Section 1.4) as well as the proven safety profile of Humira, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

2 Study Objectives

2.1 Primary Objective

- To demonstrate that CT-P17 is equivalent to Humira, in terms of efficacy as determined by clinical response according to the ACR definition of a 20% improvement (ACR20) at Week 24.

2.2 Secondary Objectives

- To evaluate additional efficacy, PK, pharmacodynamics (PD), and overall safety, including immunogenicity and biomarker.

3 Investigational Plan

3.1 Study Design

This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, PD, and overall safety including immunogenicity and biomarker of multiple single-dose (40 mg) of either CT-P17 or Humira administered by SC injection via pre-filled syringe (PFS) EOW in combination with MTX between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral (intramuscular [IM] or SC) dose (dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose).

Approximately 564 male and female patients with moderate to severe active RA will be enrolled in a 1:1 ratio (approximately 282 patients per treatment group) into the CT-P17 or Humira treatment groups.

The duration of the study will be up to 58 weeks, which includes Screening (up to 6 weeks) and the last dose at 48 weeks plus the following 4 weeks off-dose period, prior to the End-of-Study (EOS) visit.

3.2 Study Overview

The study will comprise 3 study periods including Screening Period, Treatment Period (I and II), and EOS visit.

Screening Period **(Day –42 to Day –1)**:

Screening will take place between Days –42 and Day –1 (6 weeks), prior to the first study drug administration.

Treatment Period **(Week 0 to Week 48)**:

- Treatment Period I (from Week 0 to Week 24)
- Treatment Period II (after Treatment Period I and prior to EOS visit)

On Day 1 (Week 0), patients who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned to receive either CT-P17 or

Humira prior to treatment. The patient will receive either CT-P17 or Humira, as per first and second randomization, by SC injection EOW, co-administered with MTX between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral dose (dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose). Patients will comply with all appropriate visits and assessments that will be performed at the time points specified in the schedule of events (Table 11-1).

The study drug will be administered by the trained study center staff at Week 0, Week 2, and Week 4 or until the patient or caregiver is properly trained and confident to administer the study drug at home or the investigator considers patient self-injection or injection by caregiver is appropriate (see Section 5.2.3 for details). After Week 4, patients can self-inject the study drug at home also during their study center visits, under the investigator or designated study center staff's supervision or it can be administered by the caregiver, if needed.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. At each visit, the patient will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

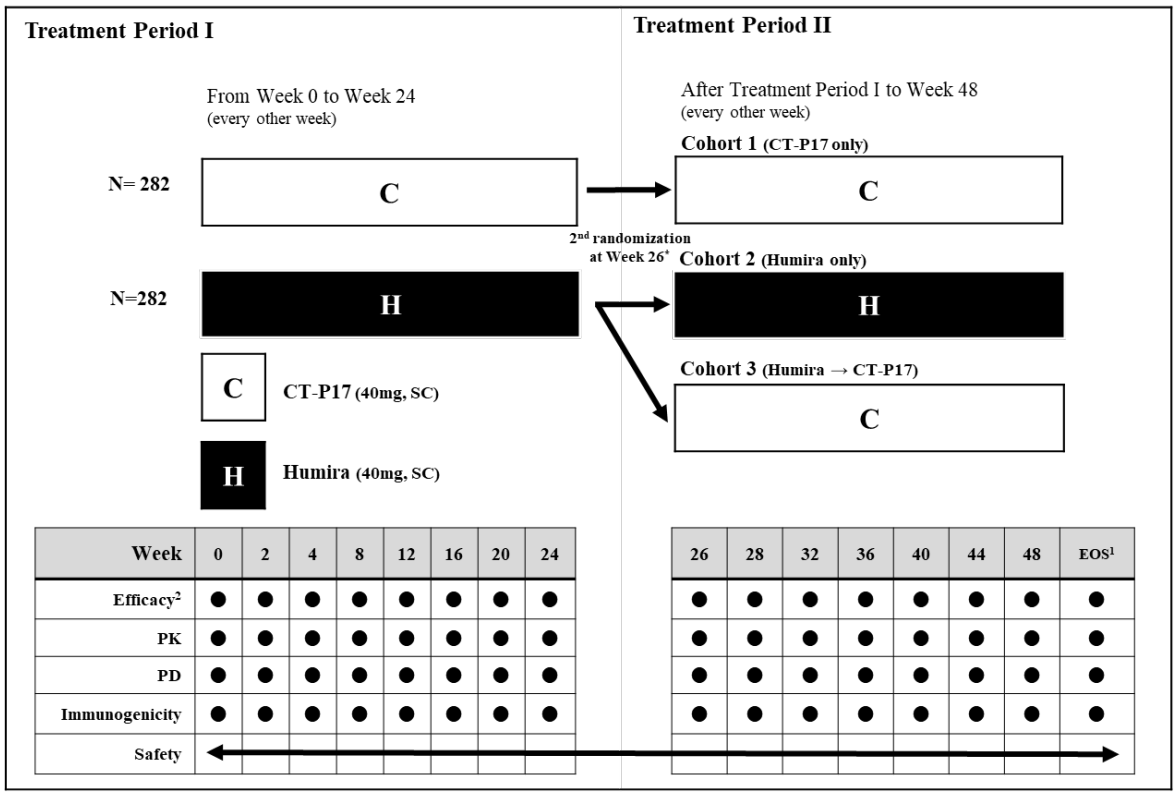
A self-reporting AE diary will be used to collect AEs experienced outside study center. Adverse events which occur during the patient's stay in the study centers, will be evaluated and recorded by the investigator and will not be entered into self-reporting AE diary. In addition, self-injection diary will be used to record details about self-injection. Diaries will be distributed to patient and will be collected and checked for completeness and legibility by the study staff at the next site visit. If needed, the patient or caregiver will be re-trained on how to perform the injection of the study drug and complete the diary.

End-of-Study **(Week 52)** *visit:*

An EOS visit will occur at Week 52 for all patients who completed or discontinued study treatment. The patients who early discontinued from the study treatment will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiate RA medication changes (including those prohibited by the protocol).

The study design and patient assessment overview is presented in Figure 1.

Figure 1 Study Design Overview



Abbreviations: C, CT-P17; EOS, end-of-study; EOW, every other week; H, Humira; N, number of patients; PK, pharmacokinetics; PD, pharmacodynamics; SC, subcutaneous.

* Prior to dosing at Week 26, all patients will undergo a second randomization process. Patients who are initially randomized to Humira will be randomized again in a ratio of 1:1 to either continue Humira or undergo transition to CT-P17. Patients who are randomized to CT-P17 or Humira will receive assigned study drug EOW from Week 26 and thereafter up to Week 48. Only the study center visit is presented in this figure.

[1] An EOS visit will occur at Week 52 for all patients who completed or discontinued study treatment. The patients who early discontinued from the study treatment will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiate RA medication changes (including those prohibited by the protocol).

[2] An independent joint count assessor assigned to each study center will assess joint counts. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period.

After database lock for data up to Week 24 for all patients, the study will be unblinded for reporting purposes and efficacy, PK, PD, immunogenicity, and safety endpoints will be evaluated by the pre-defined unblinded Sponsor and Contract Research Organization (CRO) teams. The investigators, patients, and other Sponsor and CRO teams will remain blinded until the end of the study.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 564 patients will be enrolled at approximately 60 study centers in 8 countries. Male or female patients with moderate to severe active RA diagnosed according to the 2010 ACR/EULAR classification criteria (*Aletaha et al., 2010*), despite previous treatment with MTX over at least 12 weeks, will be considered for enrollment in the study if they meet all the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 75 years old, both inclusive.
2. Patient has had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (*Aletaha et al., 2010*) for at least 24 weeks prior to the first administration of the study drug (Day 1).
3. Patient who has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed), 6 or more tender joints (of 68 assessed) and either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a serum C-reactive protein (CRP) concentration >1.0 mg/dL (>10 mg/L) at Screening.
4. Patient who has been receiving oral or parenteral MTX at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, and who has been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1).
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
    - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)
    - Serum alanine aminotransferase ≤3.0 × ULN
    - Serum aspartate aminotransferase ≤3.0 × ULN

- Serum total bilirubin ≤1.5 × ULN

6. Patient has the following hematology laboratory test results at Screening:
    - Hemoglobin >8.0 g/dL (SI units: >80 g/L or 4.96 mmol/L)
    - Absolute neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
    - Platelet count ≥75 × 10^3 cells/μL (SI units: ≥ 75 × 10^9 cells/L)
7. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, has the ability to cooperate with the investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form (ICF) with date prior to participation in the study.
8. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 6 months after the last dose of assigned treatment. Examples include the following:
    - Hormonal contraceptives (combined or progestogen-only) associated with inhibition of ovulation.
    - Intrauterine devices.
    - Sexual abstinence (not periodically, but for the entire period of risk).

    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 patients 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.
9. Patient must be able and willing to self-administer SC injections or designate a qualified person(s) to administer SC injection.

4.1.2 Exclusion Criteria

A patient meeting any of the following criteria will be excluded from the study:

1. Patient who has previously received investigational or licensed product; biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or tumor necrosis factor (TNF) α inhibitor for any purposes.
2. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
3. Patient who currently has, or has a history of, any of the following infections:
    - A known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved.
    - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1)
    - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1)
    - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.
    - Other serious infections within 24 weeks prior to the first administration of the study drug (Day 1)
4. Patient who currently has, or has a history of, any of the following TB conditions:
    - Patient who has a history of TB or a current diagnosis of TB. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.

- Patient who has had exposure to a person with active TB such as first-degree family members or co-workers.
- Patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest X-ray) at Screening. A patient who has a previous diagnosis of latent TB cannot be enrolled despite sufficient documentation of prophylaxis. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.

5. Patient who has a medical condition including one or more of the following:

- Classified as Class II or III obese by WHO classification (body mass index [BMI] ≥35 kg/m^2)
- Uncontrolled diabetes mellitus, even after insulin treatment
- Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)
- Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, AS, spondyloarthritis, systemic lupus erythematosus, Lyme disease or fibromyalgia, that may confound the evaluation of the effect of the study drug
- Significant systemic RA involvement (e.g., Sjogren's syndrome, vasculitis, pulmonary fibrosis) which would put the patient at risk if they are enrolled
- A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
- New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 24 weeks prior to the first administration of the study drug (Day 1)

- History of organ transplantation, including corneal graft/transplantation
- Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma or pleural effusion
- Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome
- Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) if it could interfere with the investigator's assessment on disease activity scores including joint counts
- Any other serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

6. Patient who has received or plans to receive any of the following prohibited medications or treatment:

    - Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and NSAID, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose must be maintained until the primary endpoint assessment at Week 24. In addition, a patient is permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.

- Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1)
- Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer
- Alkylating agents within 1 year prior to the first administration of the study drug (Day 1)
- Herbal products within 2 weeks prior to the first administration of the study drug (Day 1)
- Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1), or any planned live or live-attenuated vaccination during the study period
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1) or planned within 24 weeks after the first administration of the study drug (Day 1)

7. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV [*Hochberg et al., 1992*; Appendix 11.2], or who cannot benefit from medication)
8. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed within 6 months of the last dose of study drug.
9. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 2 years from Screening.
10. Patient who, in the opinion of their general practitioner or the investigator, should not participate in the study.

4.2 Study Treatment Discontinuation and Study Termination

Patients are free to withdraw from the study at any time for any reason. The investigator may also discontinue the study treatment at any time in the interest of patient safety. The primary reasons for the discontinuation of the study treatment and study termination must be recorded in the patient's medical record and in the electronic case report form (eCRF), with any comments (spontaneous or elicited) or complaints made by the patient. Reasons for study treatment discontinuation include the following:

- Patient develops signs of disease progression in the judgement of the investigator.
- Patient has any AE that would compromise his or her safety if he or she continues to participate in the study.
- Patient has a significant protocol deviation(s).
- Patient is pregnant.
- Investigator's decision.

As it is vital to obtain follow-up data in patients who discontinued from study treatment for any reason, they will also visit the study center by regular scheduled time interval for efficacy and safety follow-up.

Reasons for study termination include the following:

- Patient withdraws consent or refuses to procedures/observations.
- Patient is lost to follow-up.
- Patient dies.
- Study is terminated by the Sponsor.

If necessary, the investigator may discuss with CELLTRION, Inc or its designee any patient's reason for study termination or study treatment discontinuation. The sponsor may be contacted if clarification is required on a case-by-case basis. All patients who terminated from the study will retain their patient number.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and discontinue prior to study completion will not be replaced. Patients who are failed the Screening, for any reason, can be rescreened only once.

4.3 Premature Termination of the Study

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 patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the institutional review board (IRB) or independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

An interactive web response system (IWRS) will be used for the randomization. Biostatistics will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

Patients will be randomly assigned at Day 1 (Week 0) to receive CT-P17 or Humira using a 1:1 allocation ratio. The randomization to treatment assignment will be stratified by the following:

- Country
- Disease activity by SDAI at Screening; high (SDAI >26) vs. not high (SDAI ≤26)

Patients will receive CT-P17 or Humira EOW up to Week 24. Prior to dosing at Week 26, patients in the Humira treatment group will be randomly assigned in a ratio of 1:1 to either continue Humira (Cohort 2) or undergo transition to CT-P17 (Cohort 3) from Week 26. All patients who were initially randomly assigned to CT-P17 at Day 1 (Week 0) will continue their treatment with CT-P17 (Cohort 1) until EOS. Second randomization will also be conducted in Cohort 1 at Week 26 to maintain the study blind.

The second randomization to Cohorts 2 or 3 will be stratified by the following:

- Disease activity by SDAI at Week 24; remission (SDAI ≤3.3) vs. non-remission (SDAI >3.3)

The details of stratification factors will be described in the randomization specification document, which will be provided in a separate document.

5.2 Treatments Administered

The patients will receive either CT-P17 or Humira, as per the first and second randomizations, 40 mg (100 mg/mL) by SC injection via PFS EOW. Patients will be dosed at specific time points as detailed in the schedule of events (Table 11-1).

For each new injection, a different injection site will be used (e.g., injection site should be rotated). Sites for injection may either be the front of the patient's thighs or lower abdomen (except for the 5 cm around the patient's navel) or the outer area of the upper arm (except for self-injection). The same injection sites can be used only if the other sites are unavailable due to safety reasons and, in that case, it is recommended that the new injection should be given at least 3 cm away from the most recent injection site.

The study drug will be administered by the trained study center staff at Week 0, Week 2, and Week 4 or until the patient or caregiver is properly trained and confident to administer the study drug at home or the investigator considers patient self-injection or injection by caregiver is appropriate. Thereafter, the study drug can be administered by the patient or caregiver at home or by study staff at study center according to the regular study center visit schedule (Table 11-1) (see Section 5.2.3 for details). Patients can also self-inject the study drug during their study center visits, under the investigator or designated study center staff's supervision or can be administered by the caregiver, if needed.

5.2.1 Co-administration of Methotrexate and Folic Acid

Methotrexate with folic acid is co-administered to minimize or prevent AEs related to MTX side effects. Therefore, all patients should have been receiving oral or parenteral (IM or SC) MTX at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and have been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1). The same dose and route should be maintained throughout the study.

Patients are required to take folic acid (≥5 mg/week, oral dose) throughout the duration of the study (*Whittle and Hughes 2004*).

Methotrexate and folic acid should be given according to a weekly schedule on the day recommended by the investigator and details will be recorded in the source documents and the eCRF.

5.2.2 Premedication

Patient may also be pre-medicated 30 to 60 minutes prior to the study treatment administration for hypersensitivity/allergic reactions and any pre-medications (such as but not limited to antihistamine or paracetamol) can be given at the investigator's discretion.

5.2.3 Training for Home Injection of Study Drug

The investigator or designated study center staff will be trained about SC administration of study drug via PFS. The trained investigator or study center staff will be responsible for training each individual patient (or caregiver, if needed) about proper SC administration of study drug via PFS. Printed instruction for use (IFU) of PFS and instructions for self-injection of study drug will be provided to the patient that will serve as a guide while administering the study drug at home.

Patients and caregivers will be instructed to contact the investigator promptly in the event of any signs and symptoms of injection site reactions, hypersensitivity/allergic reactions.

To assess how well the patient or caregiver learned the SC injection of study drug via PFS and how well that information was retained, an actual patient/caregiver-injection of the study drug may be performed during a study center visit. During that visit, the investigator or study center staff will observe the patient or caregiver as they perform the injection without assistance or guidance provided from the investigator or study center staff.

As discussed in Section 3.2, patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. If needed, the patient or caregiver will be re-trained during this time on how to perform the injection of the study drug.

5.2.4 Other Supplies

As discussed in Section 5.2.3, printed IFU of PFS and instructions for self-injection of study drug will be provided to the patient or caregiver that will serve as their guide while administering the study drug at home.

The following will also be provided to the patient as a combined document form when the investigator considers the patient eligible for self-injection at home:

- Patient self-injection paper diary to record treatment compliance (see Section 5.6 for details)
- Patient self-reporting of AE paper diary to record any AE including injection site reactions (see Section 6.5.1.4 for details).

- A sharps bin to store used syringes. The sharps bin with the used syringes will be returned to the study center for disposal.

In addition, patient card which includes important safety risk and contact information for medical emergency will be provided.

5.3 Identity of Investigational Product

CT-P17 is a monoclonal antibody which is being developed by CELLTRION, Inc. as a potential biosimilar to Humira.

The company code of the product is CT-P17. The International Non-proprietary Name of the commercially available reference material (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 product, Humira, is 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 2017*, *Humira SmPC 2018*).

Each 40 mg/0.4 mL pre-filled syringe or pre-filled pen delivers 0.4 mL (40 mg) of Humira drug product. Each 0.4 mL of Humira contains 40 mg adalimumab, 16.8 mg mannitol, 0.4 mg polysorbate 80, and water for injection (*Humira USPI 2017*).

CT-P17 will be supplied in a single-use, pre-filled syringe at concentration of 100 mg/mL (40 mg/0.4mL) as clear to opalescent, colorless to brown liquid.

Dosing instruction described in the Humira prescribing information are to be followed (*Humira USPI 2017*, *Humira SmPC 2018*).

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

The following drug supplies will be used in the study:

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

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging, Labelling, and Storage

The appropriate number of study drug syringes will be allocated to each patient via the IWRS system at each visit.

A tear-off label will be attached to the outside of each patient 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
- Patient 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 must be stored in a secured area (e.g., a locked cabinet), protected from light. Both CT-P17 and Humira must be kept at a controlled refrigerated temperature

between 2°C and 8°C and it must not be frozen. As a reference, when needed (for example when travelling), a single CT-P17 or Humira PFS may be stored at room temperature up to a maximum of 25°C for a period of 14 days (*Humira USPI 2017*, *Humira SmPC 2018*). Once removed from the refrigerator for room temperature storage, the PFS must be used within 14 days or prior to the expiry date, whichever comes earlier, even if it was returned to the refrigerator. If the study drug is stored at temperature up to a maximum of 25°C for over 14 days at patient's home, the patient should be instructed to not administer the study drug and contact the study center (in advance, if possible). The immediate containers must be kept in the outer carton until use in order 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.

The patient should be advised to always refer to the Instructions for Self-injection of Study Drug about proper storage of the study drug.

5.4.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

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

The investigator will retain and store all original containers until these containers are inventoried by CELLTRION, Inc. Unless otherwise instructed by CELLTRION, Inc., the investigator agrees at the end of the study to return all original containers, whether empty or containing study drug, to CELLTRION, Inc.

Patients will return all the unused and empty syringes and containers. The used syringes can only be destroyed if it is written in local standard operating procedures (SOPs) and a specific

authorization is given by CELLTRION, Inc., which is required prior to a patient being randomly assigned to a treatment group. Permission will be granted by CELLTRION, Inc. on a study center-by-study center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used syringes immediately after administering to patients. 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.

5.5 Blinding

This study will be double-blind.

5.5.1 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 (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 will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and the sponsor. Any patients for whom the blind is broken may continue in the study and receive the study treatment at the investigator's discretion.

[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 prior to submission to the regulatory authorities.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 24 for all patients. The unblinded team will be pre-defined and documented prior to performing the analyses. The study will remain blinded to the investigators, patients, and pre-defined CELLTRION, Inc. and [redacted] blinded teams until all patients have completed the study and the database has been finalized for study termination.

5.6 Treatment Compliance

Patient compliance will be determined by the study center staff by reviewing the self-injection diary regularly. As discussed in Section 5.2.3, after training about proper injection technique, the patient may self-inject the study drug or can be administered by the caregiver, if needed.

When the patient is properly trained and confident to self-administer the study drug at home or the investigator considers patient self-injection appropriate, a patient self-injection paper diary will be provided to the patient to record the following: dates, time, site of injection, used PFS kit information, and injection completion.

If the patient forgot to self-inject the study drug, the patient should inject the dose of study drug as soon as they remembered it and contact the investigator or designated staff to inform the delay in injection and reschedule the next study center visit. The next dosing schedule should be readjusted to every two weeks from the time of last study drug administration. Administration of co-administered treatments (MTX and folic acid) will be recorded throughout the study.

5.7 Prior, Concomitant, and Subsequent Therapy

Aside from MTX and folic acid, which should be administered throughout the study as described in Section 5.2.1, a patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and NSAID, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose must be maintained until the primary endpoint assessment at Week 24. If there are any changes before Week 24, in terms of dose, need to be reported to and discussed with the medical monitors of CELLTRION, Inc. or its designee in advance. In addition, patients are permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.

Killed vaccinations are acceptable during the study.

Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS visit (Week 52), will be recorded in the patient's eCRF.

Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug until the EOS visit, will be recorded in the patient's eCRF. However, in order to check eligibility, prior medications will be reviewed from date specified in the exclusion criteria #6. This will include all prescription drugs, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.8 Prohibited Therapy

The following medications, treatments, or procedures during the study period are prohibited:

- Any biological agents indicated for RA treatment or TNF α inhibitor for any purposes
- Conventional DMARDs or targeted synthetic DMARDs other than MTX
- Intra-articular corticosteroids are not allowed until Week 24. After Week 24, an intra articular injection is allowed once to 1 joint during the study. The injected joint must be considered a non-responder joint during the response evaluation.
- Alkylating agents
- Herbal products
- Live or live-attenuated vaccine
- Any other investigational device or medical product
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) are not allowed until 24 weeks after the first administration of the study drug (Day 1)

6 Study Assessments and Procedures

Prior to performing any study procedures, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered prior to signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. Patients will undergo the procedures at the time points specified in the schedule of events (Table 11-1).

6.1 Efficacy Assessments

Efficacy will be assessed by the evaluation of the ACR criteria (individual components, ACR20, ACR50, and ACR70, and hybrid ACR response), DAS28 (DAS28 [ESR], DAS28 [CRP], and individual components) score, EULAR response criteria, simplified disease activity index (SDAI), clinical disease activity index (CDAI), quality of life (SF-36), and joint damage progression at the time points specified in the schedule of events (Table 11-1).

6.1.1 Joint Count Assessment

An independent joint count assessor will be assigned to each study center. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period. Any joint that has undergone any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For assessment, the independent joint assessor will be informed about the history of the patient's joint surgery with the name of the surgery, date, and location. Standardized training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records.

6.1.2 American College of Rheumatology Criteria and Individual Components

The ACR criteria are a series of individual assessments used for the calculation of ACR20, ACR50, ACR70, and hybrid ACR response (*American College of Rheumatology Committee*

to Reevaluate Improvement Criteria 2007). The ACR core set of variables (individual components) for this study include the following:

- Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling
- Patient's and physician's global assessment of disease activity measured on visual analogue scale (VAS) (Appendices 11.3 and 11.4)
- Patient's assessment of pain measured on VAS (Appendix 11.5)
- Health Assessment Questionnaire (HAQ) estimate of physical ability (Appendix 11.6)
- ESR (Section 6.3.2)
- CRP (Section 6.3.2)

6.1.3 Disease Activity Score Using 28 Joint Counts

Disease Activity Score using 28 joint counts (ESR) and DAS28 (CRP) will be evaluated at time points specified in the schedule of events (Table 11-1). The core set of variables for DAS28 for this study include the following:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 for swelling
- Patient's global assessment of disease activity measured using VAS (Appendix 11.3)
- ESR (Section 6.3.2)
- CRP (Section 6.3.2)

6.1.4 Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified and clinical disease activity will be measured using SDAI and CDAI (Aletaha and Smolen 2009). The core set of variables for SDAI and CDAI for this study include the following:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 joints assessed for swelling
- Patient's global assessment of disease activity (VAS) (Appendix 11.3)
- Evaluator/physician global assessment of disease activity (VAS) (Appendix 11.4)
- CRP (for SDAI only) (Section 6.3.2)

6.1.5 Quality of Life

Quality of life will be assessed using the 36-item short form health survey (SF-36) questionnaire at the time points specified in the schedule of events (Table 11-1).

6.1.6 Joint Damage Progression

One image of each hand and each foot (both the right and left hands and feet, a total of 4 images) for analysis of efficacy will be obtained at the time points specified in the schedule of events (Table 11-1). Joint damage, progression as determined by radiography, will be assessed in the central laboratory by the change in total Sharp score using the modified total Sharp scoring system (*Plant et al., 1994*, *Sharp et al., 1971*, *Sharp et al., 1985*) and the blind regarding the time point at which the displayed images will be obtained. The baseline radiographs will be assessed within 42 days prior to the first administration of the study drug (Day 1).

6.2 Pharmacokinetic Assessments

For all patients, blood samples for the determination of serum concentration of study drug will be collected prior to dosing at the time points specified in the schedule of events (Table 11-1).

Details of the PK endpoint and PK analysis are presented in Section 7.2.

6.3 Pharmacodynamic Assessments

Blood samples for PD assessments (rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP], CRP, and ESR) will be collected prior to dosing at the time points specified in the schedule of events (Table 11-1).

Details of the PD endpoints and PD analyses are presented in Section 7.3.

6.3.1 Rheumatoid Factor and Anti-cyclic Citrullinated Peptide

Blood samples for RF and anti-CCP will be collected at the time points specified in the schedule of events (Table 11-1), at the same time as the clinical laboratory blood samples. The blood samples will be tested in the central laboratory.

6.3.2 C-Reactive Protein and Erythrocyte Sedimentation Rate

Blood samples for CRP (central laboratory) and ESR (local laboratory using kits supplied centrally) will be collected at the time points specified in the schedule of events (Table 11-1).

Where CRP and ESR are required for efficacy, PD, and safety (clinical laboratory testing) assessments, the same sample can be used.

A standard ESR kit using the Westergren method of assessment will be supplied to the study centers for use; normal level will be considered to be no more than 20 mm/hour for women and no more than 15 mm/hour for men.

6.4 Biomarker Assessments (Optional)

For patients who sign a separate ICF for the biomarker assessments, blood samples for evaluation of genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected prior to dosing on Day 1 (Week 0).

Details of the biomarker analysis are presented in Section 7.4.

6.5 Safety Assessments

Safety assessments will be performed on AEs (including serious AEs), AEs of special interest (AESI) (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), immunogenicity, hypersensitivity monitoring (via monitoring of vital signs, including BP, heart and respiratory rates, and body temperature), vital sign and weight measurement, ECGs, physical examination findings, IGRA, chest X-ray, hepatitis B and hepatitis C and HIV status, pregnancy testing, clinical laboratory analyses, local site pain using 100 mm VAS, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study.

At each visit, patients will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

6.5.1 Adverse Events

6.5.1.1 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 in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after ICF was signed if any symptoms develop (see Section 6.5.1.4). Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent AE (TEAE).

A TEAE is defined as any event not present prior to exposure to study drug or any event already present that worsens in either 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

If the patient's RA worsens temporarily, disease aggravation will be captured as the (S)AE(s) term. However, if disease has worsened continuously in the judgment of the investigator (e.g., worsened for >8 weeks), this will be considered disease progression and not disease aggravation; disease progression will not be captured as an (S)AE. If disease progression is decided by the investigator, the patient will be discontinued from the study by investigator's

judgement and the disease aggravation reported in the previous visit will be deleted in the eCRF.

Diagnostic or therapeutic non-invasive or invasive procedures, such as surgery, should not be reported as AEs. However, they will be recorded as treatment(s) of the AE(s), if medical condition for which the procedure was performed meets the definition of an AE. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

6.5.1.1.1 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 tuberculosis, 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.

6.5.1.1.2 Serious Adverse Events

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

- Results in death
- Is immediately life threatening
- Requires inpatient 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 patient 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

6.5.1.1.3 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., IB) for an unapproved investigational product or the label (e.g., package insert or summary of product characteristics/US product insert) for an approved product. Assessment of expectedness will be made with the use of the IB and the summary of product characteristics.

6.5.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until EOS visit.

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.

At every study visit, patients will be asked a standard non-leading 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 over the counter medications).

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

6.5.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, action taken with study drug, 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 must also be reported. Adverse events will be recorded according to the 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 patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

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

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 6.5.1.7 and 6.5.1.8, 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.

6.5.1.4 Patients' Self-reporting of Adverse Events

A diary will be distributed to all patients and patients and caregivers will be instructed on how to appropriately complete the diary according to the patient diary instructions.

If there are any signs and symptoms from the time patients leave the study centers until the next visits, patients will record them in the patient diary and study center staff will review the diary at each visit throughout the study up to and including EOS visit. However, patients will be advised to contact the investigator if any severe symptoms develop; the investigator will determine whether the patient should be referred to the emergency room/hospital or to continue the next dose administration. If needed, the patient or caregiver will be re-trained on how to complete the diary. All AEs entered in the diary will be recorded on the AE page in the eCRF.

6.5.1.5 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.5.1.1.2) must be reported to [redacted] PVG within 24 hours from the time study center staff first learn about the event. The following contact information is to be used for SAE reporting:

[redacted]

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 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 patient is hospitalized during an SAE or because of

an SAE, a copy of the hospital discharge summary will be faxed 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. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the principal investigator or sub-investigator deems the event to be chronic or not clinically significant or the patient to be stable.

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 Hamonisation (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., patient 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
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient

If a patient is hospitalized purely for convenience (e.g., for easier performance of study assessments), the hospitalization does not qualify as an SAE. If a patient is hospitalized solely due to disease progression without any other adverse events, the hospitalization does not qualify as an SAE.

6.5.1.6 Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the sponsor will assess the expectedness of these events using the applicable reference documents (e.g., study drug investigator's brochure).

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.5.1.7 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient'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; non-invasive 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 should be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an AE upgrades in severity or changes from a non-serious to a serious event, a new AE needs to be reported. If an AE downgrades in intensity, 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.

6.5.1.8 Assessment of Causality

As discussed in Section 6.5.1.3, 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, e.g., 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.

6.5.1.9 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is stable.

6.5.2 Other Safety Assessment

6.5.2.1 Immunogenicity Testing

Serum samples for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of events (Table 11-1). Additional immunogenicity will be assessed when immune-related AEs occur. Immune-related AEs are defined as the following:

- Hypersensitivity/allergic reactions due to study drug (within 24 hours after study drug administration)

- Delayed hypersensitivity/allergic reactions due to study drug (after 24 hours after study drug administration)

Blood sample for immunogenicity for patients with immune-related AEs will be obtained on onset date of immune-related AEs, if possible, or blood sample can be used if it was obtained at the same date of study drug administration.

Sample analysis will be performed at the central laboratory.

6.5.2.2 Injection Site Reaction

Injection site reactions will be assessed 30 minutes (±10 minutes) after the end of the study drug administration, as specified in the schedule of events (Table 11-1).

For injections that will be given at home, patients or caregivers should be advised to call the study center or get immediate medical help if they experience the symptoms of injection site reactions (Section 6.5.1.1.1).

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

6.5.2.3 Hypersensitivity/Allergic Reactions Monitoring

Hypersensitivity/allergic reactions will be assessed prior to the study drug administration and 1 hour (±10 minutes) after the end of the study drug administration, as specified in the schedule of events (Table 11-1), by additional vital sign measurements including BP, heart and respiratory rates, and body temperature. If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study center or get immediate help.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms (see Section 6.5.1.4). In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed.

For patients who experience or develop life-threatening treatment-related anaphylactic reactions, study drug must be stopped immediately and the patient withdrawn from the study.

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

6.5.2.4 Vital Signs and Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in the schedule of events (Table 11-1). Vital signs (including BP, heart and respiratory rates, and body temperature; while sitting) and weight will be measured by the investigator or his or her designee after 5 minutes of rest. In addition, measurement of height will be documented at Screening. All measurements will be documented at each study center visit. Details will be recorded in both the source documents and the eCRF.

Vital sign measurements will also be monitored prior to and after study drug injection as part of the hypersensitivity monitoring (Section 6.5.2.3).

6.5.2.5 Electrocardiogram

All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 11-1) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The investigator will then report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion. In case of hypersensitivity, any type of ECG can be performed (Section 6.5.2.3).

6.5.2.6 Physical Examination

Physical examinations with particular attention to injection site reactions, hypersensitivity/allergic reactions, infections, and malignancy will be performed prior to study drug administration at the time points specified in the schedule of events (Table 11-1).

Investigators should carefully evaluate patients for any indication of infections and injection site reactions and pursue further investigation and treatment indicated in accordance with the investigator's medical judgment.

Physical examinations will be performed when patients visit the study center by regular scheduled time intervals for clinical assessments.

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 in both the source documents and eCRF.

6.5.2.7 Tuberculosis Assessment

At Screening, a history of TB or a current diagnosis of TB will result in patient exclusion from the study. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.

Patients with latent TB or who have had exposure to person with active TB such as first-degree family members or co-workers will not be included in the study.

A patient who has an indeterminate result for IGRA or latent TB at Screening will not be included in the study. Latent TB is defined as the presence of a positive IGRA (Section 6.5.2.7.2) with a negative examination of chest X-ray (Section 6.5.2.7.1). If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the IGRA result is again indeterminate or positive, the patient should be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study. A patient with confirmed latent TB during Screening cannot be enrolled. A patient who has a previous diagnosis of latent TB cannot be enrolled even if there is sufficient documentation of prophylaxis.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. Patients with active TB based on the chest X-ray result and/or the clinical signs and symptoms must be withdrawn from the study.

If the result of the IGRA is positive during the study, patients will be referred to the clinician immediately to investigate the presence of active TB based on medical history and any clinical signs and symptoms including chest X-ray result. Even in the absence of clinical suspicion for active TB, study drug administration will be temporarily stopped. It is recommended that study drug administration is resumed in patients who have received at least 3 weeks of country-specific TB therapy and who intend to complete the entire course of

TB therapy. However, study drug administration can be resumed simultaneously with the start of country-specific TB therapy after discussion with the medical monitors of CELLTRION, Inc. or its designee in advance.

If the patient is exposed to a person with active TB during the study period, an IGRA test will be done immediately and country-specific TB therapy will be initiated immediately regardless of the IGRA test result being negative or positive. The IGRA test will be repeated 8 weeks after the initial IGRA test and country-specific TB therapy can be discontinued if the repeated result is negative.

No further IGRA testing is required during the treatment period and at EOS visit for patients who have at least 1 positive result for IGRA test and have completed the prophylaxis at least for required duration by country specific legislation.

6.5.2.7.1 Chest X-Ray

A chest X-ray (both posterior–anterior and lateral views) should be taken during Screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of current or previous active or latent TB. If a chest X-ray within 42 days prior to the first administration of the study drug (Day 1) is available, a chest X-ray is not required at Screening, and the result will be recorded in both the source documents and the 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. Any abnormal x-ray changes should be discussed with the medical monitor prior to the first administration of the study drug (Day 1). The chest X-ray should be available to the investigator for review prior to the first administration of the study drug (Day 1) of the patient.

6.5.2.7.2 Interferon- γ Release Assay

Given the seriousness of TB in this patient population, an IGRA will be used to identify positive conversion of negative results for patients. Samples for this analysis will be obtained at the time points specified in the schedule of events (Table 11-1). The IGRA will be performed at the central laboratory.

As described in the literature (*Park et al., 2009*), IGRA can be used as a method of identifying patients with a false negative response to latent TB infections or new TB infections in patients with RA. Specifically, these assays detect cell-mediated immune responses to TB infections by quantifying interferon-γ in the presence of specific antimicrobial agents.

6.5.2.8 Hepatitis B and Hepatitis C and Human Immunodeficiency Virus

At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (total or IgG) will be assessed in all patients as specified in Table 6-1.

Table 6-1 Eligibility based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	**HBsAb**	**HBcAb**	**HBV DNA**	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
			–	Eligible[1]
–	+/–	–	Not applicable	Eligible

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

1. Testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at Week 26 and EOS visit.

If the HBsAg test result is positive, the patient will be excluded from the study. If a patient has HBsAg negative, HBsAb negative or positive, and HBcAb positive, a hepatitis B virus (HBV) DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at Week 26 and the EOS visit. If the patient develops hepatitis B reactivation, the study drug must be stopped and the patient withdrawn from the study.

Hepatitis C antibody and HIV will be assessed at Screening in all patients. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.

6.5.2.9 Pregnancy

For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted at Screening and EOS visit by central laboratory and urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit specified in the schedule of events (Table 11-1) or more frequently if required by country-specific legislation. Only patients with a negative serum pregnancy test results can be enrolled in the study. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.

In an event of unexpected pregnancy during study participation and for 6 months after the last dose of study drug, patients will be counselled to inform the investigator. If a female patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to CELLTRION, Inc. and [redacted] Safety Department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug and be withdrawn from the study. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to CELLTRION, Inc. and [redacted] Safety Department within 24 hours after acquisition of the consent for the pregnancy form.

Pregnant patients or the pregnant partners of male patients 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. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.5.1.5).

6.5.2.10 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Table 11-1). Blood samples do not need to be performed in a fasting state unless required in the opinion of the investigator.

The following clinical laboratory analyses will be performed:

Clinical chemistry	total protein, serum bilirubin (total, direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-MB, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, and high-density lipoprotein cholesterol
Hematology	red blood cells, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen and microscopic examination.

Creatinine clearance will be calculated using serum creatinine level only at screening for inclusion and recorded on eCRF. Clinical laboratory (clinical chemistry, hematology, and urinalysis) test samples will be analyzed at the central laboratory. Pharmacodynamic markers of CRP will also be analyzed with clinical laboratory analyses and CRP and ESR will be reported as safety parameter as well.

6.5.2.11 Patient's Assessment of Local Site Pain

All patients will assess local site pain using 100 mm VAS immediately (within 15 minutes) after the administration of study drug at the time points specified in the schedule of events (Table 11-1). Patient assessment of pain is measured by the patient indicating the extent of their pain by marking one line (|) through the 100-mm line (Appendix 11.5).

6.6 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.

6.6.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained accordance with the laboratory manual from each patient at the time points specified in the schedule of events (Table 11-1). All samples should be collected as close as possible to the scheduled time point.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.2 Pharmacodynamic Blood Sampling

Blood samples for PD (CRP, ESR, RF, and anti-CCP) will be obtained in accordance with the laboratory manual from each patient at the time points specified in the schedule of events (Table 11-1). All samples should be collected at the scheduled time point.

Blood sample for CRP will be drawn at the same time as the collection of blood samples for clinical laboratory testing. Blood sample for ESR will be analyzed at the study center local laboratory using centrally distributed kits.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.3 Biomarker Blood Sampling (Optional)

For patients who sign a separate ICF for the biomarker assessments, blood samples for evaluation of genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected in accordance with the laboratory manual prior to dosing on Day 1 (Week 0) (Table 11-1). These samples will be used for research purposes to identify dynamic biomarkers that may be predictive of response to CT-P17 treatment (in terms of dose, efficacy, safety, and tolerability).

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.4 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained prior to study drug administration at the time points specified in the schedule of events (Table 11-1), or when immune-related AEs occur.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.5 Interferon-γ Release Assay Blood Sampling

Blood samples for IGRA will be obtained at the time points specified in the schedule of events (Table 11-1). All samples should be collected at the scheduled time point.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.6 Routine Safety Blood Sampling

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 events (Table 11-1).

An additional blood for hepatitis B and hepatitis C and HIV testing 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.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.7 Labelling, Storage, and Transportation of Samples

6.7.1 Sample Labelling

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

6.7.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, PD, immunogenicity, safety, and/or biomarker 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, immunogenicity, and/or biomarkers 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, immunogenicity, and/or biomarkers is not required, the sample 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 SAP, which will be finalized prior to database lock. 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).

Continuous variables will be summarized by reporting the following descriptive statistics: the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

7.1 Efficacy Analyses

7.1.1 Primary Efficacy Analysis

The proportion of patients achieving clinical response (responder/non-responder) according to ACR20 criteria at Week 24 will be analyzed. The 95% CI for the difference in proportion between the 2 treatment groups (CT-P17 and Humira) will be produced. Therapeutic equivalence of clinical response according to ACR20 criteria will be concluded if the 95% CIs for the treatment difference are entirely within the limits of –15% to 15% at Week 24.

The primary efficacy endpoint will be analyzed using the ITT and PP populations. The ITT population will be the primary population for the primary endpoint. The logistic regression model with treatment group as fixed effect using country and disease activity by SDAI at Screening (high, not high) as covariates will also be performed in the ITT and PP population.

7.1.1.1 ACR20

A patient is defined as a responder according to ACR20 criteria if the following are fulfilled:

- A decrease of at least 20% in the number of tender joints (based on 68 joints)
- A decrease of at least 20% in the number of swollen joints (based on 66 joints), and

- A 20% improvement in at least 3 of the following:
    - Patient's assessment of pain on the VAS
    - Patient's global assessment of disease activity (VAS)
    - Physician's global assessment of disease activity (VAS)
    - HAQ estimate of physical ability
    - Serum CRP concentration or ESR

The VAS range is from 0 to 100 mm, with higher scores indicating poorer status or more severe pain (therefore an improvement in status or pain is reflected by a decrease in VAS).

The proportion of patients demonstrating ACR20 will be summarized by treatment group.

7.1.2 Secondary Efficacy Analysis

All secondary efficacy endpoints will be analyzed using the ITT and PP populations. These will be summarized by treatment group as appropriate and listed. The following secondary efficacy endpoints will be assessed for all patients during the study:

- ACR20 (except for Week 24), ACR50, and ACR70
- Individual components of the ACR
- Hybrid ACR response
- DAS28 (CRP) and DAS28 (ESR)
- Individual components of the DAS28
- EULAR response classification
- SDAI and CDAI
- SF-36 version 2
- Joint damage progression based on radiographic evaluations

7.1.2.1 ACR20, ACR50, ACR70 and Individual Components

The ACR20 (except for Week 24), ACR50, and ACR70 are calculated similarly to ACR20 (Section 7.1.1.1); however, an improvement of 50% and 70% must be achieved for ACR50 and ACR70, instead of 20%.

The proportion of patients demonstrating ACR50 and ACR70 will be summarized by treatment. Descriptive statistics for actual value and change from baseline of components of the ACR will be summarized by treatment group.

7.1.2.1.1 Health Assessment Questionnaire Disability Index

General health status will be assessed using the Health Assessment Questionnaire (HAQ) (Appendix 11.6). Descriptive statistics for actual value and change from baseline of HAQ index will be summarized by treatment group.

The following are the 8 categories within the HAQ:

- Dressing and grooming (Questions 1, 2)
- Arising (Questions 3, 4)
- Eating (Questions 5, 6, 7)
- Walking (Questions 8, 9)
- Hygiene (Questions 10, 11, 12)
- Reach (Questions 13, 14)
- Grip (Questions 15, 16, 17)
- Activities (Questions 18, 19, 20)

7.1.2.2 Hybrid ACR Response

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, the ACR70, and a continuous score of the mean improvement in core set measures (*American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007*). The hybrid ACR will

be summarized by treatment using descriptive statistics. The possible scores are displayed in Table 7-1.

Table 7-1 Scoring Method for the Hybrid ACR

ACR Status	Mean % Change in Core Set Measures			
	<20	**≥20, <50**	**≥50, <70**	**≥70**
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

Abbreviations: ACR, American College of Rheumatology; ACR20, ACR 20% improvement criteria; ACR50, ACR 50% improvement criteria; ACR70, ACR 70% improvement criteria.
Reference: *American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007*.

7.1.2.3 DAS28

Disease activity score in 28 joints (Appendix 11.8) will be assessed using the following equation:

$$DAS28\ (ESR) = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.70 \times \ln[ESR]) + (0.014) \times GH)$$

$$DAS28\ (CRP) = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.36 \times \ln[CRP + 1]) + (0.014 \times GH) + 0.96$$

Where:

- TJC28 = number of tender joints (0-28): tender joint count (TJC)
- SJC28 = number of swollen joints (0-28): swollen joint count (SJC)
- ESR = ESR measurement (mm/hour)
- CRP = CRP measurement (mg/L)
- GH = patient's global disease activity measured on 100 mm VAS (Appendix 11.3)

Descriptive statistics for actual value and change from baseline of DAS28 (ESR and CRP) and components of the DAS28 (ESR and CRP) will be summarized by treatment group.

7.1.2.4 EULAR Response Criteria

Response criteria according to EULAR are measured using DAS28 (ESR and CRP) according to Table 7-2. The proportion of patients achieving the EULAR response categories will be summarized by treatment group.

Table 7-2 EULAR Response Criteria

Present DAS28	DAS28 Improvement		
	>1.2	>0.6 to ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 to ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Abbreviations: DAS28, disease activity score in 28 joints; EULAR, European League Against Rheumatism.
Reference: *Fransen 2005*.

7.1.2.5 Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified and clinical disease activity will be measured using SDAI and CDAI calculated from the formulas presented in Table 7-3. Descriptive statistics for actual value and change from baseline of SDAI and CDAI will be summarized by treatment group.

Table 7-3 Calculation of Disease Activity Indices

Index	Formula
SDAI	SJC28 + TJC28 + PGA + EGA + CRP
CDAI	SJC28 + TJC28 + PGA + EGA

SJC28 = swollen joint count (0-28)
TJC28 = tender joint count (0-28)
PGA = patient global assessment of disease activity (VAS: 0-10 cm)
EGA = evaluator/physician global assessment of disease activity (VAS: 0-10 cm)
CRP = C-reactive protein (mg/dL)
Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; EGA, evaluator's global assessment of disease activity (physician global assessment); PGA, patient global assessment of disease activity; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.
Reference: *Aletaha and Smolen 2009*.

7.1.2.6 Short-Form Health Survey

General health status will be assessed using the SF-36 version 2 (Appendix 11.7). The following 8 aspects of the health status will be assessed:

- General and mental health
- Physical function
- Social function
- Physical and emotional health
- Pain
- Vitality

The score on each subscale ranges from 0 (worst) to 100 (best). The individual aspects of the survey will be grouped into a physical component and a mental component summary score, each of which will be assigned a mean (±SD) score of 50 with an SD of 10 on the basis of an assessment of the general population without chronic conditions. Individual scores will be compared with the normalized scores for the general population. Descriptive statistics for actual value and change from baseline of SF-36 score will be summarized by treatment group.

7.1.2.7 Joint Damage Progression

Joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet, a total of 4 images) will be assessed by the change in the total Sharp score using the modified total Sharp scoring system (*Plant et al., 1994*, *Sharp et al., 1971*, *Sharp et al., 1985*) at EOS visit. Descriptive statistics for actual value and change from baseline of joint damage progression will be summarized by treatment group.

7.2 Pharmacokinetic Analyses

Serum concentrations will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation [CV%], as appropriate) by treatment group,

study visit, and time point. Pharmacokinetic parameter will also be summarized using quantitative descriptive statistics (including geometric mean and CV%, as appropriate).

Pharmacokinetic parameters will be computed by non-compartmental methods using appropriate validated software such as Phoenix WinNonlin (Pharsight, St Louis, Missouri, USA) and, if applicable, SAS.

The following PK parameter will be assessed up to Week 52:

- C_{trough}: Trough concentration (concentration prior to the next study drug administration)

The PK population will be used for PK analysis.

7.3 Pharmacodynamic Analyses

The PD endpoints (CRP, ESR, RF, anti-CCP) will be summarized using descriptive statistics (including geometric mean and CV%, as appropriate) by treatment group and study visit.

The PD population will be used for PD analyses.

7.4 Biomarker Analyses

Analyses will be performed on genotypes (FcγRIIa, IIIa, and/or any necessary genotypes) in the ITT population. Genotypes will be summarized using frequency tables.

7.5 Safety Analyses

Safety analyses will be performed on the safety population at the time points specified in the schedule of events (Table 11-1) by presenting data about the following:

- AEs including SAEs
- AESI (injection site reactions, hypersensitivity/allergic reactions, infection and malignancies)
- Immunogenicity testing
- Hypersensitivity/allergic reactions monitoring

- Vital sign measurements and weight
- ECGs
- Physical examination findings
- Monitoring of TB signs and symptoms (see Section 6.5.2.7 for details)
- Chest X-ray (see Section 6.5.2.7.1 for details)
- IGRA (see Section 6.5.2.7.2 for details)
- Hepatitis B and hepatitis C and HIV
- Pregnancy testing
- Clinical laboratory analyses
- Patient's assessment of local site pain
- Previous and concomitant medications

7.5.1 Demographic and Baseline and Background Characteristics

Demographics (including gender, age, ethnicity, and race) and baseline and background characteristics (including RA history) 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.

7.5.2 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 6.5.1.1. The following TEAE summaries will be reported by SOC, PT, and treatment group:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 treatment-emergent SAE

- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with TEAEs of special interest (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies)

7.5.3 Immunogenicity

All data will be listed and summarized by treatment group, where appropriate.

7.5.4 Clinical Laboratory Analyses, IGRA and Pregnancy

Clinical laboratory tests (hematology, clinical chemistry, urinalysis, CRP, and ESR), IGRA, and pregnancy testing will be summarized by treatment at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all scheduled collection times after the first administration of study drug.

7.5.5 Electrocardiograms, Physical examination, Vital Signs, and Weight

Electrocardiograms, physical examination, vital signs (systolic and diastolic BP, heart rate, respiratory rate, and body temperature) and weight will be summarized by treatment at each scheduled collection time. Change from baseline will also be summarized for all scheduled collection times after the first administration of study drug.

7.5.6 Patient's assessment of Local Site Pain

Local site pain measurements by VAS will only be assessed immediately after the administration of study drug at each scheduled collection time and will be summarized by treatment group.

7.5.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. All prior and concomitant medications data will be listed and summarized by treatment group as appropriate.

7.5.8 Other Safety Analyses

All other safety data will be listed and summarized by treatment group as appropriate.

7.6 Sample Size Calculation

A sample size of 450 patients (225 patients in each treatment group of CT-P17 and Humira) leads to 83% statistical power for the demonstration of similarity of ACR20 at Week 24 based on the expected ACR20 rate of 64% with an equivalence margin of –15% to 15% using a two one-sided 2.5% significance level of an equivalence test. The drop-out rate has been hypothesized at 20%; therefore, approximately 564 patients (282 patients in each treatment group of CT-P17 and Humira) will be randomized. nQuery Adviser (version 7.0) was used to determine these sample size calculations.

7.7 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-treat (ITT) Population: The ITT population is defined as all patients enrolled and randomly assigned to receive a dose of either of the study drugs, regardless of whether or not any study drug dosing was completed. Patients will be assigned to treatment groups based on randomization.

Per-Protocol (PP) Population: The PP population is defined as all randomly assigned patients who have received all doses of study drug up to Week 22 (total of 12 injections) and have an ACR assessment at Week 24. A major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will be excluded from PP population. Final determinations of the PP population will be made at the blinded data review meeting (DRM) held in accordance with ICH harmonised tripartite guideline E9. Patients will be assigned to treatment groups based on randomization.

Pharmacokinetic Population: The PK population will consist of all patients who receive at least 1 dose (full) of either of the study drugs and have at least 1 post treatment PK concentration data. The PK population will be the primary population for the summary of PK data. If any patients are found to be non-compliant with respect to dosing, a decision will be made on a case-by-case basis at the blinded DRM prior to code breaking.

Pharmacodynamic Population: The PD population will consist of all patients who receive at least 1 dose (full) of either of study drugs and have at least 1 post treatment PD result. The PD population will be the primary population for the summary of PD data.

Safety Population: The safety population will consist of all patients who receive at least 1 dose (full or partial) of either of the study drugs. Patients will be assigned to treatment groups based on treatment actually received. The safety population will be the primary population for the summary of safety data.

7.8 Interim Analyses

No interim analyses are planned for this study.

7.9 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 (GCP) guidelines on quality and risk management.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff prior to the study, periodic monitoring visits by CELLTRION, Inc. or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRF 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. Patient 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 changed based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/IEC 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 patient 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 patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities or the IRB/IEC.

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

8.2 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of human patients in research studies. Prior to study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC 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/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines shall be obtained from each patient prior to entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both prior to IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval prior to the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Prior to recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient’s right to withdraw from the clinical study at any time without giving reasons and without jeopardizing the patient’s further course of medical treatment

- The existence of patient insurance coverage and a summary of what is included in this coverage

- Adequate time and opportunity to satisfy questions will be given to the patients.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or sub-investigator and the patient's legal representatives (according to the local regulations) prior to the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator's study file. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IRB/IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRF, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.5.1.5. In addition, the principal investigator or sub-investigator agrees to submit annual reports to his or her IRB/IEC as appropriate.

8.5 Financial Disclosure and Obligations

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

Neither the sponsor nor [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 patient's disease.

8.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae (CV) for the principal investigator and each sub-investigator listed on Form FDA 1572. Current licensure must be noted on the CV. The CV 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 21 CFR 54. 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.
- IRB/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

8.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The analytical assays will be conducted according to the general principles of the Organization for Economic Cooperation and Development Principles of Good Laboratory Practice for testing of chemicals C(81)30(Final).

Prior to the study onset, the protocol, informed consent, advertisements to be used for patient recruitment and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with the ICH E6(R2) guidelines will be maintained by the study center and will be available for review by the sponsor or its designee.

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

The principal investigator or designated sub-investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or designated sub-investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the patients 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 patient 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).

An eCRF is 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.

8.9 Adherence to Protocol

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

8.10 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in Section 6.5.1.5. In addition, the investigator agrees to submit annual reports to the study center IRB/IEC as appropriate.

8.11 Investigator's Final Report

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

8.12 Records Retention

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

Essential documents should 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 should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

8.13 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 patients by assigned number only.

8.14 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 CELLTRION, Inc., the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

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

9 Study Management

9.1 Sponsor

[redacted]

9.2 Vendor Contact

[redacted]

[redacted]

The names and addresses of the investigators and clinical study centers involved in the study are presented separately together with the investigators' signatures.

9.3 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. The following analytical facilities will be used:

[redacted]

[redacted]

9.4 Monitoring

9.4.1 Data Safety Monitoring Board

This study will be monitored by an independent data safety monitoring board (DSMB) consisting of a PK specialist, statistician, independent physician, and an independent chairing physician. The DSMB will review and evaluate accumulating safety data to ensure the safety of study patients.

Additionally, study results when the CSR is available will be reviewed by the DSMB.

Further details will be provided in the independent DSMB charter.

9.4.2 Monitoring of the Study

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

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

9.4.3 Inspection of Records

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

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from CELLTRION, Inc. or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments

should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or investigator that results in a significant and additional risk to the patient's rights, safety, and well-being. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined prior to unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

9.6 Study Termination

Although CELLTRION, Inc. has every intention of completing the study, CELLTRION, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

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

9.7 Final Report

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

The sponsor plans to prepare 2 CSRs to report the following:

- Data for each patient up to Week 24
- All data after completion of the study

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

10 Reference List

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11 Appendices

11.1 Schedule of Events

Table 11-1 Schedule of Events

	Screening	Treatment Period I								Treatment Period II							EOS [1]
		Dose 1	Dose 2	Dose 3	Dose 5	Dose 7	Dose 9	Dose 11	Dose 13	Dose 14	Dose 15	Dose 17	Dose 19	Dose 21	Dose 23	Dose 25	
Study visit[2] (Week)	**–6**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit[2] (Day)	**–42 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Informed consent	X																
Demographics, height, medical history	X																
Hepatitis-B/C and HIV-test[3]	X									(X)							(X)
Serum pregnancy test[4]	X																X
Chest X-ray[5]	X																X
IGRA[6]	X					X[7]			X[7]								X
Inclusion/ exclusion criteria	X	X[7]															
Randomization		X[8]								X[8]							
Efficacy assessments[7,9]– Pre-dose																	
Swollen joint count (66 joints/ 28 joints)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tender joint count (68 joints/ 28 joints)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS pain score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS global assessment of disease activity (patient/physician) scores	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health assessment questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR (local)[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QoL (SF-36) assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand and foot x-ray[11]	X																X
Safety and other assessments[7] – Pre-dose																	
Physical examination, vital signs, and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period I								Treatment Period II							EOS [1]
		Dose 1	Dose 2	Dose 3	Dose 5	Dose 7	Dose 9	Dose 11	Dose 13	Dose 14	Dose 15	Dose 17	Dose 19	Dose 21	Dose 23	Dose 25	
Study visit[2] (Week)	**–6**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit[2] (Day)	**–42 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Urine pregnancy test[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[13]	X	X							X								X
Immunogenicity[14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sampling[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid factor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-CCP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker[16]		X															
Study treatment[17,18]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hypersensitivity/ allergic reactions monitoring[19] and injection site reaction[20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Local site pain by VAS[21]		X	X	X	X		X		X	X		X	X		X	X	
Prior, concomitant medications[22]	X																
TB clinical monitoring[23]	X																
AEs[24]	X																

Abbreviations: AE, adverse event(s); anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; ECG, electrocardiogram; eCRF, electronic case report forms; EOS, end-of-study; EOW, every other week, ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IGRA, Interferon-Gamma Release Assays; ICF, informed consent form; IM, intramuscular; QoL, quality of life; SC, subcutaneous, TB, tuberculosis; VAS, visual analogue scale.

Note: Only the study center visits are presented in this table. As the study drug will be administered EOW, the planned injections on Weeks 6, 10, 14, 18, 22, 30, 34, 38, 42 and 46, which are not specified in this table can be self-administered or by caregiver at home. The patients who early discontinued from the study treatment will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they initiate RA medication changes (including those prohibited by the protocol). However, any assessment(s) that could jeopardize the patients' safety could be skipped, as per investigator judgement.

1. An EOS visit will occur at Week 52 for all patients who completed or discontinued study treatment.
2. A visit window of ±2 days is allowed, based on the previous dosing date, from Dose 2 up to the EOS visit.

3. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (total or IgG) will be assessed in all patients. If the HBsAg test result is positive, the patient will be excluded from the study. If a patient is negative for HBsAg, negative or positive for HBsAb, and positive for HBcAb, an HBV DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, HBV DNA, aspartate aminotransferase, alanine aminotransferase, and total bilirubin will be performed at Week 26 and EOS visit. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
4. For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted at Screening and EOS visit by central laboratory and a urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory. For patient who early discontinued study treatment, urine pregnancy test is unnecessary after the discontinuation.
5. A chest X-ray (both posterior-anterior and lateral views) is not required at Screening if a chest X-ray from within the 42 days prior to the first administration of the study drug (Day 1) is available.
6. The IGRA testing will be performed at the central laboratory. No further IGRA testing is required during the treatment period and at EOS visit for patients who have at least 1 positive result for IGRA test and have completed the prophylaxis at least for required duration by country specific legislation.
7. Procedures will be performed at the study center prior to the study drug administration.
8. Patients will be randomly assigned to receive either CT-P17 or Humira prior to dosing on Day 1 (Week 0) (first randomization). Patients will be randomized again prior to dosing on Week 26 (second randomization).
9. An independent joint count assessor will be assigned to each study center. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period.
10. Both CRP and ESR rate are considered as efficacy, PD, and safety (clinical laboratory test) endpoints. CRP samples will be drawn and analyzed at the same time as the clinical laboratory blood samples and ESR samples will be analyzed at the local laboratory using kits supplied centrally.
11. One image of each hand and each foot (both the right and left hands and feet, a total of 4 images) for analysis of efficacy will be obtained at the scheduled times. The baseline radiographs will be assessed within 42 days prior to the first administration of the study drug (Day 1). Joint damage progression as determined by radiography, will be assessed using the modified total Sharp scoring system by the central independent reviewer.
12. Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed at the central laboratory.

Clinical chemistry	total protein, serum bilirubin (total, direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-MB, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol
Hematology	red blood cells, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen and microscopic examination

13. All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in supine position. If patients have signs and symptoms of hypersensitivity or other cardiac origin, an ECG could be performed at any time during the treatment period. Regardless of the 12-lead ECG result, further

evaluation with a cardiologist can be done depending on the investigator's discretion.

14. Samples will be drawn prior to dosing of study drug at the same time as the clinical laboratory tests where applicable. Analysis will be performed at the central laboratory. Additional immunogenicity will be assessed when immune-related AEs occur.
15. Blood samples for PK analysis will be obtained only at pre-dose (just prior to study drug injection) for all PK sampling time points up to and including Week 48. For EOS visit, PK samples will be obtained anytime during the day. For patient who early discontinued study treatment, PK samples will be obtained until 4 weeks after the last administration of study drug.
16. Only for patients who sign a separate ICF for the biomarker assessment, a blood sample for evaluation of any necessary genotypes will be collected prior to dosing on Week 0.
17. A single dose of CT-P17 (40 mg) or Humira (40 mg) will be administered by SC injection via PFS EOW. For each new injection, a different injection site will be used (e.g., injection site should be rotated). The same injection sites can be used only if the other sites are unavailable due to safety reasons and in that case, it is recommended that new injection should be given at least 3 cm away from the most recent injection site. The study drug will be administered by the trained study center staff at Week 0, Week 2, and Week 4 or until the patient or caregiver is properly trained and confident to administer the study drug at home or the investigator considers patient self-injection or injection by caregiver is appropriate. Thereafter, the study drug can be administered by the patient or caregiver at home or by study staff at study center according to the regular study center visit schedule (see Section 5.2.3 for details). Patients may also self-inject the study drug during their study center visits, under the investigator or designated study center staff's supervision or can be administered by the caregiver, if needed.
18. Methotrexate (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or parenteral [IM or SC] dose, and dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose) will be administered throughout the treatment period.
19. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature will be monitored for possible hypersensitivity/allergic reactions 1 hour (±10 minutes) after SC injection of study drug. For patient who early discontinued study treatment, monitoring of hypersensitivity/allergic reactions are unnecessary after the discontinuation.
20. Injection site reaction will be assessed 30 minutes (±10 minutes) after SC injection of study drug. For injections that will be given at home, injection site reactions will be recorded by the patient or their caregiver in the patient self-reporting of AE diary. For patient who early discontinued study treatment, assessment of injection site reaction is unnecessary after the discontinuation.
21. Local site pain using 100 mm VAS will be assessed immediately (within 15 minutes) after SC injection of study drug. For injections that will be given at home, local site pain will also be recorded by the patient or their caregiver in the patient self-reporting of AE diary. For patient who early discontinued study treatment, assessment of local site pain is unnecessary after the discontinuation.
22. Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS visit (Week 52), will be recorded in the patient's eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug until the EOS visit, will be recorded in the patient's eCRF. However, in order to check eligibility, prior medications will be reviewed from date specified in the exclusion criteria #6.
23. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. The IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
24. Adverse events will be assessed from the date the ICF is signed until the EOS visit. After the EOS visit, serious adverse drug reactions will be reported to CELLTRION, Inc. or its designee. Adverse events of special interest (e.g., injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies) should be closely monitored.

* If a study center is not equipped to perform the specified tests, this will be discussed and arranged with the sponsor or the sponsor's designee.

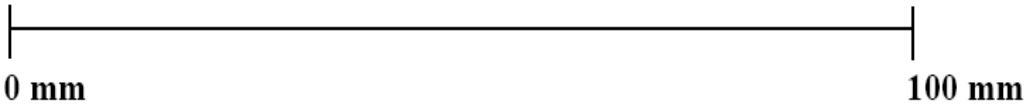
11.2 ACR Revised Criteria for Classification of Functional Status in RA

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Note: Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.
Reference: *Hochberg et al 1992*.

11.3 VAS Patient's Global Assessment of Disease Activity

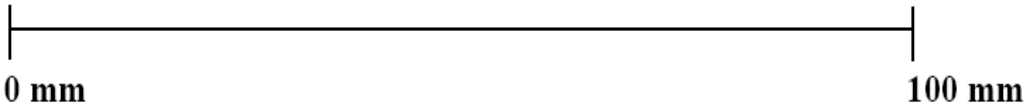
Patient's global assessment of disease activity is measured by the patient indicating the patient's current disease activity by marking one line (|) through the 100-mm line (0 mm equals very well and 100 mm equals very poor disease activity). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF. The converted score (in cm) for SDAI or CDAI will be calculated using 0.1 cm interval.



Very well Very poor

11.4 VAS Physician Global Assessment of Disease Activity

Physician's global assessment of disease activity is measured by the physician indicating the patient's current disease activity by marking one line (|) through the 100-mm line (0 mm equals very well and 100 mm equals very poor disease activity). This is an evaluation based on the patient's disease signs, functional capacity and physical examination, and should be independent of the patient's global assessment of disease activity. The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF. The converted score (in cm) for SDAI or CDAI will be calculated using 0.1 cm interval.

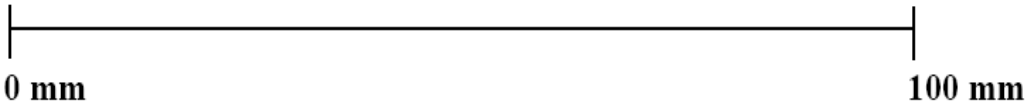


0 mm **100 mm**

Very well Very poor

11.5 VAS Patient's Assessment of Pain

Patient assessment of pain is measured by the patient indicating the extent of their current 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 patient's eCRF.



No pain Most severe pain

11.6 Health Assessment Questionnaire and Scoring of the Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

PATKEY#_____
QUESTDAT_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

PMSVIS_____

RASTUDY_____

QUESTNUM_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

DRESSNEW_____

RISENEW_____

EATNEW_____

WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

DRSGASST_____

RISEASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST_____

WALKASST_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____Raised toilet seat
_____Bathtub seat
_____Jar opener (for jars previously opened)
_____Bathtub bar
_____Long-handled appliances for reach
_____Long-handled appliances in bathroom
_____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene
_____Reach
_____Gripping and opening things
_____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ——————————— SEVERE PAIN 100

PAINSCAL_____

11.7 General Health Status (Medical Outcomes Study Short-Form Health Survey)

Study centers are using the validated questionnaire for their country; this appendix is included for information only and is not to be used as the official questionnaire to collect patient data.

For each of the following questions, please select the one response that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing several flights of stairs	○	○	○
e. Climbing one flight of stairs	○	○	○
f. Bending, kneeling, or stooping	○	○	○
g. Walking more than a mile	○	○	○
h. Walking several hundred yards	○	○	○
i. Walking one hundred yards	○	○	○
j. Bathing or dressing yourself	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Were limited in the kind of work or other activities	○	○	○	○	○
d. Had difficulty performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Did work or other activities less carefully than usual	○	○	○	○	○

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	○	○	○	○	○
b. Have you been very nervous?	○	○	○	○	○
c. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d. Have you felt calm and peaceful?	○	○	○	○	○
e. Did you have a lot of energy?	○	○	○	○	○
f. Have you felt downhearted and depressed?	○	○	○	○	○
g. Did you feel worn out?	○	○	○	○	○
h. Have you been happy?	○	○	○	○	○
i. Did you feel tired?	○	○	○	○	○

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	○	○	○	○	○
b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

11.8 DAS28

The DAS28 score uses a calculation that requires the assessment of 28 joints for swelling and tenderness. The 28 joints are shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees.

More information on DAS28 can be found at http://www.das-score.nl

		Left Swollen	tender	Right Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		swollen		Tender	

Abbreviations: MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints
Reference: DAS28.