CELLTRION Inc.

CT-P17 3.1

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

19th June 2020
Statistical Analysis Plan

Version 2.0

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
Anti-CCP	anti-cyclic citrullinated peptide
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
BLQ	below lower limit of quantification
BMI	body mass index
BP	blood pressure
CDAI	clinical disease activity index
CI	confidence interval
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration
CV	curriculum vitae
CV%	percent coefficient of variation
DAS28	Disease Activity Score in 28 joints
DRM	data review meeting
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOW	every other week
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IGRA	interferon-γ release assays
IM	intramuscular

Abbreviation	Definition
ITT	intent-to-treat
IWRS	interactive web response system
JSN	joint space narrowing
LLN	lower limit of normal
MCP	metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
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
SF-36	Short-Form Health Survey
SI	Système International d'Unités
SIAQ	Self-Injection Assessment Questionnaire
SJC	swollen joint count
SOC	system organ class
TB	tuberculosis
TEAE(s)	treatment-emergent adverse event(s)
TJC	tender joint count
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organizations

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc. (hereinafter referred to as "CELLTRION"). The clinical monitoring and medical writing are being performed [redacted]. The data management and statistical analyses including pharmacokinetics parameter analysis are being performed by CELLTRION.

2. INTRODUCTION

This Statistical Analysis Plan (SAP) defines the statistical methods to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P17 3.1, entitled as "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".

There are two clinical study reports (CSRs) planned for the following time points, with provision of additional CSRs if required for regulatory or academic purposes:

- After all eligible patients have completed the Week 24 assessment
- After all patients have completed or terminated from the study

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

- Study Protocol Version 3.0 – 6th August 2018
- Study Protocol Version 3.0, including country specific A.0 – 14th December 2018
- Study Protocol Version 3.0, including country specific B.1 – 18th February 2019
- Unique Case Report Form Version 2.1 – 15th May 2019

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

2.1. Data Cut-off for Analysis

The 1st CSR will include all analysis results, using data up to Week 24 of the Treatment Period of each patient. For the data that are monitored continuously (e.g. data collected on 'Adverse Events', 'Prior & Concomitant Medications' and 'Joint Surgery' Electronic case report form (eCRF) pages), the data reported on or prior to the visit date of Week 24 will be included.

For patients who have terminated the study participation up to Week 24 (actual or planned), all collected data will be included. For patients who skipped visit of Week 24, the data on or prior to the last scheduled visit before Week 24 will be included. In addition, if patients who have discontinued study treatment before Week 24 (planned), the discontinuation data collected on 'Study Treatment Discontinuation and Study Treatment' (eCRF) page will be included.

The final CSR will include all analysis results collected up to the completion or termination of all patients from the study.

3. Study Objective

Primary and secondary objectives are described as below.

3.1. 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 definition of a 20% improvement (ACR20) at Week 24.

3.2. Secondary Objectives

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

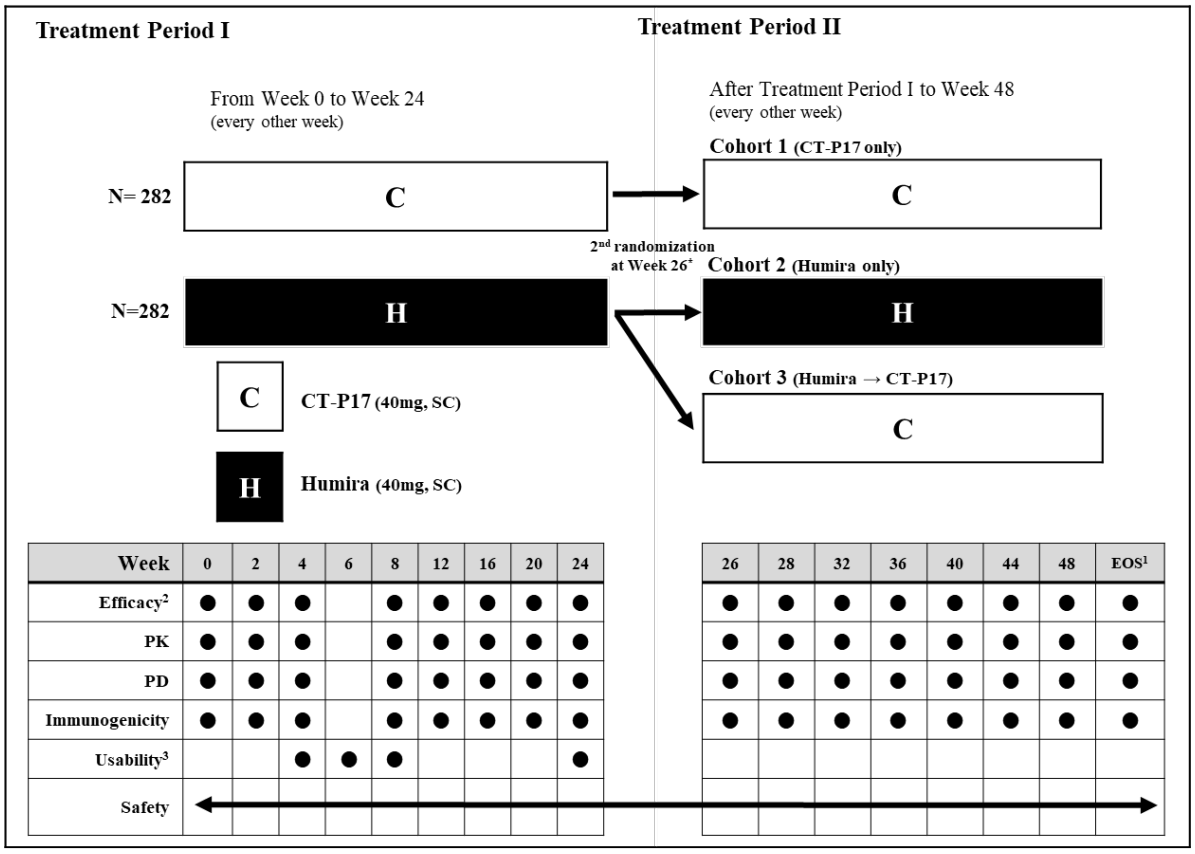
4. INVESTIGATIONAL PLAN

4.1. Study Design and Plan

This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, PD, usability and overall safety including immunogenicity and biomarker of multiple single-dose (40 mg [100 mg/mL]) of either CT-P17 or Humira administered by subcutaneous (SC) injection via pre-filled syringe (PFS) every other week (EOW) in combination with methotrexate (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 end-of-study [EOS]) and folic acid (≥5 mg/week, oral dose).

The study design and patient assessment overview is presented in Figure 1. Usability assessments will only be performed according to the protocol including country specific A.0.

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.

[3] Usability assessments will be performed only for patients who self-inject the study drug. For patient who the caregiver or trained study center staff injects the study drug, usability assessment are unnecessary.

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 EOS visit.

The study will comprise 3 study periods including Screening Period, Treatment Period (I and II) and 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 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 using a 1:1 allocation ratio. 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.

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 that will be performed at the time points specified in the schedule of events (Appendix 1).

For the patients who will undergo usability assessments according to the protocol including country specific A.0., the study drug will be administered by the trained study center staff at Weeks 0 and 2. After patients are properly trained, the study drug will be administered by patient at Weeks 4, 6, 8 and 24 at the study center for usability assessments. For remained visits, patients can self-inject the study drug at home or during their study center visits under the supervision of the investigator or designated study center staff, or it can be administered by the caregiver, if needed. If the patient or caregiver is improperly trained or unconfident to administer the study drug at home, the study drug can be administered at the study center by trained study center staff. For patients who the caregiver or trained study center staff injects the study drug, usability assessment are unnecessary.

For the other patients who will not undergo usability assessments, 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. After Week 4, patients can self-inject the study drug at home or during their study center visits under the supervision of the investigator or designated study center staff, 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 adverse events (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 patients and will be collected and checked for completeness and legibility by the study center

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 other medications for rheumatoid arthritis (RA) (including those prohibited by the protocol).

4.2. Country Specific Study Design

4.2.1. Protocol including Country Specific A.0

Usability assessments will be performed additionally, and the study design overview is described in Section 4.1 and illustrated in Figure 1 and Appendix 1.

4.2.2. Protocol including Country Specific B.1

There is no change in study design.

5. GENERAL STATISTICAL CONSIDERATIONS

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

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

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

Categorical data will be summarized using frequency tables showing numbers and percentages of patients. Percentages will be rounded to one decimal place and will be suppressed when the

count is zero. A row denoted "Missing" will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of patients within each treatment group for the population of interest, unless otherwise specified.

If there are repeated measurements at a time point, the initial scheduled measurement at that time point will be used in the summary tables.

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

When combining data from eCRF and analytical facilities [redacted], discrepancy will be handled as following:

1) Recorded as sample collected in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date from eCRF;
2) No corresponding records in eCRF for results from analytical facility – listing will display only specimen collection visit/date and results from analytical facility;
3) Discrepancy in sample collection date from eCRF and analytical facility – listing will display results from analytical facility and visit/date from eCRF if not missing; if sample collection date is missing in eCRF then use specimen collection visit/date from analytical facility.

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

This statistical analysis plan (SAP) could be updated after the DRM but prior to database hard lock to document any deviations.

5.1. Software

[redacted]

5.2. 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. [redacted]

5.3. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for the randomization. Unblinded biostatistician 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 followings:

- 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 EOS. Second randomization will also be conducted in Cohort 1 at Week 26 to maintain the study blind. The second randomization to Cohort 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)

This study will be double-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 determine the identity of the study drug by using the applicable procedure in the IWRS. The date, time and reason for the unblinding must be documented in the appropriate field of the eCRF and will be listed along with information of patient disposition.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 24 and data up to study completion 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. [redacted] until all patients have completed the study and the database has been finalized for study termination.

5.4. Analysis sets

The following analysis sets are defined: Intent-to-Treat (ITT), Per-Protocol (PP), PK, PD, Safety and Usability populations. The following analysis subsets are also defined: ITT Population – Treatment Period II subset, PP Population – Treatment Period II subset, PK Population – Treatment Period II subset, PD Population – Treatment Period II subset, and Safety Population – Treatment Period II subset. Analysis populations will be used for the summary of the Treatment Period I (Week 0 to Week 24 visit and before study drug administration of Week 26 visit). Analysis subsets will be used only for the summary of the Treatment Period II (Baseline, Week 26 to Week 48 visit and EOS visit). Patients to be excluded from analysis population because of major protocol deviation is defined in Section 5.6. Each analysis set will be specified in related sections.

For ITT population and PP population, patients will be assigned to either CT-P17 or Humira treatment group according to the treatment they were randomized to. The other populations will be analyzed according to actual treatment. The actual treatment group will be assigned according to their actual treatment, not according to the randomized treatment, even if there is a discrepancy between the actual treatment and the randomized treatment. If there is a patient with such a discrepancy, patients receiving at least one CT-P17 will be treated as "CT-P17" treatment group. All other patients will be treated as "Humira" treatment group.

For ITT population – Treatment Period II subset and PP population – Treatment Period II subset, patients will be assigned to "CT-P17 Maintenance", "Humira Maintenance" and "Switched to CT-P17" according to the treatment they were randomized. The other subsets will be analyzed according to actual treatment they received during Treatment Period I and Treatment Period II. The actual treatment group for Treatment Period II subset will be assigned according to their actual treatment received in Treatment Period I and Treatment period II, not according to the randomized treatment, even if there is a discrepancy between the actual treatment and the randomized treatment. Patients receiving at least one CT-P17 for Treatment Period I will be treated as "CT-P17 Maintenance" treatment group. Patients who receive Humira only for Treatment Period I and receive at least one CT-P17 for Treatment Period II will be treated as "Switched to CT-P17" treatment group. All other patients will be treated as "Humira Maintenance" treatment group.

For the summary of Overall Period, analysis population defined above will be used, and patients will be assigned to "CT-P17", "Humira", "CT-P17 Maintenance", "Humira Maintenance" and "Switched to CT-P17", as defined above. In case of Overall Period summary, it will be presented only in some analyses and is mentioned in each section.

The number of patients in all populations will be tabulated by the treatment group on ITT population and ITT population – Treatment Period II subset. A listing will also be produced displaying data on ITT population.

5.4.1. 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.

5.4.1.1. Intent-to-Treat (ITT) Population – Treatment Period II subset

The ITT population – Treatment Period II subset is defined as all patients in ITT population who are randomly assigned to receive a dose of either of the study drugs prior to dosing at Week 26, regardless of whether or not any study drug dosing was completed.

5.4.2. Per-Protocol (PP) Population

The PP population is defined as all randomly assigned patients who have received all full doses of study drug up to Week 22 (total of 12 injections) and have an ACR assessment at Week 24. If a patient received all doses of study drug up to Week 22 (total of 12 injections) but delayed study drug administration more than 7 days from the previous dosing, before Week 24, then the patient will be excluded from PP population. 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 of Harmonisation (ICH) harmonised tripartite guideline E9.

5.4.2.1. Per-Protocol (PP) Population – Treatment Period II subset

The PP population – Treatment Period II subset will consist of all patients in PP population who receive at least 1 dose (full) of either of the study drugs on or after Week 26 and have at least 1 post treatment efficacy assessment after first study drug administration in Treatment Period II.

5.4.3. 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.

5.4.3.1. Pharmacokinetic Population – Treatment Period II subset

The PK population – Treatment Period II subset will consist of all patients in PK population who receive at least 1 dose (full) of either of the study drugs on or after Week 26 and have at least 1 post treatment PK concentration data after first study drug administration in Treatment Period II.

5.4.4. 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.

5.4.4.1. Pharmacodynamic Population – Treatment Period II subset

The PD population – Treatment Period II subset will consist of all patients in PD population who receive at least 1 dose (full) of either of the study drugs on or after Week 26 and have at least 1 post treatment PD result after first study drug administration in Treatment Period II.

5.4.5. 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. The safety population will be the primary population for the summary of safety data.

5.4.5.1. Safety Population – Treatment Period II subset

The safety population – Treatment Period II subset will consist of all patients in Safety population who receive at least 1 dose (full or partial) of either of the study drugs on or after Week 26.

5.4.6. Usability Population

The usability population will consist of all patients in the safety population who self-inject either of the study drugs and have at least 1 evaluable usability measurement. The usability population will be the primary population for the summary of usability data.

5.5. Definition of Baseline

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

5.6. Protocol Deviations

Protocol deviation will be categorized as "major" or "minor". A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare, and will be identified prior to study unblinding. Major protocol deviations and population to be excluded are defined as follows: CELLTRION will identify major protocol deviation prior to database lock, and it will be discussed during the blinded DRM.

- Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any point during the study)
- Non-adherence to Inclusion or Exclusion criteria which affect efficacy result
- Significant GCP non-compliance
- Receipt of joint surgery, synovectomy or intra-articular injection before Week 24 without discontinuation
- Receipt of prohibited medication which affect efficacy result before Week 24 without discontinuation (based on agreement of each as from [redacted] prior to database lock)

Patients with mis-randomizations up to Week 22 will be excluded from PP, PK and PD population. Patients with mis-randomizations after Week 22 will be excluded only from Treatment Period II subset of PP, PK and PD population. Patients with Non-adherence to Inclusion and Exclusion criteria which affect efficacy result will be excluded from PP population. Patients with significant GCP non-compliance will be excluded from all analysis populations. Patients who receive joint surgery, synovectomy or intra-articular injection before Week 24 without discontinuation will be excluded from PP population. Patients with protocol prohibited medication initiation which affects primary efficacy endpoint before Week 24 without discontinuation will be excluded from PP population.

The major protocol deviations and other categories used for exclusion will be summarized for the ITT population. A listing of major protocol deviations and other categories for each patient will also be provided by treatment group for the ITT population.

5.7. Outliers

Any outliers that are detected during the review of the data will be investigated and discussed during the DRM. In general, outliers will not be excluded. Sensitivity analyses and exploratory analyses may be conducted using imputation or excluding outliers to ensure robustness of study conclusions. Details of outliers detected will be presented in the footnotes of the relevant outputs.

6. PATIENT DISPOSITION

The number of patients who were screened and failed at screening will be displayed along with the primary reason for screening failure. A patient will be considered to be enrolled if the patient is successfully screened based on the 'Screening Pass/Fail' page of eCRF.

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

- Inclusion/Exclusion criteria not met
- Patient withdrew consent
- Other

A listing of patients reported as screening failures will be provided.

The number of patients who were randomized, treated, discontinued from the study treatment and terminated from the study in each period will be displayed for the ITT population and for the ITT population – Treatment Period II subset along with percentage by treatment group, if applicable. The number and percentage of patients who complete the study will also be displayed in Treatment Period II.

Patient disposition will be defined as follows:

- A patient will be considered to be randomized in the Treatment Period I if a randomization ID was allocated to the patient at Day 1 (Week 0) based on the 'Randomization' page of eCRF.

- A patient will be considered to be initiated in the Treatment Period I if it is recorded as 'Yes' to study drug administration on the 'Study Drug Administration' page of eCRF in the Treatment Period I.

- A patient will be considered to be randomized in the Treatment Period II if a randomization ID was allocated to the patient prior to dosing at Week 26 based on the 'Randomization' page of eCRF.

- A patient will be considered to be initiated in the Treatment Period II if it is recorded as 'Yes' to study drug administration on the 'Study Drug Administration' page of eCRF after Week 24.

- A patient will be considered to have completed the study if it is recorded that the patient completed the study ('Yes' box checked) on the 'Study Treatment Discontinuation and Study Termination' page of eCRF.

- A patient will be considered to have discontinued the study treatment if it is recorded that the patient was discontinued from the study treatment ('Yes' box checked) on the 'Study Treatment Discontinuation and Study Termination' page of eCRF. If the patient has been assigned with study treatment at 2nd randomization and discontinued the study treatment after the 2nd randomization, the patient will be considered to have discontinued the study treatment in the Treatment Period II, whereas if discontinuation of study treatment occurred before 2nd randomization, the patient will be considered to have discontinued the study treatment in Treatment Period I.

- A patient will be considered to have terminated the study if it is recorded that the patient was terminated from the study ('Yes' box checked) on the 'Study Treatment Discontinuation and Study Termination' page of eCRF. If the patient has been assigned with study drug at 2nd randomization and terminated the study after 2nd randomization, the patient will be considered to have terminated the study in the Treatment Period II, whereas if termination of study occurred before 2nd randomization, the patient will be considered to have terminated the study in Treatment Period I.

The number and percentage of patients who discontinued the study treatment will be displayed by primary reason for study treatment discontinuation and treatment group. The number and percentage of patients who were terminated from the study will also be displayed by reasons for study termination and treatment group. Primary reasons for study treatment discontinuation and study termination will be presented respectively, based on the 'Study Treatment Discontinuation and Study Termination' page of eCRF. Summaries will be presented for the ITT population and for the ITT population – Treatment Period II subset by treatment group.

In addition, time on study treatment prior to discontinuation will also be summarized, for those patients who initiate the study treatment and prematurely discontinue for the ITT population and for the ITT population – Treatment Period II subset by treatment group. The treatment duration in days will be calculated as (date of last administration – date of first administration+1). The date of first administration of study drug will be taken as the earliest date recorded on the 'Study Drug Administration' page of eCRF. The date of last dose of study drug will be taken as recorded as on the 'Study Treatment Discontinuation and Study Termination' page of eCRF.

Patient disposition data will be listed for the ITT population by treatment group.

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics and Stratification Details

The following demographic measures and stratification details will be summarized for the ITT population and for the ITT population – Treatment Period II subset by treatment group: Age (years); Gender (male, female); Female Fertility Status (pre-menarche, surgically sterilized,

post-menopausal, potentially able to bear children, other); Race (Asian, White, Black or African American, not allowed by investigator country regulations, other); Ethnicity (Hispanic or Latino, non-Hispanic or non-Latino, unknown); Height (cm), Weight (kg) and Body Mass Index (BMI) (kg/m^2) as recorded at Screening; Country; SDAI at Screening (high (SDAI>26) vs. not high (SDAI≤26)) and SDAI at Week 24 (remission (SDAI≤3.3) vs. non-remission (SDAI>3.3)). The number and percentage of SDAI at Week 24 will only be presented in the summary of Treatment Period II.

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

Results of SDAI at Screening and at Week 24 will be automatically calculated in eCRF system based on Disease Activity Score in 28 Joints (DAS28), Visual Analogue Scales (VAS) and C-Reactive Protein (CRP) at Screening and at Week 24, respectively.

The stratification factors will be summarized using the final data collected on eCRF. Demographics and stratification details will be presented in separate listings for the ITT population by treatment group.

7.2. Congestive Heart Failure Assessment

Congestive heart failure will be assessed by New York Heart Association (NYHA) functional criteria at Screening. If a patient had cardiac disease, corresponding NYHA class will be selected. The criteria for congestive heart failure are defined as follows:

Table 1. New York Heart Association Functional Classification

Class	Symptoms
I (Mild)	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.
II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or angina pain.
IV (Severe)	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Patients who did not have cardiac disease which can be classified by NYHA will be classed as "No Class" in the listing. NYHA criteria assessment data will be listed for the ITT population by treatment group.

7.3. Physical Capacity Assessment

Physical capacity will be assessed by American College of Rheumatology (ACR) revised criteria at Screening. The criteria of functional status are defined as follows:

Table 2. American College of Rheumatology Revised Criteria of Functional Status

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

ACR revised criteria assessment data will be tabulated for the ITT population and ITT population – Treatment Period II subset and listed for the ITT population by treatment group.

7.4. Hepatitis B and C and Human Immunodeficiency Virus Test

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

- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis C Antibody
- Human Immunodeficiency Virus (HIV)

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. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, and HBV DNA will be performed at Week 26 and EOS visit.

Viral serology results at Baseline will be tabulated by treatment group for the ITT population and for the ITT population – Treatment Period II subset. If the confirmatory test is conducted, only the result of the confirmatory test will be used for the summary and presented in listing. All viral serology results including HBV DNA test results will be listed for the ITT population by treatment group.

7.5. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 22.0 or the higher version). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the ITT population and for the ITT population – Treatment Period II subset. Medical history will be listed for the ITT population by treatment group.

7.6. Rheumatoid Arthritis History

Rheumatoid arthritis (RA) history is captured at Screening and is based on the Rheumatoid Arthritis Classification Criteria 2010 (Aletaha *et al.*, 2010). The summary for each RA criterion and time since RA diagnosis will be tabulated for ITT population and for the ITT population – Treatment Period II subset by treatment group. Time (years) since RA diagnosis will be calculated as [(the first administration date of study drug – date of RA diagnosis)/365.25]. If an incomplete date of RA diagnosis is recorded for a patient, the date will be imputed using the latest possible date as below.

- Missing day (e.g. XXMAR2019): Assume the last day of the month (e.g. 31MAR2019).
- Missing day and month (e.g. XXXXX2019): Assume December 31st (e.g. 31DEC2019).
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as missing.

If the imputed date is later than the first administration date of study drug, it will be imputed using the first administration date of study drug. If the whole date is missing, time since RA diagnosis will not be calculated. RA history will also be listed for the ITT population by treatment group.

7.7. Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria can be found in Sections 4.1.1 and 4.1.2 of the protocols (CT-P17 3.1). All recorded inclusion/exclusion criteria status for patients who passed Screening will be presented in separate listings.

A number of inclusion and exclusion criteria may be modified during protocol revisions. The listing will indicate which protocol the patient was recruited under and hence which criteria applied.

8. BIOMARKER ASSESSMENTS (Optional)

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

Results of each genotype will be summarized for the ITT population and for the ITT population – Treatment period II subset by treatment group. Percentages will be calculated by using the number of patients who sign an ICF for biomarker assessments as the denominator. All results of biomarker assessments will be listed for the ITT population.

9. TREATMENTS AND MEDICATIONS

9.1. Prior and Concomitant Medications

All medications except for the treatment of RA used during the study, taken within 42 days prior to the date of first study drug administration and until the EOS visit will be collected on the eCRF. All medications for the treatment of RA, from the diagnosis of disease until the EOS visit, will be collected on the eCRF. All medications will be coded according to the World Health Organization drug dictionary (WHO Drug Dictionary March 2019 or the later version).

Medications will be classed as either prior or concomitant.

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

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

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

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

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

- Missing day: Assume the first day of the month.

However, if the partial start date and the date of first study drug administration (defined as the earliest date recorded on the 'Study Drug Administration' page of eCRF) lie within the same month and year, and the date of first study drug administration is not after the stop date of the medication, set to the date of first study drug administration. If the date of first study drug administration is after the stop date of the medication, then set to stop date of the medication.

- Missing day and month: Assume January 1st.

However, if the partial start date and the date of first study drug administration lie within the same year, and the date of first study drug administration is not after the stop date of the medication, set to the date of first study drug administration. If the date of first study drug administration is after the stop date of the medication, then set to stop date of the medication.

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

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

- Example 1:

  Medication start: UNJAN2019

  Medication end: 20MAY2019

  Date of first study drug administration: 16MAY2019

  Medication start imputed: 01JAN2019

- Example 2:

  Medication start: UNMAY2019

  Medication end: 20MAY2019

  Date of first study drug administration: 16MAY2019

  Medication start imputed: 16MAY2019

- Example 3:

  Medication start: UNMAY2019

  Medication end: 20MAY2019

  Date of first study drug administration: 24MAY2019

  Medication start imputed: 20MAY2019

A prior medication is defined as any medication where the start and stop dates or imputed start and stop dates are before the date of first study drug administration, and will be classified as following.

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

A concomitant medication is defined as any medication that has an actual or imputed stop date on or after the date of first study drug administration or missing, and any medication not classified as a prior medication will be classified as a concomitant medication. Concomitant medications will be classified for Treatment Period I and Treatment Period II, defined as follows: a concomitant medication with a start date prior to the first study drug administration of study drug in Treatment Period II, or concomitant medication for those patients who did not administered study drug during Treatment Period II will be included in Treatment Period I. Concomitant medication with a start date on or after the date of first study drug administration

in Treatment Period II will be included in Treatment Period II.

The prior medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication for the Safety population. The prior medications will be summarized using the same analysis population and treatment groups used for the summary of Overall Period. The separate tables will be also generated for the concomitant medications by treatment group, drug class (using ATC level 2), and PT along with the total number of concomitant medications and the number and percentage of patients with at least one concomitant medication for the Safety population and the Safety population – Treatment Period II subset. The concomitant medications will also be summarized for Overall Period. When ATC Level 2 for drug class is not available, Level 1 will be used instead.

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

9.1.1. Co-administration of Methotrexate and Folic Acid

Data on co-administration of methotrexate and folic acid will be collected separately from all other medications. The same rules for date imputation and definitions of prior and concomitant will apply. The number of patients with prior and concomitant administration of methotrexate or folic acid will be summarized separately. Additionally, the methotrexate dose (mg/week) at the first study drug administration of each treatment period will be summarized. Summaries will be based on the Safety population and the Safety population – Treatment Period II subset and presented by treatment group.

A listing will be provided by treatment group showing the details of co-administration of methotrexate and folic acid for each patient in the Safety population.

9.2. Exposure to Study Drug

The number and percentage of patients with dose administered will be summarized by treatment group at each scheduled dose week, along with the number and percentage of patients who did and did not have whole volume of study drug administered successfully. For patients who are not administered study drug, the number and percentage of patients with each reason why the dose was not administered (AE, other) will be displayed by visit. In addition, descriptive statistics for the total number of doses received will be summarized by treatment group. Summaries will be based on the Safety population and the Safety Population – Treatment Period II subset. For the descriptive statistics of the total number of doses received, summary will also be conducted for Overall Period on the Safety Population.

A listing will be provided by treatment group for the Safety population showing the details of study drug administration. This will include all data collected on the ‘Study Drug Administration’ page of eCRF.

10. EFFICACY ANALYSIS

ACR20 response at Week 24 is the primary efficacy endpoint. The primary efficacy analysis will be conducted on both the ITT and the PP population. In addition, sensitivity analysis by logistic regression will be conducted on both the ITT and the PP population.

The secondary efficacy endpoints are as below.

- ACR criteria (individual components, ACR20 except for Week 24, ACR50 and ACR70)
- Hybrid ACR response
- DAS28 (individual components, DAS28[ESR] and DAS28[CRP])
- European League Against Rheumatism (EULAR) response criteria
- Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)
- Short-Form Health Survey (SF-36)
- Joint Damage Progression

All analysis for the secondary efficacy endpoints will be conducted on the ITT and PP population and on its corresponding subset (ITT population – Treatment Period II subset or PP population – Treatment Period II subset) at the time points specified in the schedule of events (Appendix 1) unless otherwise specified.

All efficacy listings will be based on the ITT population.

10.1. ACR20, ACR50, ACR70 Criteria and Hybrid ACR

10.1.1. Number of tender/swollen joints

The number of tender joints and number of swollen joints will be assessed, with a total of 68 joints assessed for tenderness, and 66 joints assessed for swelling. This assessment is performed independently of the assessment of 28 tender/swollen joints for the DAS28 (Section 10.2.1).

Descriptive statistics for actual value and change from baseline for both the number of tender joints and the number of swollen joints will be presented at each scheduled visit. A listing will be provided by visit, showing the number of tender and swollen joints at each scheduled visit, along with the change from baseline.

10.1.2. Visual Analogue Scale (VAS)

The VAS ranges from 0 to 100 mm, with higher scores indicating poorer status or more severe pain. A VAS is used to record the Patient's Assessment of Pain, the Patient's Global Assessment of Disease Activity, and the Physician's Global Assessment of Disease Activity at each scheduled visit.

Descriptive statistics for actual value and change from baseline for these scales will be

presented at each scheduled visit using the standardized VAS automatically calculated in the eCRF system based on the VAS scale result and the total length of VAS scale on the questionnaire. A listing will also be provided showing VAS measurements at each scheduled visit, along with the change from baseline.

10.1.3. Health Assessment Questionnaire (HAQ) Estimate of Physical Ability (HAQ Disability Index)

The arthritis-related functional disability will be measured using the disability index of the Health Assessment Questionnaire (HAQ), a validated, self-administered form that assesses functional ability in a number of relevant areas.

There are 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)

The answer to each question will be scored as follows: Without any difficulty = 0, With some difficulty = 1, With much difficulty = 2, Unable to do = 3.

There are 3 steps to scoring the HAQ:

(1) Take the highest score within each category. Note that the maximum score is taken among the non-missing values. If all questions in a category are missing, the score of the category is recorded as missing.

(2) Adjust the score based on the patient's use of aids/devices or help from another person for that category. Categories of HAQ, aids/devices and help from another person are described in Table 3. If the category score after step (1) is 0 or 1, and any of the aids/devices/help from another person fields are marked, the score is increased to 2. If the category score is 2 or 3, no adjustment is made.

Table 3. HAQ Categories of Aids/Devices and Help from another Person

HAQ Category	Aids or Devices	Help from another Person
Dressing and Grooming	Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)	Dressing and Grooming
Arising	Special or Built up chair	Arising
Eating	Built up or special utensils	Eating
Walking	Cane	Walking
	Walker	
	Crutches	
	Wheelchair	
Hygiene	Raised toilet seat	Hygiene
	Bathtub seat	
	Bathtub bar	
	Long handled appliances in bathroom	
Reach	Long handled appliances for reach	Reach
Grip	Jar opener (for jars previously opened)	Gripping and opening things
Activities		Errands and chores

Note: The assignment of devices to particular disability categories assumes that the devices are used only for their intended purposes. Other aids/devices or help from another person will be collected but will not be used to adjust scores.

(3) If a patient has scores for 6 or more categories, the HAQ estimate of physical ability is average of the adjusted scores after step (2) for the available categories. Otherwise, the HAQ estimate of physical ability cannot be computed and will be recorded as missing.

Descriptive statistics for actual value and change from baseline of the HAQ estimate of physical ability will be presented by treatment group at each scheduled visit. A listing will be provided showing the patient's score for each category and HAQ estimate of physical ability. Listings will also be provided showing the raw scores for each category, the responses to the "Aids/Devices" categories, and the "Help from another person" categories. These listings will be displayed by treatment group and visit.

10.1.4. C-Reactive Protein and Erythrocyte Sediment Rate

Both CRP and ESR will be summarized for the PD population, and this is described in the PD section (Section 12). CRP and ESR will be listed along with the other PD parameters on the ITT population. For both CRP and ESR used as component of efficacy endpoint, if duplicated measurements are recorded in the unscheduled visit with same date, the highest value will be used.

10.1.5. Proportion of ACR20, ACR50 and ACR70 Responders

The American College of Rheumatology (ACR) criteria are standard measures of clinical activity in RA patients. The ACR criteria used in this study are ACR20, ACR50 and ACR70.

A patient is defined as a responder according to ACR20 criteria if the followings 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 (VAS scale, mm)
  - Patient's global assessment of disease activity (VAS scale, mm)
  - Physician's global assessment of disease activity (VAS scale, mm)
  - HAQ estimate of physical ability
  - Serum CRP (mg/dL) concentration or ESR (mm/h)

Note: Percentage change = 100×(post-baseline value – baseline value)/(baseline value)

The following categories of patients are considered non-responders:

- Patients with an improvement according to the ACR criteria of less than 20%
- Patients who terminated from the study prior to the week of interest
- Patients who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest
- Patients with incomplete data for evaluation of ACR20 criteria at the week of interest ; if ACR20 criteria could be fulfilled with non-missing component, regardless of missing component, the patient is considered as responder.

The ACR50 and ACR70 are evaluated similarly to ACR20. However, a decrease of 50% and 70%, respectively, must be achieved.

The proportion of patients achieving clinical response according to the criteria for ACR20, ACR50 and ACR70 will be summarized. The summary will only be conducted for Overall Period on ITT population, for Treatment Period I on PP population, and for Treatment Period II on PP Population – Treatment Period II subset at each scheduled visit. Denominator will be the number of patients on the corresponding population. A listing will be provided by treatment group and visit, showing ACR20, ACR50 and ACR70 responder status at each visit.

10.1.5.1. Primary Analysis

The proportion of patients achieving clinical response (responder/non-responder) according to ACR20 criteria at Week 24 will be analyzed as a primary endpoint. The analysis will be conducted by the exact binomial approach using a Farrington-Manning score method (Chan and Zhang, 1999; Inverting two one-sided test), and the 95% CI for the difference in proportion between the 2 treatment groups 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.

In addition, a summary table will be produced presenting the number and proportion of responders and non-responders of ACR20 at Week 24 by ADA status and treatment group for the ITT population and PP population. However, if the number of either subset is very small (≤ 5% of PP or ITT population) then the subset will not be summarized since it is not statistically meaningful. The difference estimate of ACR20 response will be presented only for ITT and PP population. In the ITT and PP population, patients who show at least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 24 will be considered as "at least one ADA positive subgroup". All patients who only have "Negative" results in post treatment immunogenicity test up to Week 24 will be considered as "all ADA negative subgroup".

10.1.5.2. Sensitivity Analysis

As the exact binomial approach does not allow for stratification, a sensitivity analysis will be performed on the primary efficacy endpoint, using the logistic regression model with treatment group as a fixed effect and country and disease activity by SDAI at Screening as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region may be used instead. Categorization of the region will be discussed in DRM. From the resulting odds ratio, estimate of the difference in proportion between the 2 treatment groups and corresponding 95% CI will be calculated using the process below:

1) The individual odds and standard errors (SEs) for both treatments will be obtained from the model. For the purposes of this algorithm, let the estimate of the odds of being a responder in the CT-P17 group be denoted by θ_a and the estimate of the odds of being a responder in the Humira group be denoted by θ_b.

2) Calculate the variances of these estimates, $\mathrm{Var}(\theta_a)$ and $\mathrm{Var}(\theta_b)$ respectively from the SEs obtained from the model.

3) Calculate the estimates of the corresponding proportions, denote p_a and p_b respectively, for each of the treatment groups, from the estimated odds using the following formula:

$$p_a = \frac{\theta_a}{1+\theta_a}, \qquad p_b = \frac{\theta_b}{1+\theta_b}$$

And hence calculate the estimate of the difference of proportions $(p_a - p_b)$.

4) Using Taylor expansions and the Delta method, the following formula for approximation can be obtained:

$$Var[f(X)] \approx f'[E(X)]^2 Var(X)$$

Applying this approximation specifically to this case, and using the formula specified in step (3), the formula below was obtained which should be used to calculate $\mathrm{Var}(p_a)$ and $\mathrm{Var}(p_b)$.

$$Var(p_a) = \frac{Var(\theta_a)}{(1+\theta_a)^4}, \qquad Var(p_b) = \frac{Var(\theta_b)}{(1+\theta_b)^4}$$

5) Calculate the variance of the difference in proportions $\mathrm{Var}(p_a - p_b)$ as the sum of $\mathrm{Var}(p_a)$ and $\mathrm{Var}(p_b)$. Use this to obtain the SE of the difference, and hence calculate the 95% CI using the formula:

$$95\%\ \text{Confidence Interval} = (p_a - p_b) \pm 1.96[\mathrm{SE}(p_a - p_b)]$$

Note: this method assumes that the ACR20 response rate of CT-P17 group is independent of the ACR20 response rate of Humira group.

The sensitivity analysis will be conducted in the ITT and the PP population.

10.1.6. Hybrid ACR

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, and the ACR70 and a continuous score of the mean improvement in core set measures (tender joint count, swollen joint count, physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, HAQ and CRP [or ESR]).

Note that CRP will be used for the hybrid ACR score derivation, unless it is missing, in which case ESR will be used.

The steps to calculate the hybrid ACR are as follows:

(1) For each core set measure, calculate improvement percentage as 100×(baseline value – post-baseline value)/(baseline value).

(2) If a core set measure worsened by > 100%, that improvement percentage is set to -100%.

(3) Mean % change is average of the improvement percentage for all core set measures.

(4) The hybrid ACR score is determined from the following table. The ACR20, ACR50, or ACR70 status of the patient (left column) is taken, along with the mean % change in core set items calculated in step (3); the hybrid ACR score is where they intersect in the table.

Table 4. Scoring Method for Hybrid ACR

	Mean % change in core set measures			
ACR Status	**<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

Reference: American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007.

Descriptive statistics of the hybrid ACR score will be presented by treatment group at each scheduled visit. A listing will also be provided by treatment group and visit, showing the hybrid ACR score, ACR responder status, (%) change from baseline and the mean % change in core set measures. Hybrid ACR score will be displayed to two decimal places in ACR listing.

10.2. DAS and EULAR Response Criteria

10.2.1. Number of tender/swollen joints

The number of tender and swollen joints will be assessed with a total of 28 joints for tenderness and 28 joints for swelling. This assessment is performed independently of the assessment of 68 tender joints/66 swollen joints for the ACR criteria (Section 10.1.1).

Descriptive statistics for actual value and change from baseline for both the number of tender and swollen joints will be presented at each scheduled visit. A listing will be provided by visit, showing number of tender and swollen joints by category.

10.2.2. DAS28

Disease activity score in 28 joints (DAS28) will be assessed using the following equations:

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

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

Where:

- TJC28 = tender joint count (0-28)

- SJC28 = swollen joint count (0-28)
- ESR = erythrocyte sedimentation rate measurement (mm/h)
- CRP = C-reactive protein measurement (mg/L)

  Note: CRP in SI unit will be converted from 'mg/dL' to 'mg/L'

- GH = patient's global disease activity measured on VAS (0 – 100 mm)

Descriptive statistics for actual value and change from baseline in disease activity measured by DAS28 (ESR) and DAS28 (CRP) will be presented. The summary will only be conducted for Overall Period on ITT population, for Treatment Period I on PP population, and for Treatment Period II on PP Population – Treatment Period II subset at each scheduled visit. DAS28 components, DAS28 value and change from baseline for both DAS28 (ESR) and DAS28 (CRP) will be listed. The DAS28 will be displayed to two decimal places.

10.2.3. EULAR Response Criteria

The European League Against Rheumatism (EULAR) response criteria categorizes the DAS28 response (i.e., good, moderate, or none) based on changes in DAS28 from baseline.

Table 5. European League Against Rheumatism Response Criteria

	DAS28 Improvement from baseline		
Present DAS28	>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

Reference: Fransen et al 2005

Frequencies and percentages of EULAR response categories (based on both DAS28 [ESR] and DAS28 [CRP]) will be presented at each scheduled visit. The EULAR response categories will be listed in the DAS28 listing.

10.3. Clinical Disease Activity Index and Simplified Disease Activity Index

Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) are calculated at each scheduled visit using the following equations (Aletaha and Smolen 2009):

- CDAI = SJC28 + TJC28 + PGA + EGA
- SDAI = SJC28 + TJC28 + PGA + EGA+ CRP

Where:

- TJC28 = tender joint count (0-28)
- SJC28 = swollen 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 measurement (mg/dL)

Note: Prior to calculation of the CDAI and SDAI, the PGA and EGA on VAS results should be converted from 'mm' to 'cm'. If one or more component measurements are missing, the CDAI/SDAI will not be calculated.

Descriptive statistics for actual value and change from baseline of CDAI and SDAI will be presented at each scheduled visit. In addition, individual components, CDAI and SDAI values and change from baseline for both CDAI and SDAI will be listed.

10.4. Short-Form Health Survey (SF-36)

General health status will be assessed using the SF-36 questionnaire consisting of 36 questions regarding the quality of life of the patient. Results for each of the 36 questions will be recorded and grouped into the following 8 subscales.

- Physical Functioning (PF): Questions 3a to 3j
- Role-Physical (RP): Questions 4a to 4d
- Bodily Pain (BP): Questions 7 and 8
- General Health (GH): Questions 1 and 11a to 11d
- Vitality (VT): Questions 9a, 9e, 9g and 9i
- Social Functioning (SF): Questions 6 and 10
- Role-Emotional (RE): Questions 5a to 5c
- Mental Health (MH): Questions 9b, 9c, 9d, 9f and 9h

The 8 subscales will also be used to derive 2 component summary measures:

- Physical Component Summary (PCS): Subscales PF, RP, BP and GH
- Mental Component Summary (MCS): Subscales VT, SF, RE and MH

The 8 subscale scores and 2 component summary scores will be derived using Optum® PRO CoRE. The scores of the SF-36 survey ranges from 0 (worst) to 100 (best), with a higher score indicating a better health-related quality of life. Norm-Based Scores (NBS) and maximum data recovery with Missing Data Estimation (MDE) will be used while deriving summary scores from the software.

Descriptive statistics for actual value and change from baseline will be presented for each of the 8 subscales and 2 summary component measures, by treatment group and visit. A listing will be presented showing the raw scores for each of the 36 questions for each patient, by treatment group and visit. In addition, a listing will be presented showing the results of the derived subscales and summary component measures for each patient, by treatment group and visit.

10.5. 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 each scheduled visit.

Two types of joint damage are evaluated: erosion and joint space narrowing.

- Erosion: Erosion is assessed in the 10 Metacarpophalangeal (MCP) joints, the 8 Proximal Interphalangeal (PIP) joints, the 2 Interphalangeal (IP) joints, the right and left first Metacarpal base (MCB), the right and left distal radius bones, the right and left distal ulna bones, the right and left trapezium bones, the right and left scaphoid bones, the right and left lunate bones, the right and left triquetrum bones, the 10 Metatarsophalangeal (MTP) joints, and the 2 IP joints of the great toes. The score range of erosion is from 0 (Normal) to 5 (Extensive destruction with >80% joint involvement).

- Joint space narrowing (JSN): JSN is assessed in the 10 MCP joints, the 8 PIP joints, the 2 IP joints, the right and left third metacarpal (MC)-capitate joints, the right and left fourth MC-hamate joints, the right and left fifth MC-hamate joints, the right and left scaphoid-trapezium joints, the right and left scaphoid-capitate joints, the right and left radiocarpal joints and the 10 MTP joints. The score range of JSN is from 0 (Normal) to 4 (Complete narrowing).

The maximum erosion score is 170 for hands and 60 for feet, and the maximum JSN score is 128 for hands and 40 for feet. The total sharp score is the sum of the erosion score (from 0 to 230 for both hands and feet) and the JSN score (from 0 to 168 for both hands and feet), thus it ranges from 0 to 398. At least two independent readers will produce scores at each visit for each patients. If the change in score from baseline to the follow-up time point differs between two readers by more than 5 in different directions (one positive, one negative) or more than 10 in same direction (both positive or both negative including score change of 0), an adjudicator will read the images as a third independent reader.

For cases that are not adjudicated, the average of the two readers' scores will be considered as the final score. In cases that are adjudicated, the average of two readers with the closest change score from baseline will be provided as the final score. If the change score for both the primary readers is equidistant to the adjudicator, the average of all three readers will be provided as the final score.

Descriptive statistics for actual value and change from baseline will be presented for total sharp score by treatment group and visit. The summary will only be conducted for Overall Period on

ITT population, and for Treatment Period II on PP Population – Treatment Period II subset. Raw scores for each joint will be listed by treatment group, visit and reader. In addition, total scores, subtotal scores and change from baseline will be listed on the ITT population.

10.6. Joint Surgery

A listing will be produced displaying patients undergoing any surgical joint procedure (including bone or joint surgery or synovectomy [including joint fusion or replacement]). That will display the surgical procedure performed (as coded by MedDRA version 22.0 or the higher version) and the procedure date. Patients who receive joint surgery or synovectomy before Week 24 without discontinuation will be excluded from the PP population.

11. PHARMACOKINETIC ANALYSIS

All PK analyses will be performed on the PK population and on the PK population – Treatment Period II subset by treatment group unless otherwise specified. Blood samples for PK analyses will be collected at time points specified in the schedule of events (Appendix 1).

11.1. Serum Concentrations

Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for serum concentrations will be presented by treatment group at each scheduled visit. For the descriptive summary, below lower limit of quantification (BLQ) prior to the first study drug administration (Week 0, Dose 1) will be treated as zero (0), and all other BLQ values will be set to Lower Limit of Quantification (LLoQ). All concentrations BLQ will be indicated in a data listing.

Serum concentrations of adalimumab will be presented in the listing by treatment group for the Safety population.

11.2. Pharmacokinetic Parameters

The secondary PK endpoint is Trough serum concentration (C_{trough}) up to Week 52. The C_{trough} is observed concentration prior to the next study drug administration.

Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for the PK parameter will be presented by treatment group and visit. Additional summary of descriptive statistics for the PK parameter will be produced by ADA status, treatment group and visit in the same table. In PK population, patients who show at least one “Positive” result in immunogenicity test obtained after study drug exposure up to Week 24 will be considered as “at least one ADA positive subgroup”. All patients who only have “Negative” results in post treatment immunogenicity test up to Week 24 will be considered as “all ADA negative subgroup”. However, if the number of either subgroup is very small (≤5% of PK population) then the subset will not be summarized since it is not statistically meaningful.

All data for the PK parameter will be listed by treatment group for the PK population.

12. PHARMACODYNAMIC ANALYSIS

PD parameters (Rheumatoid factor [RF], Anti-cyclic Citrullinated Peptide [anti-CCP], CRP and ESR) will be summarized displaying descriptive statistics for actual value and change from baseline on the PD population and on the PD population – Treatment Period II subset by treatment group at each scheduled visit and time points specified in the schedule of events (Appendix 1). Descriptive statistics will consist of n, mean, SD, geometric mean, CV%, minimum, median and maximum. All numeric values recorded BLQ or above the upper limit of qualification are set to the respective limit for all summaries.

In addition, RF and anti-CCP will be categorized as following and summarized in shift table from baseline to each post-baseline visit displaying the number and percentage of patients within each category (Negative, Positive) by treatment group.

- RF: ≤10 IU/ml then Negative; >10 IU/ml then Positive
- Anti-CCP: <17 U/ml then Negative; ≥17 U/ml then Positive

All PD data for RF, anti-CCP, CRP and ESR will be listed for the ITT population.

13. SAFETY ANALYSIS

All safety analyses will be performed in the Safety population by treatment group presenting data on adverse events (AEs, including serious AEs), AEs of special interest(AESI) (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), clinical laboratory results (clinical chemistry, hematology, urinalysis), vital sign measurements, ECGs, hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature), weight, physical examination findings, signs and symptoms of tuberculosis (Interferon-gamma Release Assay (IGRA) and Chest X-ray), local site pain (VAS), pregnancy tests, and immunogenicity tests. For the data related with AEs and AESI, summaries will be repeated for Treatment Period II on Safety population – Treatment Period II subset and for Overall Period on Safety population. All other safety data will be repeated on the Safety population – Treatment Period II subset, unless otherwise specified. All safety data will be listed for the Safety population.

13.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study by signing the 'Informed Consent' page of eCRF, regardless of its causal relationship to study drug.

A treatment-emergent adverse event (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.

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or the higher version will be used to code all AEs. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

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

- Missing day (e.g. XXFEB2019): Assume the last day of the month. (e.g. 28FEB2019)
- Missing day and month (e.g. XXXXX2019): Assume December 31st. (e.g. 31DEC2019)
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as Missing.

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

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

- If the day of an Adverse Event is missing (e.g. XXFEB2019), the month and year of the partial date will be compared to the date of the first exposure to study drug.
    - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first exposure to study drug.
    - If the month or year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01FEB2019).
- If the day and month is missing (e.g. XXXXX2019), the year of the partial date will be compared to the date of the first exposure to study drug.
    - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first exposure to study drug.
    - If the year is not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2019).

If the AE start date is missing (e.g. XXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing (e.g. XXXXXXXXX), the AE start date will be imputed as the date of the first exposure to study drug.

The recorded/imputed dates of AEs will be used for decision whether the event is TEAE and classification of treatment periods.

TEAEs will be classified for Treatment Period I and Treatment Period II, defined as follows: a TEAE with a start date prior to the first administration of study drug in Treatment Period II, or TEAE for those patients who did not administered study drug during Treatment Period II will be included in Treatment Period I. A TEAE with a start date on or after the date of first administration of study drug in Treatment Period II will be included in Treatment Period II.

Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date/time; TEAE flag, treatment period (Treatment Period I, Treatment Period II), frequency (continuous, intermittent, transient); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); any treatment received (no, medication treatment, non-medication treatment, both

medication and non-medication treatment); intensity (CTCAE Grade 1 to 5); action taken with study drug (no action taken, drug interrupted, drug withdrawn, not applicable); relationship with study drug (unrelated, possible, probable, definite); whether the event was serious (no, yes); whether the AE is hypersensitivity/allergic reaction or injection site reaction (ISR); and infection/malignancy flag. All AEs will be listed.

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

13.1.1. Incidence of Treatment-Emergent Adverse Events

The TEAEs during the study will be summarized by treatment group and SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE over all SOCs will also be displayed. TEAEs with PT reported for at least 3% of patients in either treatment group will be summarized separately.

Additionally, TEAEs, TESAEs and TEAEs leading to Study Drug Discontinuation will be summarized by treatment group, SOC, PT and intensity, regardless of relationship, displaying the number and percentage of patients experiencing at least one TEAE using only the worst intensity.

13.1.2. Deaths

All patients who have a Serious Adverse Event (SAE) with serious criteria of "Death" will be presented in a listing and the following variables will be included; date of first/last dose, date of last visit, date of death, time to death from first/last dose, days on study, TEAE flag, SOC/ PT, cause of death, autopsy after death (yes, no), completion of death certificate (yes, no) and relationship to study drug. Time (days) to death from first/last dose will be calculated as (date of death – date of first/last dose + 1). In case of death during the study, days on study will be calculated as (date of death – date of first dose +1). Otherwise, days on study will be calculated as (date of last visit – date of first dose +1).

13.1.3. Serious Adverse Events

An SAE is defined as any event that 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 or results in death. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

Additionally, TESAEs will be summarized by treatment group, SOC, PT and intensity regardless of relationship, displaying the number and percentage of patients experiencing at least one TESAE using only the worst intensity.

All SAEs will be listed including a subset of the variables detailed in Section 13.1. Serious criteria and SAE description will be presented in an additional information listing.

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

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

Additionally, TEAEs leading to study drug discontinuation will be summarized by treatment group, SOC, PT and intensity regardless of relationship, displaying the number and percentage of patients experiencing at least one TEAE leading to study drug discontinuation using only the worst intensity.

All TEAEs leading to study drug discontinuation will be listed including a subset of the variables detailed in Section 13.1.

13.1.5. Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest are as following:

- Hypersensitivity/allergic reactions
  TEAEs recorded as Hypersensitivity/allergic reactions in the eCRF will be included.
- Injection site reactions (ISR)
  TEAEs classified as ISR in the eCRF will be included.
- Infection
  TEAEs coded with a SOC of 'Infections and Infestations' will be included.
- Malignancy
  TEAEs coded with a SOC as 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' excluding events whose any of the High Level Group Term (HLGT), High level Term (HLT), PT, and Lowest Level Term (LLT) contains 'benign' will be classified as Malignancy. It will be determined to be included by medical review.

TEAEs of special interest will be summarized in separate tables. These are displayed by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the most severe TEAE recorded at each levels of summarization. The total number of events and number of patients with at least one TEAE of special interest will also be displayed. In addition, tables for signs and symptoms regarding Hypersensitivity/allergic reactions and ISR will be provided separately by SOC, PT (as coded by MedDRA version 22.0 or the higher version) and intensity.

TEAEs classified as Hypersensitivity/allergic reactions and ISR will be presented in separate listings including a subset of the variables detailed in Section 13.1. Experienced signs and

symptoms will be presented in additional information listings for Hypersensitivity/allergic reactions and ISR, separately. Infection and malignancy will be flagged in listings for AEs.

13.2. Clinical Laboratory Evaluations

Clinical chemistry, hematology, urinalysis and CRP test samples will be analyzed at the central laboratory at each scheduled visit. ESR samples will be analyzed at the local laboratory using kits supplied centrally. All summaries and listings will be based on the SI (System International) units, and only the parameters specified in the protocol will be analyzed and listed (Appendix 1).

Actual value and change from baseline of all numeric laboratory parameters including clinical chemistry, hematology, urinalysis (if applicable, except for microscopic examination), CRP and ESR will be summarized using descriptive statistics by treatment group, laboratory category, test parameter and visit. All numeric values recorded BLQ or above the upper limit of qualification are set to the respective limit for all summaries.

The central laboratory test results for parameters including urinalysis, clinical chemistry and hematology (if applicable) are categorized with Normal and Abnormal and then will be summarized in a shift table from baseline to each scheduled visits. The number and percentage of patients will be displayed for post-baseline visits by treatment group, laboratory category, test parameter and visit.

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

The number and percentage of patients by laboratory category, treatment group and CTCAE term will be summarized using the most severe grade after the first study drug administration for each Treatment Period and for Overall Period. The most severe grade will be selected including all post-baseline scheduled and unscheduled visits.

All clinical laboratory results of clinical chemistry, hematology and urinalysis including microscopic examination will be presented in separate listings along with high and low flags, if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters. Creatinine clearance will only be listed at Screening. CRP and ESR will be listed along with the other PD parameters on the ITT population.

13.3. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and weight will be assessed at scheduled visits prior to beginning of the study

drug administration. For hypersensitivity monitoring, vital signs will also be assessed at the following time points of scheduled visit:

- Prior to the study treatment administration
- 1 hour (±10 minutes) after the end of the study treatment administration

All vital signs data and weight will be summarized using descriptive statistics of actual value and change from baseline by treatment group and parameter at each scheduled visit.

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

Table 6. Hypersensitivity Classification for Vital Signs

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

All vital signs data including hypersensitivity monitoring results and weight will be listed for each patient by treatment group, visit, time points and parameter. High and low flags will also be presented in the listing to show whether a value is outside of the normal range.

13.4. Electrocardiograms

12-lead ECGs will be performed at the time points specified in the schedule of events (Appendix 1). Findings of 12-lead ECG will be classified as either "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant". The number and percentage of patients will be summarized by treatment group and visit, in the form of a shift table to detect changes from baseline. All 12-lead ECG data will be listed for each patient by treatment group and visit.

13.5. Physical Examination

Physical examinations will be performed at the time points specified in the schedule of events (Appendix 1). The following body systems will be examined:

- General Appearance
- Head, Ears, Eyes, Nose, Throat
- Neck and Thyroid
- Skin
- Cardiovascular System
- Respiratory System
- Abdominal System

- Neurological System
- Musculoskeletal System
- Lymph Nodes
- Urogenital System
- Other

Findings of physical examination will be collected as either "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant". The number and percentage of patients will be summarized in a table by treatment group, visit and body system, in the form of a shift table to detect changes from baseline. All physical examination data will be listed for each patient by treatment group, visit and body system.

13.6. Tuberculosis Assessment

Tuberculosis (TB) will be assessed using IGRA and Chest X-ray, and clinically monitored throughout the study.

Results for IGRA will be classified as either "Positive", "Indeterminate" or "Negative". If retest is conducted because the IGRA result is indeterminate, the result of the retest will be used for the summary. Both the first and retest results will be listed. The number and percentage of patients with IGRA results will be summarized for baseline (as defined in Section 5.5) and each visit in Treatment Period.

Results for Chest X-ray will be classified as either "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant". The patients will be monitored throughout the study to confirm the presence of any signs or symptoms indicative of TB.

Each patient's IGRA, Chest X-ray and TB clinical monitoring results will be separately listed by treatment group and visit.

13.7. Local Site Pain

Local site pain measurements using 100 mm VAS will be performed immediately (within 15 minutes) after the end of the study drug administration at the time points specified in the schedule of events (Appendix 1). Local site pain data will be summarized using descriptive statistics by treatment group and visit. All local site pain data will be listed by treatment group and visit.

13.8. Pregnancy Test

Pregnancy tests will be conducted and summarized only for female patients of childbearing potential. Pregnancy tests consist of serum and urine pregnancy tests. Urine pregnancy tests will be performed locally prior to dosing on each scheduled visit. Serum pregnancy tests will be performed by a central laboratory at Screening and EOS. Urine pregnancy test results will be classified as either "Positive" or "Negative". If a urine pregnancy test result is "Positive", a confirmatory serum pregnancy test should be performed. Serum pregnancy test results will be classified as either "Positive", "Negative" or "Indeterminate".

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

13.9. Immunogenicity

Serum sample for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of events (Appendix 1). Additional serum samples for immunogenicity testing may be collected if a patient experiences immune-related AEs. Immunogenicity assessments consist of both anti-drug antibody (ADA) and neutralizing antibody (NAb) assays.

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

Samples that are positive in the ADA specificity/confirmatory assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be: {"Positive" or "Negative"}.

The results of the final ADA and the screening NAb assay will be summarized. The summary will only be conducted for Overall Period on the Safety Population. The number and percentage of patients will be presented by treatment group and test at each scheduled visit.

In addition, positive conversion in ADA and NAb will be summarized including all scheduled and unscheduled visits. The proportion of patients who reported at least one ADA positive result after the first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II, and had not any ADA positive result before the first study drug administration will be presented for the Safety Population. The proportion of patients who reported at least one NAb positive result after the first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II, and had not any NAb positive result before the first study drug administration will also be presented for the Safety Population.

For the Safety Population – Treatment Period II subset, proportion of patients who reported at least one ADA positive result after the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment

Period II and had not any ADA positive result before the first study drug administration in Treatment Period II will be presented. The proportion of patients who reported at least one NAb positive result after the first study drug administration in Treatment Period II in patients who had at least one ADA result after the first study drug administration in Treatment Period II and had not any NAb positive result before the first study drug administration in Treatment Period II will also be presented.

For the summary of Overall Period, proportion of patients who reported at least one ADA positive result after the first study drug administration in Treatment Period I in patients who had at least one ADA result after the first study drug administration in Treatment Period I and had not any ADA positive result before the first study drug administration in Treatment Period I will be presented. The proportion of patients who reported at least one NAb positive result after the first study drug administration in Treatment Period I in patients who had at least one ADA result after the first study drug administration in Treatment Period I and had not any NAb positive result before the first study drug administration in Treatment Period I will also be presented.

A listing showing immunogenicity test results for each patient will be provided by treatment group and visit.

14. USABILITY ANALYSIS

The following Usability endpoints will be assessed:

- The usability assessed by patient rating using PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ)
- The observer rating of successful self-injection using Self-Injection Assessment Checklist

The usability endpoints will be assessed only for self-injections by patients at Weeks 4, 6, 8, and 24. If the study drug is administered by caregiver or by trained study center staff, usability assessments are unnecessary.

All usability tables and listings will be generated by treatment group, using all data for the Usability population. As a sensitivity analysis to assess usability in self-SC injection naïve patients, all usability tables will be generated for the patients who checked ‘No’ to “Does the patient have any self-SC injection experience in lifetime?” on the eCRF.

14.1. Self-Injection Assessment Questionnaire (SIAQ)

Usability will be assessed using the SIAQ prior and after self-injection of the study drug at Weeks 4, 6, 8 and 24. PRE-SIAQ module is a 7-item questionnaire that investigates 3 domains such as feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection (each item graded on a 5-points). The POST module of the SIAQ is a 27-item questionnaire that assesses feelings about injection, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection (injection-

site reactions), ease of use of the self-injection device (PFS), and satisfaction with self-injection. Each item will be graded on either a 5-point or 6-point scale.

Item score will be transformed to obtain a score ranging from 0 to 10 for each item, based on below algorithm:

- For 5-point semantic Likert-type scale: Transformed = ([raw score]-1) x 2.5
- For 6-point semantic Likert-type scale: Transformed = ([raw score]-1) x 2

The domain score will be defined as the mean of the transformed item scores included in the domain. Domain scores will be calculated only if at least half of the domain items are completed. Otherwise, domain score will be missing.

The domain scores of PRE and POST module of SIAQ will be summarized using descriptive statistics by each scheduled visit and domain. In addition, the 95% CI of mean domain scores of treatment groups and the difference in mean domain scores between treatment groups will be calculated by each scheduled visit and domain. A listing for PRE and POST module of SIAQ will be presented showing the raw scores for each questions and domain scores. The domain scores will be displayed to one decimal places.

14.2. Successful Self-injection

Patients' ability to successfully follow the steps in the Instruction for Use to self-administer will be assessed using self-injection assessment checklist at Weeks 4, 6, 8 and 24. The investigator or designated study center staff will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection. Successful self-injection will be coded as successful if N7, N10, N11 and N12 of the self-injection assessment checklists are checked as Yes.

Summary table will display proportion of patients completing the successful self-injection (based on 4 assessments above) and proportion of patients completing all 14 instructions, respectively, by each scheduled visit. The number of patients who have full assessment of self-injection assessment checklist will be used as the denominator. All answers for checklists will be listed along with whether this injection is successful and all instructions are completed.

15. Changes in the Planned Analysis

15.1. Changes in the Protocol

- Section 7.5 of the protocol (ver 3.0) states that viral serology analysis (Hepatitis B, Hepatitis C and HIV) will be performed on the Safety population. Analysis population of the viral serology analysis will be modified to ITT population in the SAP section 7.4 since results of those analyses are related to the exclusion criteria #3.

- In the logistic regression model for the primary efficacy analysis (Section 10.1.5.2 of SAP), the SDAI at Screening will be included in covariates instead of the stratification

level of SDAI (high, not high) which described in Section 7.1.1 of the protocol (ver 3.0).

16. Reference List

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17. APPENDIX

Appendix 1: Schedule of Events

	Screening	Treatment Period I									Treatment Period II							EOS [1]
		Dose 1	Dose 2	Dose 3	Dose 4[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**	**6[3]**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit[2] (Day)	**–42 to –1**	**1**	**15**	**29**	**43[3]**	**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[4]	X										(X)							(X)
Serum pregnancy test[5]	X																	X
Chest X-ray[6]	X																	X
IGRA[7]	X						X[8]			X[8]								X
Inclusion/ exclusion criteria	X	X[8]																
Randomization		X[9]									X[9]							
Efficacy assessments[8,10]– 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[11]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ESR (local)[11]	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[12]	X																	X
Safety and other assessments[8] – 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[13]	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 4[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**	**6[3]**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit[2] (Day)	**–42 to –1**	**1**	**15**	**29**	**43[3]**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Urine pregnancy test[5]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[14]	X	X								X								X
Immunogenicity[15]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sampling[16]		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[17]		X																
Study treatment[18,19]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
PRE- and POST-SIAQ[20]				X	X	X				X								
Self-injection assessment checklist by observer[21]				X	X	X				X								
Hypersensitivity/ allergic reactions monitoring[22] and injection site reaction[23]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Local site pain by VAS[24]		X	X	X		X		X		X	X		X	X		X	X	
Prior, concomitant medications[25]	X																	
TB clinical monitoring[26]	X																	
AEs[27]	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; SIAQ, self-injection assessment questionnaire; 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 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. For patient who the caregiver or trained study center staff injects the study drug, usability assessment are unnecessary.

4. 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.
5. 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.
6. 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.
7. 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.
8. Procedures will be performed at the study center prior to the study drug administration.
9. 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).
10. 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.
11. 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.
12. 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.
13. 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

14. 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.

15. 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.
16. 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.
17. 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.
18. 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 Weeks 0 and 2. After patients are properly trained, the study drug will be administered by patients at Weeks 4, 6, 8 and 24 at the study center for usability assessments. For remained visits, the study drug can be administered by the patient or caregiver at home or by study center staff according to the regular study center visit schedule (see Section 5.2.3 of Protocol 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. If the patient or caregiver is improperly trained or unconfident to administer the study drug at home, the study drug can be administered at the study center by trained study center staff.
19. 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.
20. PRE- and POST-SIAQ will be completed by patient prior to and after self-injection of the study drugs at Weeks 4, 6, 8 and 24. Patients will complete PRE-SIAQ immediately before the administration of study drug and POST-SIAQ within 20 to 40 minutes after the administration of study drug. If the study drug is administered by caregiver or by trained study center staff, PRE- and POST-SIAQ assessment is unnecessary.
21. The investigator or designed study center staff will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection at Weeks 4, 6, 8 and 24. If the study drug is administered by caregiver or by trained study center staff, self-injection assessment checklist assessment is unnecessary.
22. Hypersensitivity/allergic reactions will be assessed prior to the study drug administration and 1 hour (±10 minutes) after end of the study drug administration by additional vital sign measurement. For patient who early discontinued study treatment, monitoring of hypersensitivity/allergic reactions are unnecessary after the discontinuation.
23. 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.
24. 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.
25. 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. For usability analysis, the experience of self-SC injection will be recorded in the patient's eCRF.
26. 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.
27. 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.

Appendix 2: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL;<30 - 20 g/L	<2 g/dL;<20 g/L	-
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Leukocytosis	White Blood Cells	High	-	-	>100,000/mm^3	-
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3;<LLN - 3.0 x 10e9 /L	<3000 - 2000/mm^3;<3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3;<2.0 - 1.0 x 10e9 /L	<1000/mm^3;<1.0 x 10e9 /L
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased [1)]	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Eosinophilia	Eosinophils (Absolute Ct)	High	>ULN and >Baseline	-	-	-
GGT increased	Gamma Glutamyl Transferase (GGT)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Hypoglycemia	Glucose	Low	<LLN-55mg/dL;<LLN-3.0 mmol / L	< 55 -40mg/dL;< 3.0 – 2.2 mmol / L	< 40 -30mg/dL;< -2.2 – 1.7 mmol / L	<30mg/dL; <1.7mmol/L
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L; <LLN – 6.2 mmol/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	-
Blood lactate dehydrogenase increased	Lactate Dehydrogenase (LDH)	High	>ULN	-	-	-
Lymphocyte count decreased	WBC Differential, Lymphocytes	Low	<LLN - 800/mm^3;<LLN - 0.8 x 10e9/L	<800 - 500/mm^3;<0.8 - 0.5 x 10e9 /L	<500 - 200/mm^3;<0.5 - 0.2 x 10e9 /L	<200/mm^3;<0.2 x 10e9 /L
Lymphocyte count increased	WBC Differential, Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3;<LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3;<75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3;<50.0 - 25.0 x $10e^9$ /L	<25,000/mm3;<25.0 x $10e^9$ /L
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L regardless of symptoms	<120 mmol/L
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L

Neutrophil count decreased	WBC Differential, Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L

LLN = lower limit of normal, ULN = upper limit of normal.
1) The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.
Note: The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory at each relevant transfer. In case numeric value for grading is identical such as Hypokalemia, CTCAE grade which includes numeric value will only be applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.