**CELLTRION, Inc.**

**CT-P17 3.2**

# A Phase III, Open-label, Single-arm, Multiple-dose Study to Evaluate Usability of Subcutaneous Auto-injector of CT-P17 in Patients with Moderate to Severe Active Rheumatoid Arthritis

**22JUN2020**

Statistical Analysis Plan

**Final Version 3.0**

Prepared by:

[redacted]

***Document History – Changes compared to previous version of SAP:***

| Version | Date Issued | SAP Section | Detail of Changes |
|---|---|---|---|
| 1.0 | 29AUG2019 | | |
| 2.0 | 09DEC2019 | General | Updated SAP Based on the protocol amendment given in Protocol, Version 2.0, 11 November 2019 |
| | | Section 1 | Updated the statement related to number of CSR.<br>Version of protocol and CRF updated |
| | | Section 3.1 | Figure of Study Design overview updated |
| | | Section 3.2 | Added anaphylactic reactions and removed electrocardiogram [ECGs] from overall safety analysis |
| | | Section 4 | Added cutoff rule for Week 4 analysis |
| | | Section 4.1 | Updated sample size |
| | | Section 5.1 | Updated to “Patient continuing the study” Instead of “Completed study treatment up to Week 4” in disposition table for Week 4 analysis |
| | | Section 10.1.5 | Added Anaphylactic reactions and related summary details |
| | | Section 11 | Removed the section 11 related to changes in the planned analysis. Currently there is no changes compared to protocol in SAP in analysis |
| | | Section 12.4 | Marked TLFs with (*) to understand Week 4 analysis related outputs |
| 3.0 | 22JUN2020 | Section 4 | Added a statement to remove Early discontinuation visit from summary tables |
| | | Section 10.2 | A description added to explain that Creatine Kinase MB will be available only in listing. This parameter will not be available in tables. |
| | | Section 12.3 | Removed the toxicity term Glucosuria |
| | | Section 12.4 | Listing 16.2.7.2 to Listing 16.2.7.8 are renamed to Listing 14.3.2.1 to Listing 14.3.2.7. |

## Table of Contents

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ACR | American College of Rheumatology |
| AE | adverse event |
| AI | auto-injector |
| AESI | adverse events of special interest |
| ATC | Anatomical Therapeutic Chemical |
| BMI | body mass index |
| CRP | C-reactive protein |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DAS | disease activity score |
| DNA | deoxyribonucleic acid |
| DSMB | Data and Safety Monitoring Board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ED | early discontinuation |
| EOS | end-of-study |
| EOW | every other week |
| ESR | erythrocyte sedimentation rate |
| HbsAb | hepatitis B surface antibody |
| HbsAg | hepatitis B surface antigen |
| HbcAb | hepatitis C core antibody |
| HBV | Hepatitis B virus |
| HIV | human immunodeficiency virus |
| IFU | instructions for use |
| IGRA | interferon-γ release assay |
| IM | intramuscular |
| ITT | intent-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | methotrexate |
| NYHA | New York Heart Association |
| PGA | patient global assessment |
| PT | preferred term |
| RA | rheumatoid arthritis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SD | standard deviation |
| SIAQ | Self-Injection Assessment Questionnaire |
| SJC | swollen joint count |
| SoA | schedule of activities |
| SOC | system organ class |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |

| | |
|---|---|
| TESAE | treatment-emergent serious adverse event |
| TJC | tender joint count |
| TLF | tables, listings, figures |
| VAS | visual analogue scale |
| WHO | World Health Organization |

# 1. Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations to be used by [redacted] in the analysis and presentation of data for the analysis of CELLTRION study number CT-P17 3.2, entitled "A Phase III, open-label, single-arm, multiple-dose study to evaluate usability of subcutaneous auto-injector of CT-P17 in patients with moderate to severe active rheumatoid arthritis".

The first Statistical analysis will be performed for regulatory submission on the usability data up to Week 4 and the final statistical analysis will be performed for all data after completion of the study. There is one clinical study report (CSR) planned for all data after completion of the study.

The purpose of the Week 4 data analysis is to assess the primary endpoint at Week 4. This analysis will be performed once all patients have completed Week 4 or withdrawn from the study before the Week 4 assessment. Only data up to and including Week 4 will be included in this analysis.

CT-P17 has been developed by CELLTRION, Inc. and is intended to be developed as a biosimilar to Humira.

Rheumatoid Arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, occurring in approximately 0.8% of the global population[1, 2]. It is characterized by a progressive inflammatory synovitis of the joints, which may result in irreversible joint erosion from as early as 6 months of disease onset[3]. It has a significant negative impact on the ability to perform daily activities and health related quality of life, and it increases mortality[1]. Therefore, early identification and appropriate treatment should be the primary focus when managing patients with RA to reduce disease progression and loss of function.

The purpose of this Phase III study is to evaluate the usability of CT-P17 auto-injector (AI) assessed by patients and observers following the recommendations of the guidance for industry, "Rheumatoid Arthritis: Developing Drug Products for Treatment"[4]. For products intended for self-administration by an RA patient, the device should be durable, and the dexterity and visual acuity required to use the device should be within the capacity of RA patients[4]. In addition, the safety and efficacy of CT-P17 will also be assessed.

This study is designed to take into consideration the characteristic of the RA population and their user environment in AI device use by assessing whether usability is within the capability of RA patients.

This SAP covers all specified analysis for the final study reports based on the following document(s):

- Final Protocol, Version 2.0, 11 November 2019
- Electronic case report form (eCRF) Version 2.0, 14 October 2019

## 2. Objectives

### 2.1. Primary Objective

- To evaluate usability of CT-P17 AI assessed by patients at Week 4.

### 2.2. Secondary Objectives

- To evaluate change in usability assessed by patients and observer over time up to Week 24
- To evaluate overall efficacy.
- To evaluate overall safety.

## 3. Investigational Plan

### 3.1. Overall Study Design and Plan

This study is a Phase III, open-label, single-arm, multiple-dose study to evaluate usability, safety and efficacy of subcutaneous (SC) AI of CT-P17 (the study drug) in patients with moderate to severe active RA. The study drug will be administered every other week (EOW) by SC injection via AI from Week 0 to Week 24 in combination with methotrexate (MTX) (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or intramuscular [IM]) and folic acid (≥5 mg/week, oral). The patient must have been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug on Day 1. The same dose and route should be maintained throughout the study.

The study includes a Screening Period (6 weeks), a Treatment Period (24 weeks), and a Follow-up Period (4 weeks).

**Screening Period (6 weeks):** Screening Period will be from Day -42 to Day -1 (6 weeks), prior to the first study drug administration.

**Treatment Period (24 weeks):** Treatment Period will be from Week 0 to Week 24.
On Day 1 (Week 0), patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. The patients will receive CT-P17 from Week 0 to Week 24 EOW by SC injection via AI, co-administered with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM; dose and route must be maintained from Screening to end-of-study [EOS]/early discontinuation [ED]) and folic acid (≥5 mg/week, oral). Patients will comply with all appropriate visits and assessments.

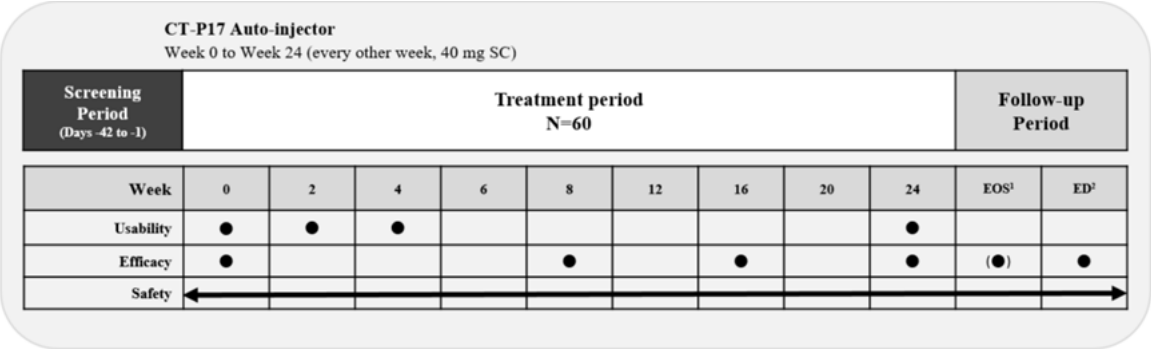
The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection on Day 1 (Week 0) visit. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.

**Follow-up Period (4 weeks):** An EOS visit will occur after 4 weeks from when the last dose of study drug is received (at Week 24) or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.

An ED visit will occur after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

The schedule of activities (SoA) is presented in Appendix 12.1 and the study design overview is illustrated in Figure 1 below.

Figure 1:Study Design Overview




Abbreviations: AI=auto-injector; EOS=end-of-study; ED=early discontinuation; N=number of patients; RA=rheumatoid arthritis; SC=subcutaneous.
Note: The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection at Week 0. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.
[1] The EOS assessments need to be completed after 4 weeks from when the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.
[2] The ED visit needs to be completed after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

### 3.2. Study Endpoints

Primary and secondary endpoints of each objectives are explained in Table 1 below.

Table 1: Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate usability of CT-P17 AI assessed by patients at Week 4. | The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ) at Week 4. |
| **Secondary** | |
| To evaluate change in usability assessed by patients and observer over time up to Week 24. | The usability as assessed by patients rating using PRE- and POST-SIAQ at Weeks 0, 2 and 24.<br>The observer rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2, 4 and 24. |
| To evaluate overall efficacy. | Mean change from baseline in disease activity score (DAS) 28 (C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR]) up to Week 24. |
| To evaluate overall safety. | Adverse events (AEs) (including serious AEs [SAEs]), AEs of special interest (AESIs) (injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies), hypersensitivity monitoring (via monitoring of vital signs), vital signs measurements, ECGs, physical examination findings, interferon-γ release assay (IGRA), chest X-ray, pregnancy testing, clinical laboratory analyses, signs and symptoms of tuberculosis (TB), and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) status will be tested for the patient's eligibility determination. |

## 4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be described using the count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation/ standard error will be displayed to two levels of precision greater than the data collected.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for missing values**.** The denominator for all percentages will be the number of patients within the analysis set of interest, unless otherwise specified. Percentages will be presented to one decimal place.

Data will be displayed in all listings sorted by patient number and visit, if applicable. Listings will include all visits including unscheduled visits.

The following cut off rules will be used for the first statistical analysis for the regulatory submission on the usability data up to Week 4.

- All scheduled records up to and including Week 4, and all unscheduled records on or before the date of the Week 4 dose will be included. If the Week 4 dose date is missing, then unscheduled visits on or before the date of the Week 4 visit will be included.
- All records up to study discontinuation date will be used if the patient discontinued prior to Week 4 visit.

"No data available for this report" will be presented when there are no data available to report.

Unless otherwise specified, baseline will be defined as the last non-missing value collected before the first study drug administration. Study day is defined as:

- Visit/examination date – date of first study drug administration when date is prior to the date of first study drug administration (day 1).
- Visit/examination date – date of first study drug administration + 1 when date is after day 1

For summaries by visit, if multiple records fall on the same visit, then the record which is the earliest value will be chosen.

Unscheduled and Early discontinuation results will not be summarized but will be listed, unless otherwise specified. Post baseline summaries will include all values collected after the date of first study drug administration.

For the purpose of inclusion in tables, incomplete start and stop dates (e.g. AEs and prior/concomitant medication) will be imputed as follows:
Missing start dates (where UK and UKN indicate unknown or missing day and month respectively) will be handled as follows:

1. UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the stop date (after any

imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date;

2. DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the stop date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date.

Missing stop dates (where UK and UKN indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

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

All analyses of the data will be conducted using [redacted]

### 4.1. Sample Size

Approximately 60 male or female adult patients will be enrolled. In this usability study, a sample size justification based on a formal statistical hypothesis is not relevant, since a formal statistical inference will not be made.

### 4.2. Randomization, Stratification, and Blinding

This study is a single-arm, open-label study and so there is no randomization or blinding.

### 4.3. Analysis Set

The analysis sets that will be analyzed are:

- Intent-to-treat (ITT) Population
- Safety Population
- Usability Population

#### 4.3.1. Intent-to-Treat (ITT) Population

The ITT Population includes all enrolled patients to receive a dose of study drug, regardless of whether any study drug dosing was completed. This definition includes all patients who are enrolled in the study.

#### 4.3.2. Safety Population

The Safety Population includes all patients who received at least 1 dose (full or partial) of study drug.

#### 4.3.3. Usability Population

The Usability Population includes all patients in the Safety Population who have evaluable usability measurements at Week 4 and who do not have major protocol deviations (Section 5.2) that may affect the interpretation of the study results. The usability measurement is defined as "evaluable" at Week 4 if the patient has a non-missing domain score for both the PRE- and POST-SIAQ at Week 4.

## 5. Patient Disposition

### 5.1. Disposition

A summary of screen failures will be provided including the number and percentage of patients for the following categories: patients screened, patients who failed screening and the primary reason for screen failure ("Inclusion/Exclusion criteria not met", "Withdrew consent" and "Other").

A listing of screen failures will be presented.

A summary of the analysis sets includes the number and percentage of patients in ITT, Safety and Usability Populations. Percentages will be based on the ITT Population. This summary will also include the number and percentage of patients for the following categories:

- Patients excluded from the Safety Population and reasons
- Patients excluded from the Usability Population and reasons

Percentages for exclusion reasons will be based on the number of patients excluded from the specific analysis set being summarized. Patients could be excluded from an analysis set for more than one reason.

A listing will be produced showing each patient and in which populations they are included. This listing will be based on the ITT population.

Patient disposition will be summarized for the ITT Population for Week 4 and EOS separately. For the analysis of Week 4, the disposition of patients includes the number and percentage of patients for the following categories: patients who initiated treatment, patients who are continuing the study and patients who discontinued study treatment on or before Week 4. For the analysis of EOS, the disposition of patients includes the number and percentage of patients for the following categories: patients who initiated treatment, patients who completed study treatment up to Week 24, patients who discontinued study treatment on or before Week 24, patients who completed the study, that is, who completed EOS and patients who terminated from the study, that is, who completed up to Week 24 but did not complete EOS. All percentages will be based on the number of patients in the ITT Population.

The reasons for study treatment discontinuation prior to Week 4 and prior to EOS will also be summarized separately in the above mentioned patient disposition tables. The reason for discontinuation of study treatment are:

- Progressive Disease
- Adverse Event
- Protocol Deviation
- Lost to Follow-up
- Death
- Investigator Decision
- Withdrawal by Patient
- Pregnancy
- Study Terminated by Sponsor
- Other

The reasons for termination of study participation prior to Week 4 and prior to EOS will also be summarized separately in the above mentioned patient disposition tables. The reason for termination of study participation are:

- Withdrawal by Patient
- Lost to Follow up
- Death
- Other

Patient disposition data will be presented in a listing for the ITT Population.

### 5.2. Protocol Deviations

A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare. Patients with major protocol deviations will be excluded from the Usability Population and the major protocol deviations are defined as follows:

- Non-adherence to Inclusion or Exclusion criteria which affect the usability result. These are defined as:
    - Inclusion criterion #2: Patient must be able and willing to self-administer SC injections via auto-injector.
    - Exclusion criterion #3: Patient who has previous or current use of other SC self-injected drugs (e.g., insulin, MTX).
- Significant Good Clinical Practice non-compliance

The major protocol deviations will be summarized and listed for the ITT Population.

# 6. Demographics and Baseline Characteristics

## 6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (years), gender, race, and ethnicity. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) ($kg/m^2$) and fertility status (applicable for female patients).

Age and BMI will be automatically calculated in the eCRF.

Age (years), baseline height (cm), baseline weight (kg), and baseline BMI ($kg/m^2$) will be summarized using descriptive statistics. The number and percentage of patients by sex (Male, Female), race (Asian, White, Black or African American and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino and Unknown), will also be reported. Percentages will be based on the total number of patients in the ITT Population. In addition, fertility status (Surgically Sterilized, Post-Menopausal, potentially able to bear children and Other) will also be summarized. Percentages for the fertility status summary will be based on the number of female patients.

Patient demographic and baseline characteristics will be presented in a listing.

## 6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized and listed for the ITT Population:

- Time since RA diagnosis: This will be calculated as follows:
  Time since RA diagnosis (Days) = First administration date of study drug - Initial RA diagnosis date + 1.
  Incomplete initial RA diagnosis date will be imputed using the imputation rule of stop date given in Section 4. Additionally, if the imputed date is later than first administration date of study drug, then it will be imputed using the first administration date of study drug. If the whole date is missing, the date will not be imputed and time since RA diagnosis will not be calculated.
- Total number of tender joints: Summary for tender joint count (68) will be presented.
- Total number of swollen joints: Summary for swollen joint count (66) will be presented.
- New York Heart Association (NYHA) Functional Classification Assessment (categorized as Class I, Class II, Class III and Class IV). A separate summary table and listing will be produced.
- American College of Rheumatology (ACR) Revised Criteria for Classification of Functional Status (categorized as Class I, Class II, Class III and Class IV). A separate listing will be produced.

### 6.3. Viral Serology

Viral serology tests will be performed for determination of the patient's eligibility. The following tests will be summarized and listed for the ITT population:

- Hepatitis B Test: HbsAg (hepatitis B surface antigen), HbsAb (hepatitis B surface antibody) and HbcAb (hepatitis B core antibody). Results will be classified as "Negative", "Positive" or "Not done".
- Hepatitis C Test: Result will be classified as "Negative", "Positive" or "Not done".
- HIV Test: Result will be classified as "Negative", "Positive" or "Not done".
- HBV (Hepatitis B virus) DNA (deoxyribonucleic acid) Test: Result will be classified as "Negative", "Positive" or "Not applicable". This test will be summarized by the HbcAb result ("Negative" or "Positive").

### 6.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0 or higher). The total number of medical history events and the number and percentage of patients with at least one medical history event will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of patients in the ITT Population.

Patient medical history data including specific details will be presented in a listing.

### 6.5. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in sections 4.1 and 4.2 of the protocol and will be listed for the ITT Population.

## 7. Treatments and Medications

### 7.1. Prior and Concomitant Medications

All medications used from 42 days prior to the date of first dose of study drug until the EOS/ED visit will be collected on the patient's source documents and the eCRF. All medications will be coded according to the World Health Organization (WHO) Drug Dictionary version MAR2019 or later.

A prior medication is defined as any medication where the start date and stop date are before the date of first dose of study drug. A concomitant medication is defined as one where the start or stop date is either on or after the date of first dose of study drug.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed using the imputation rule given in Section 4.

If the stop date is completely missing, then the question on the eCRF; 'If stop date is unknown, was this drug stopped before the first administration of study drug?' will be used for classification of the medication. If the answer is "Yes" then the medication will be

classed as prior medication and if the answer is "No" then the medication will be classed as concomitant medication.

The total number of prior and/or concomitant medications and the number and percentages of patients with at least one prior and/or concomitant medication will be summarized overall. The number and percentages of all prior and/or concomitant medications will be summarized and listed by drug class using ATC (Anatomical Therapeutic Chemical) level 2 and preferred term. If the ATC level 2 for the drug class is not available, level 1 will be used instead. At each level of summarization, a patient is counted once if the patient reported one or more medication at that level. All summaries and listings will be presented for the Safety Population.

#### 7.1.1. Co-administration of Methotrexate and Folic acid

Information about the co-administration of methotrexate and folic acid will be collected separately. The same rules for date imputation and definitions of prior and concomitant given in Section 4 and Section 7.1 will apply. A summary table will be produced showing the number and percentage of patients who used methotrexate and folic acid at any time during the study. This table will also display descriptive statistics of the methotrexate dose (mg/week) and folic acid dose (mg/week) taken concomitantly with the first study drug administration. This summary will be based on the Safety Population and these data will also be listed.

### 7.2. Study Treatments

The number and percentage of patients with dose administered will be summarized at each scheduled dose visit, along with the number and percentage of patients who did and did not have the 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. Summaries will be based on the Safety Population.

A listing will be provided for the Safety Population showing the details of study drug administration.

## 8. Usability Analysis

The primary usability endpoint is the patient rating using PRE- and POST- SIAQ at Week 4. The secondary usability endpoints are:

- Patient rating using PRE- and POST-SIAQ at Weeks 0, 2 and 24;
- Observer rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2, 4 and 24.

The primary and secondary usability endpoint analyses will be performed on the ITT and Usability Populations.

### 8.1. SIAQ

Usability is assessed by patients' rating using PRE- and POST-SIAQ [5, 6]. PRE- and POST-SIAQ will be completed by the patient prior to and after self-injection of CT-P17 SC via AI. 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.

The PRE-SIAQ module is a 7-item questionnaire that investigates 3 domains; feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection (each item graded on a 5-point or 6-point semantic Likert-type scale). The POST-SIAQ module is a 27-item questionnaire that assesses feelings about injections, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection site reactions, ease of use of the self-injection device, and satisfaction with self-injection (each item graded on either a 5-point or 6-point semantic Likert-type scale). The best or worst patient's experience level of each item score is mentioned in Table 2 below.

The above mentioned 5-point or 6-point item score will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item, based on the algorithm below:

- 5-point semantic Likert-type scale: Transformed item score = (raw score – 1) x 2.5
- 6-point semantic Likert-type scale: Transformed item score = (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. No imputation will be used to calculate the domain score if more than half of the domain items are missing.

The questions included in each domain are given in Protocol Section 9.4 Appendix 4 and Table 2 below.

Table 2: PRE- and POST- module domains

| | Items | Score - Experience level | Transformed item score | Domain score calculation | Domain score range |
|---|---|---|---|---|---|
| **PRE-module domain** | | | | | |
| Feeling about self-injection | 1-3 | 1 – best, 5 – worst | (5-raw score) x 2.5 | Mean of transformed item scores | 0-10 |
| Self-confidence | 4-6 | 1 – worst, 5 – best | (raw score-1) x 2.5 | | |
| Satisfaction with self-injection | 7 | 1 – worst 5 – best | (raw score-1) x 2.5 | | |
| **POST-module domain** | | | | | |
| Feeling about self-injection | 1-3 | 1 – best, 5 – worst | (5-raw score) x 2.5 | Mean of transformed item scores | 0-10 |
| Self-image | 4 | 1 – best 5 – worst | (5-raw score) x 2.5 | | |
| Self confidence | 5-7 | 1 – worst, 5 – best | (raw score-1) x 2.5 | | |
| Pain and skin reactions during or after the injection | 8-15 | 1 – best 5 – worst | (5-raw score) x 2.5 | | |
| Ease of use of the self-injection device | 16-20 | 1 – worst, 6 – best | (raw score-1) x 2 | | |
| Satisfaction with self-injection | 21-27 | 1 – worst 5 – best | (raw score-1) x 2.5 | | |

The individual questions under each domain of PRE-and POST module of SIAQ will be summarized using a frequency table by scheduled visit. The domain scores of the PRE- and POST- modules of SIAQ will be summarized using descriptive statistics by scheduled visit and domain. A 95% confidence interval (CI) of the mean domain scores for the PRE- and POST- modules will also be presented. The 95% CI will be computed using the t distribution. A listing for the PRE- and POST- modules of SIAQ will be presented showing the raw and transformed scores for each question and the domain scores. The domain scores will be displayed to one decimal place.

### 8.2. Successful self-injection

Patients' ability to successfully follow the steps in the Instruction for Use to self-administer will be assessed using the self-injection assessment checklist (Appendix 12.2) at Weeks 0,

2, 4 and 24. The investigator or designated study center staff will observe the patient's self-injection and complete the checklist within 15 minutes after the patient's self-injection.

The self-injection assessment will be defined as "Successful" if the following 4 instructions (N7, N9, N10 and N11) of the self-injection assessment checklist are checked as Yes.

- N7: Removed the cap from the AI (Auto-injector)
- N9: Placed the auto-injector at 90° angle on the injection site
- N10: Pressed the auto-injector firmly against the skin to start the injection (1st loud click), and kept holding the auto-injector firmly against the skin until heard the 2nd loud click
- N11: After the 2nd loud click, continued to hold the auto-injector firmly against the skin and count slowly to five to ensure the injection was completed.

The number and percentage of successful self-injections based on 4 instructions (N7, N9, N10 and N11) will be summarized by scheduled visit.

The number and percentage of patients having overall successful completion of the self-injection assessments (N1 to N14) will be summarized in a table by scheduled visit.

The number and percentages of patients for the self-injection assessment showing whether each instruction was followed or not will be summarized by scheduled visit.

The self-injection assessment data will also be listed, including whether the self-injection was determined to be successful and whether all instructions are completed.

## 9. Efficacy Analysis

The secondary efficacy endpoints are:

- Mean change from baseline in DAS28 (CRP) up to Week 24
- Mean change from baseline in DAS28 (ESR) up to Week 24

All efficacy analysis will be performed on the ITT Population.

### 9.1. DAS28

The disease activity score in 28 joints (DAS28)[7] will be calculated at the scheduled visits using the following equations:

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

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

Where,

TJC28 = number of tender joints (0-28): tender joint count (TJC)
SJC28 = number of swollen joints (0-28): swollen joint count (SJC)

ESR = ESR measurement (mm/hour)
CRP = CRP measurement (mg/L)
PGA = patient's global disease activity measured on 100 mm VAS

The actual value and change from baseline in DAS28 (CRP) and DAS28 (ESR) will be summarized using descriptive statistics by each scheduled visit.

A line plot of the mean change from baseline in DAS28 (CRP) and mean change from baseline of DAS28 (ESR) scores over time will be provided. The DAS28 will be displayed to two decimal places. This figure will be produced for the final CSR only.

A listing will also be provided with DAS28 data.

### 9.2. Tender and Swollen Joints Count (28)

Descriptive statistics for actual value and change from baseline for the number of tender joints and the number of swollen joints will be presented by scheduled visit.

A listing will be provided showing number of tender and swollen joints at each visit, along with the change from baseline.

### 9.3. C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)

Descriptive statistics for actual value and change from baseline will be presented for both parameters by scheduled visit. The data will also be listed.

### 9.4. Patient's Global Assessment of Disease Activity Measured using VAS

Patients will rate their overall status with respect to RA signs and symptoms and functional capacity by marking one line through the 100-mm line. The VAS scale ranges from 0 to 100 mm, 0 mm equals very well, and 100 mm equals very poor disease activity.
For this scale, descriptive statistics for actual value and change from baseline will be presented by scheduled visit. A listing will be provided by showing the VAS measurement at each visit, along with the change from baseline.

## 10. Safety Analysis

All safety analysis will be performed on the Safety Population unless otherwise specified.

### 10.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug.

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study drug;

- begins before the first dose of study drug and worsens in either severity or frequency on or after the first dose of study drug;
- is completely missing a start date and stop date;
- is completely missing a start date and the stop date is on or after the first dose of study drug.

For the purpose of inclusion in TEAE tables, incomplete AE start and stop dates will be imputed using the imputation rule given in Section 4. The imputed dates of AEs will be used for the decision whether the event is a TEAE.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (Version 22.0 or higher). The severity of the AE will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. AEs that are missing a severity will be presented on tables as "Unknown" but will be presented in the listing with a missing severity.

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are "Unrelated", "Possible", "Probable" and "Definite". Events will be summarized as "Related" if the relationship is "Possible", "Probable" or "Definite". AEs with no relationship recorded will be summarized separately under "Missing".
A patient with two or more TEAEs within the same SOC, PT, and relationship to study drug will be counted only once using the most severe event. If a patient has both related and unrelated events within the same SOC and PT, they will be counted in both categories.

Unless otherwise specified, all TEAE tables including TEAE, TESAE, TEAE leading to treatment discontinuation and TEAE of special events will be summarized by relationship to study drug, severity, SOC and PT (by alphabetical order) for the Safety Population. These summaries will include the total number of events and the number and percentage of patients experiencing at least one TEAE. Percentages will be based on the number of patients in the Safety Population.

All AEs recorded will be presented in a listing for the Safety Population.

#### 10.1.1. Overall Summary of Adverse Events

An overall summary of AEs will include the total number of AEs, TEAEs, SAEs, number and percentage of patients with at least one AE, SAE, TEAE, Treatment-Emergent Serious Adverse Event (TESAE), drug-related TEAE, drug-related TESAE, TEAE leading to treatment discontinuation, TESAE leading to treatment discontinuation, TEAE leading to death, TEAE due to injection site reactions, TEAE due to hypersensitivity/allergic reaction, TEAE due to infections and TEAE due to malignancies.

### 10.1.2. Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

The following are the list of serious criteria included in this study:

- Hospitalization: Initial
- Hospitalization: Prolongation
- Life-threatening
- Congenital Anomaly/Birth Defect
- Important Medical Event
- Disability/Incapacity
- Death

TESAE will be summarized as detailed in Section 10.1. All SAEs will be presented in a listing for the Safety Population.

### 10.1.3. Treatment-Emergent AEs Leading to Treatment Discontinuation

A summary of TEAEs with a study drug action taken of "Drug Withdrawn" on the "Adverse Events" page in the eCRF will be presented detailed in Section 10.1.
All TEAEs leading to study drug discontinuation will be listed.

### 10.1.4. Treatment-Emergent Adverse Events Leading to Death

All patients who have an AE with an outcome of "Fatal" will be presented in a listing.

### 10.1.5. Treatment-Emergent Adverse Events of Special Interest (AESIs)

The following will be considered as AEs of special interest:

- Hypersensitivity/allergic reactions: TEAEs recorded as Hypersensitivity/allergic reactions in the eCRF will be included. Signs and symptoms of hypersensitivity/allergic reactions will be captured on separate eCRF pages. Signs and symptoms of hypersensitivity/allergic reactions will be coded using MedDRA Version 22.0 or higher.
- Anaphylactic reactions: No additional summaries will be presented for TEAEs recorded as Anaphylactic reactions in the eCRF. The Hypersensitivity/allergic reaction related summary tables and listings will be reviewed, and any Anaphylactic

reactions will be described in the Hypersensitivity/allergic reaction section of the CSR.

- Injection site reactions (ISR): TEAEs classified as ISR in the eCRF will be included. Signs and symptoms of ISRs will be captured on separate eCRF pages. Signs and symptoms of ISRs will be coded using MedDRA Version 22.0 or higher.
- Infection: 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, following a medical review.

The AESI will be summarized in separate tables by relationship to study drug, severity, SOC and PT (by alphabetical order) as detailed in Section 10.1 for the Safety Population.

Signs and symptoms of hypersensitivity/allergic reactions and ISRs will also be summarized separately by severity, SOC and PT (by alphabetical order) as detailed in Section 10.1 for the Safety Population.

AESI will be presented in separate data listings for the Safety Population. Additional information for signs and symptoms of hypersensitivity/allergic reactions and ISR will be listed.

### 10.2. Clinical Laboratory Evaluations

Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed at the local laboratory. All summaries and listings will be presented in SI units.

If multiple results fall on the same visit, these will be handled as per the rules mentioned in Section 4.

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g. <0.2 will become 0.2) for summaries but left as recorded in the listing.

Actual value and change from baseline of all numeric laboratory parameters including clinical chemistry, hematology, urinalysis (if applicable, except for microscopic examination), will be summarized using descriptive statistics in separate tables, by test parameter and visit.

All relevant clinical laboratory tests will be interpreted as "Normal", "Abnormal, Clinically Significant" or "Abnormal, Not Clinically Significant" where applicable. These categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit.

The numeric parameters will be graded using CTCAE v5.0, where applicable. The CTCAE grades for 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. Unit conversion will be performed if the clinical laboratory unit is not consistent with the unit in CTCAE v5.0. The CTCAE terms and ranges for applicable parameters are listed in Appendix 12.3. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only; the lower grade will be used if different grades share the same criteria.

The number and percentage of patients will be summarized by CTCAE term and CTCAE grade for the Safety Population, where this summary includes only the most severe case during the overall post-baseline visits. If a patient's most severe result does not satisfy any CTCAE criteria, this patient will be summarized as 'No Grade'. All hematology, clinical chemistry and urinalysis data will be listed in separate listings along with clinical significance and normal range flags (where applicable) for the Safety Population.

Table 3: Clinical Laboratory Tests

| | |
|---|---|
| Clinical Chemistry | • Total protein<br>• Serum bilirubin (Total, direct)<br>• Alanine aminotransferase<br>• Aspartate aminotransferase<br>• Alkaline phosphatase<br>• γ-Glutamyl transferase<br>• Blood urea nitrogen<br>• Creatinine<br>• Creatine kinase<br>• Creatine kinase MB*<br>• Albumin<br>• Sodium<br>• Potassium<br>• Calcium<br>• Chloride<br>• Inorganic phosphorous<br>• Glucose<br>• Lactate dehydrogenase<br>• Total cholesterol<br>• Triglyceride<br>• High-density lipoprotein cholesterol |
| Hematology | • Red blood cells |

| | |
|---|---|
| | • Total and differential white blood cell count<br>• Absolute neutrophil count<br>• Lymphocyte count<br>• Platelet count<br>• Hemoglobin<br>• Mean corpuscular volume<br>• Mean corpuscular hemoglobin<br>• Mean corpuscular hemoglobin concentration<br>• Hematocrit |
| Urinalysis | • Bilirubin<br>• Blood<br>• Glucose<br>• Ketones<br>• Leukocytes<br>• Nitrite<br>• pH<br>• Protein<br>• Specific gravity<br>• Urobilinogen<br>• Clarity<br>• Color<br>• Microscopic examination<br>▪ Slime band<br>▪ Flat epitheliums<br>▪ Bacteria<br>▪ White blood cells<br>▪ Red blood cells<br>▪ Casts<br>▪ Crystals<br>▪ Epithelial cells |

*Creatine kinase MB will not be included in summary tables but will be listed

### 10.3. Vital Sign Measurements

A summary table with actual values and change from baseline will be presented for vital sign data (systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min) and body temperature (ºC)) by scheduled visit.

The number and percentage of patients who have clinically notable hypersensitivity/allergic reactions vital sign measurements will be summarized overall, by visit, time point, and parameter.

The criteria for clinically notable results are defined in Table 4 below.

Table 4: Clinically notable results criteria

| 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 |

Vital signs and hypersensitivity monitoring vital signs will be listed for the Safety Population. High and low flags will be presented to show whether a hypersensitivity/allergic reaction result is outside of the clinically notable ranges.

### 10.4. Physical Examination

Physical examinations will be performed at each visit. The body systems will be examined, and the findings will be classified as "Normal", "Abnormal, Not Clinically Significant" and "Abnormal, Clinically Significant". A shift table comparing the categorical results at each scheduled post-baseline visit with those at baseline will be summarized overall and by body system and visit.

All physical examination data will be listed by body system and visit.

### 10.5. Electrocardiogram

12-lead ECGs will be performed at Screening, Day 1 and EOS/ED visits and interpreted as "Normal", "Abnormal, Not Clinically Significant" and "Abnormal, Clinically Significant". A shift table comparing the interpretation at each scheduled post-baseline visit with those at baseline will be presented by visit for the Safety Population.

All ECG data will be listed by visit.

### 10.6. Tuberculosis Assessment

Tuberculosis clinical monitoring will be performed at all visits and a chest x-ray will be performed at the screening and EOS/ED visits. Additional chest x-rays could be performed at the Investigator's discretion based on the signs and symptoms of TB monitoring throughout the study. Clinical monitoring results will be either "Yes" or "No". Chest X-ray results will be interpreted as "Normal (Clear, No findings)", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically significant". A summary table will be presented by visit and data will be listed for the Safety Population.

### 10.7. Interferon-γ Release Assay

IGRA is the protocol-required method of screening for TB and will be performed at the screening and EOS/ED visits. Additional assessment could be performed at the Investigator's discretion based on the signs and symptoms of TB monitoring throughout the study. The results will be classified as "Positive", "Negative" or "Indeterminate". If a retest is conducted because the IGRA result is indeterminate, the result of the retest will be used for the summary. A summary table will be presented by visit and data will be listed for the Safety Population.

### 10.8. Pregnancy Test

A serum pregnancy test will be performed at Screening and at the EOS/ED visit. A urine pregnancy test will be performed to confirm patients are not pregnant prior to dosing at each scheduled visit. The results will be classified as "Positive" or "Negative". A summary table will be presented by visit and listed for the Safety Population, with percentages calculated using the number of female patients of childbearing potential who have not been surgically sterilized as the denominator.

## 11. References

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3. van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. J Rheumatol. 2010; 37(11):2237-2246.
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for Industry, Rheumatoid Arthritis: Developing Drug Products for Treatment. Draft Guidance. May 2013. Available at: https://www.fda.gov/files/drugs/published/Rheumatoid-Arthritis--Developing-Drug-Products-for-Treatment.pdf
5. Keininger D, Coteur G. Self-Injection Assessment Questionnaire (SIAQ). ePROVIDE-Mapi Research Trust. March 2019. [cited 2019 Jun 19]. Available at: https://eprovide.mapi-trust.org/instruments/self-injection-assessment-questionnaire
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7. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995; 38(1): 44-48.

# 12. Appendices

## 12.1. Schedule of Activities (SoA)

| | Screening Period | Treatment Period | | | | | | | | | Follow-up Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 7 | Dose 9 | Dose 11 | Dose 13 | EOS [1] | ED [2] |
| **Study visit[3] (Week)** | **–6** | **0** | **2** | **4** | **6** | **8** | **12** | **16** | **20** | **24** | **28** | |
| **Study visit[3] (Day)** | **–42 to –1** | **1** | **15** | **29** | **43** | **57** | **85** | **113** | **141** | **169** | **197** | |
| Informed consent | X | | | | | | | | | | | |
| Demographics, height, weight and medical history | X | | | | | | | | | | | |
| Hepatitis B/C and HIV test[4] | X | | | | | | | | | | | |
| Serum pregnancy test[5] | X | | | | | | | | | | X | X |
| Chest X-ray[6] | X | | | | | | | | | | X | X |
| IGRA[7] | X | | | | | | | | | | X | X |
| Inclusion/exclusion criteria | X | X[8] | | | | | | | | | | |
| **Usability assessments** | | | | | | | | | | | | |
| PRE- and POST-SIAQ[9] | | X | X | X | | | | | | X | | |
| Self-injection assessment checklist by observer[10] | | X | X | X | | | | | | X | | |
| **Efficacy assessments[11] – Pre-dose** | | | | | | | | | | | | |
| Swollen joint count (66 joints) | X | | | | | | | | | | | |
| Tender joint count (68 joints) | X | | | | | | | | | | | |
| Tender joint count and swollen joint count (28 joints) | X | X | | | | X | | X | | X | (X) | X |
| CRP and ESR[12] | X | X | | | | X | | X | | X | (X) | X |
| VAS global assessment of disease activity (patient) scores | X | X | | | | X | | X | | X | (X) | X |
| **Safety assessments[11] – Pre-dose** | | | | | | | | | | | | |
| Physical examination, vital signs | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical laboratory tests[13] | X | X | | X | | | X | | | X | X | X |
| Urine pregnancy test[5] | | X | X | X | X | X | X | X | X | X | | |
| 12-lead ECG[14] | X | X | | | | | | | | | X | X |
| **Study drug administration[15,16]** | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | | |
| Hypersensitivity/ allergic reactions[17] and injection site reaction[18] monitoring | | X | X | X | X | X | X | X | X | X | | |
| Prior, concomitant medications[19] | X | | | | | | | | | | | |

| | Screening Period | Treatment Period | | | | | | | | | Follow-up Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 7 | Dose 9 | Dose 11 | Dose 13 | EOS [1] | ED[2] |
| **Study visit[3] (Week)** | **–6** | **0** | **2** | **4** | **6** | **8** | **12** | **16** | **20** | **24** | **28** | |
| **Study visit[3] (Day)** | **–42 to –1** | **1** | **15** | **29** | **43** | **57** | **85** | **113** | **141** | **169** | **197** | |
| TB clinical monitoring[20] | X | | | | | | | | | | | |
| AE[21] | X | | | | | | | | | | | |

Abbreviations: AE=adverse event(s); AI=auto-injector; CRP=C-reactive protein; ECG=electrocardiogram; eCRF=electronic case report forms; ED=early discontinuation; EOS=end-of-study; EOW=every other week; ESR=erythrocyte sedimentation rate; HIV=human immunodeficiency virus; ICF=informed consent form; IgG=immunoglobulin G; IGRA=Interferon-Gamma Release Assays; IM=intramuscular; RA=rheumatoid arthritis; 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 and 22 which are not specified in this table (Dose 6, 8, 10 and 12) will be self-administered at home.

1. An EOS visit will occur 4 weeks after the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.
2. An ED visit will be completed 4 weeks after the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.
3. A visit window of ±2 days is allowed, based on the previous dosing date, from Week 2 (dose 2) up to the EOS visit.
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. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis and HIV analysis will be performed locally.
5. For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted locally at Screening and EOS/ED visit. A urine pregnancy test will also be performed locally and 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. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed.
6. A chest X-ray (both lateral and posterior-anterior 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 locally. A patient who has a previous diagnosis of latent TB cannot be enrolled even if there is sufficient documentation of completed TB prophylaxis. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening Period. If the repeated IGRA result is indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.
8. Inclusion and exclusion criteria should be confirmed on Day 1 again.
9. PRE- and POST-SIAQ will be completed by patient prior to and after self-injection of CT-P17 SC via AI. 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.
10. The Investigator or designee will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection.
11. Procedures will be performed at the study center prior to the study drug administration. Where possible, the same Investigator should perform all efficacy assessments for an individual patient.
12. Both CRP and ESR samples will be drawn and analyzed locally at the same time as the clinical laboratory blood samples.

13. Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed locally. See Section 6.4.2.6 of the protocol, for details of the clinical laboratory tests. Creatinine clearance will be calculated using serum creatinine level only at Screening for inclusion and recorded on eCRF.
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 cardiac origin, a 12-lead 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. A fixed dose of CT-P17 (40 mg) will be administered EOW by SC injection via AI from Week 0 to Week 24. 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. Patients must self-inject the study drug during their study center visits under the Investigator or designated study center staff's supervision at the indicated visits. Patients will self-inject the study drug at home at Weeks 10, 14, 18 and 22.
16. Methotrexate (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM, dose and route must be maintained from Screening to EOS/ED visit) and folic acid (≥5 mg/week, oral) will be administered throughout the study.
17. Additional vital signs will be monitored for possible hypersensitivity/allergic reactions 1 hour (±10 minutes) after injection of study drug. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, artificial ventilation and ECG equipment must be available at the study center. Any type of ECG can be performed.
18. 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 in the patient self-reporting of AE diary.
19. Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS/ED visit, 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/ED 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 #7 (Section 4.2 of the protocol).
20. 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 subsequent study drug administration.
21. AEs will be assessed from the date the ICF is signed until the EOS/ED visit. After the EOS/ED visit, serious adverse drug reactions will be reported to the Sponsor or its designee. Adverse events of special interest (e.g., injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies) should be closely monitored.

### 12.2. Self-Injection Checklist

| No. | Instruction for Use |
|---|---|
| 1 | Removed the AI (Auto-injector) from the outer carton |
| 2 | Checked expiration date on the AI (Auto-injector) label |
| 3 | Inspected the AI (Auto-injector) for damage |
| 4 | Checked the liquid for discoloration or particles |
| 5 | Washed hands with soap and water |
| 6 | Cleaned the injection site |
| 7 | **Removed the cap from the AI (Auto-injector)** |
| 8 | Held the auto-injector so that patient could see the window |
| 9 | **Placed the auto-injector at 90° angle on the injection site** |
| 10 | **Pressed the auto-injector firmly against the skin to start the injection (1st loud click), and kept holding the auto-injector firmly against the skin until heard the 2nd loud click** |
| 11 | **After the 2nd loud click, continued to hold the auto-injector firmly against the skin and count slowly to five to ensure the injection was completed** |
| 12 | Checked if the grey indicator fills the window completely |
| 13 | Removed auto-injector from injection site at 90° angle to skin |
| 14 | Disposed used auto-injector and the cap in a sharps container |

*** The bolded steps are considered as critical steps for the usability assessment.**

## 12.3. Table of CTCAE Terms and Grades

| CTCAE Term | Laboratory Parameter | Level | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| Anemia | Hemoglobin | Low | <LLN - 10.0 g/dL;<br><LLN - 100 g/L;<br><LLN - 6.2 mmol/L | <10.0 - 8.0 g/dL;<br><100 - 80 g/L;<br><6.2 - 4.9 mmol/L | <8.0 g/dL;<br><80 g/L;<br><4.9 mmol/L;<br>transfusion indicated | Life-threatening consequences; urgent intervention indicated |
| Hypoalbuminemia | Albumin | Low | <LLN - 3 g/dL;<br><LLN - 30 g/L | <3 - 2 g/dL;<br><30 - 20 g/L | <2 g/dL;<br><20 g/L | Life-threatening consequences; urgent intervention indicated |
| Alanine aminotransferase increased | Alanine Aminotransferase (ALT) | High | >ULN - 3.0 x ULN if baseline was normal;<br>1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 5.0 x ULN if baseline was normal;<br>>3.0 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal;<br>>5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal |
| Alkaline phosphatase increased | Alkaline phosphatase (ALP) | High | >ULN - 2.5 x ULN if baseline was normal;<br>2.0 - 2.5 x baseline if baseline was abnormal | >2.5 - 5.0 x ULN if baseline was normal;<br>>2.5 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal;<br>>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;<br>1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 5.0 x ULN if baseline was normal;<br>>3.0 - 5.0 x baseline if baseline was abnormal | >5.0 - 20.0 x ULN if baseline was normal;<br>>5.0 - 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal |
| Blood bilirubin increased | Total Bilirubin | High | >ULN - 1.5 x ULN if baseline was normal;<br>> 1.0 - 1.5 x baseline if baseline was abnormal | >1.5 - 3.0 x ULN if baseline was normal;<br>>1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 10.0 x ULN if baseline was normal;<br>>3.0 - 10.0 x baseline if baseline was abnormal | >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal |
| Blood lactate dehydrogenase increased | Lactate Dehydrogenase (LDH) | High | >ULN | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cholesterol high | Total Cholesterol | High | >ULN - 300 mg/dL; >ULN - 7.75 mmol/L | >300 - 400 mg/dL; >7.75 - 10.34 mmol/L | >400 - 500 mg/dL; >10.34 - 12.92 mmol/L | >500 mg/dL; >12.92 mmol/L |
| CPK increased | 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 | 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 | - | Steroids initiated | - |
| 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 |
| Hemoglobin increased | Hemoglobin | High | Increase in >0 - 2 g/dL | Increase in >2 - 4 g/dL | Increase in >4 g/dL | - |
| Hyperkalemia | Potassium | High | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L; intervention initiated | >6.0 - 7.0 mmol/L; Hospitalization indicated | >7.0 mmol/L; life-threatening consequences |
| Hypernatremia | Sodium | High | >ULN - 150 mmol/L | >150 - 155 mmol/L; intervention initiated | >155 - 160 mmol/L; hospitalization indicated | >160 mmol/L; life-threatening consequences |
| 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; life-threatening consequences |
| Hypoglycemia | Glucose | Low | <LLN-55 mg/dL; <LLN-3.0 mmol / L | < 55 – 40 mg/dL; < 3.0 - 2.2 mmol / L | < 40 -30 mg/dL; < 2.2 - 1.7 mmol / L | <30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures |
| Hypokalemia | Potassium | Low | <LLN - 3.0 mmol/L | Symptomatic with <LLN - 3.0 mmol/L; intervention indicated | <3.0 - 2.5 mmol/L; hospitalization indicated | <2.5 mmol/L; life-threatening consequences |
| Hyponatremia | Sodium | Low | <LLN - 130 mmol/L | 125-129 mmol/L and asymptomatic | 125-129 mmol/L symptomatic; | <120 mmol/L; |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 120-124 mmol/L regardless of symptoms | life-threatening consequences |
| Leukocytosis | White Blood Cells (WBC) | High | - | - | >100,000/$mm^3$ | Clinical manifestations of leucostasis; urgent intervention indicated |
| Lymphocyte count decreased | Absolute lymphocyte count | Low | <LLN - 800/$mm^3$; <LLN - 0.8 x $10e^9$/L | <800 - 500/$mm^3$; <0.8 - 0.5 x $10e^9$ /L | <500 - 200/$mm^3$; <0.5 - 0.2 x $10e^9$ /L | <200/$mm^3$; <0.2 x $10e^9$ /L |
| Lymphocyte count increased | Absolute lymphocyte count | High | - | >4000/$mm^3$ - 20,000/$mm^3$ | >20,000/$mm^3$ | - |
| Neutrophil count decreased | Absolute neutrophil count | 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 |
| Platelet count decreased | Platelet count | low | <LLN - 75,000/$mm^3$; <LLN - 75.0 x $10e^9$/L | <75,000 - 50,000/$mm^3$; <75.0 - 50.0 x $10e^9$/L | <50,000 - 25,000/$mm^3$; <50.0 - 25.0 x $10e^9$/L | <25,000/$mm^3$; <25.0 x $10e^9$/L |
| White blood cell decreased | White Blood Cells (WBC) | Low | <LLN - 3000/$mm^3$; <LLN - 3.0 x $10e^9$/L | <3000 - 2000/$mm^3$; <3.0 - 2.0 x $10e^9$/L | <2000 - 1000/$mm^3$; <2.0 - 1.0 x $10e^9$/L | <1000/$mm^3$; <1.0 x $10e^9$/L |

LLN = lower limit of normal, ULN = upper limit of normal, CTCAE = Common Terminology Criteria for Adverse Events.
Note: In cases where the numeric value for grading is identical (such as Hypokalemia), the CTCAE grade which includes a numeric value only was applied because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly. Semicolon (;) indicates “or”.

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