CELLTRION Inc.

CT-P13 3.5

A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis

26th Jun 2018
Statistical Analysis Plan

Part 1 – Final Version 3.1

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[redacted]

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
ACR20	20% response, as defined by the American College of Rheumatology
ACR50	50% response, as defined by the American College of Rheumatology
ACR70	70% response, as defined by the American College of Rheumatology
ARR	Administration-Related Reaction
ADA	Anti-Drug Antibody
AE	Adverse Event
Anti-CCP	Anticyclic Citrullinated Peptide
AUC_{τ}	Area Under the Concentration-Time Curve
BA	Bioavailability
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
CL	Clearance
C_{max}	Observed Maximum Serum Concentration
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Concentration
CT-P13	Infliximab (CELLTRION, Inc.)
CV%	Percent Coefficient Of Variation
DMARD	Disease-Modifying Anti-Rheumatic Drug
DAS28	Disease Activity Score In 28 Joints
DRM	Data Review Meeting
ECG	Electrocardiogram
EOI	End of the Infusion
eCRF	Electronic Case Report Form
EOS	End-of-Study Visit
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
ICF	Informed Consent Form
IGRA	Interferon Gamma Release Assay
IRR	Infusion-Related Reaction
ISR	Injection Site Reaction
IV	Intravenous
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
LLT	Lowest Level Term
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time

NAb	Neutralizing Antibody
PD	Pharmacodynamic
PFS	Pre-filled Syringe
PK	Pharmacokinetic
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SDAI	Simplified Disease Activity Index
SI	System International
SOC	System Organ Class
SOI	Start of the Infusion
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization

1. ADMINISTRATIVE STRUCTURE

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

2. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data for Part 1 of CELLTRION study number CT-P13 3.5, entitled as "A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis".

The clinical study report (CSR) will be generated to report all efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and safety data after completion of all visits for all patients.

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

- Study Protocol Version 4.0 – 02nd Feb 2018
- Unique CRF Version 3.0 – 14th July 2017

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

3. STUDY OBJECTIVES

Primary and secondary objectives are described as below.

3.1. Primary Objective

The primary objective of this study is to find the optimal dose of CT-P13 Subcutaneous (SC) over the first 30 weeks as determined by the area under the concentration-time curve (AUC_{τ}) at steady state between Week 22 and 30.

3.2. Secondary Objective

The secondary objective of this study is to evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This study is a randomized, multicenter, parallel group, Phase I/III study designed to evaluate efficacy, PK, PD and safety between CT-P13 SC and CT-P13 IV when co-administered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose and folic acid (≥5 mg/week, oral dose) in patients with active Rheumatoid Arthritis (RA) who are not adequately responding to methotrexate administration over at least 3 months. Approximately 40 (at least 24) male or female patients with active RA will be randomly assigned at Week 6 in 1:1:1:1 ratio into four study cohorts as presented in Table 1.

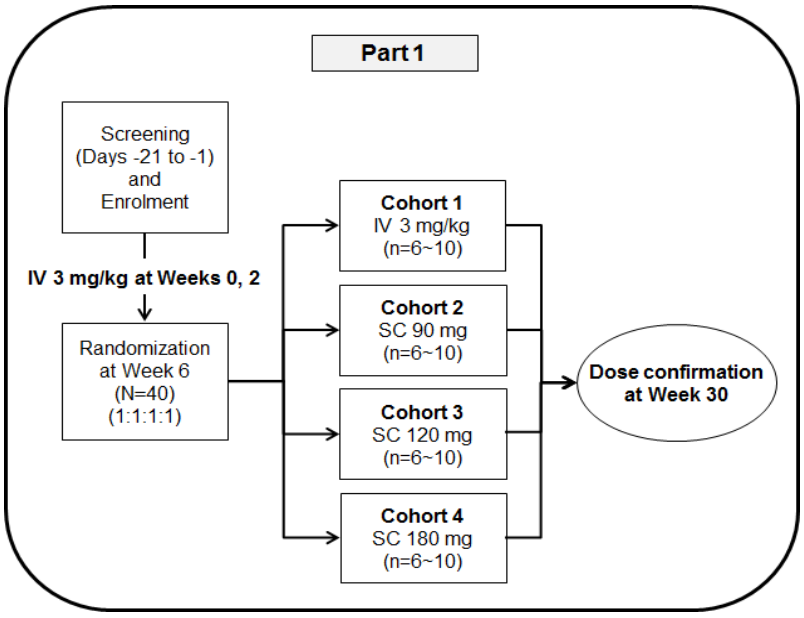
Table 1. Study Drug Randomization

Cohort Number	Dosage	Investigational Product	Method of Administration
Cohort 1	3 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Cohort 2	90 mg	CT-P13 SC 90 mg/PFS	Single SC injection
Cohort 3	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection
Cohort 4	180 mg	CT-P13 SC 90 mg/PFS	Double SC injection

IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

This study is designed to find the optimal dose of CT-P13 SC. The overview of study design is illustrated in Figure 1.

Figure 1. Overview of Study Design



IV, intravenous; SC, subcutaneous

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) and the End-of-Study.

Screening: Screening will take place between Days –21 and –1, prior to the first administration of the study drug.

Treatment Period: On Day 0, Week 0, patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study. All enrolled patients will initially receive 2 doses of CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or CT-P13 IV before treatment on Day 42, Week 6.

An oral or parenteral dose of methotrexate between 12.5 to 25 mg/week and an oral dose folic acid (≥5 mg/week) will be administered throughout the duration of the study. Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

The Dose-Loading Phase will consist of 2 doses of CT-P13 IV infusion. All patients will receive a 2 hour CT-P13 IV infusion at Week 0 and Week 2.

The Maintenance Phase of the study will consist of further doses of study treatment with the last dose administered no later than Week 54.

- **Cohort 1:** further 7 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter (Weeks 14, 22, 30, 38, 46 and 54)

- **Cohort 2, 3 and 4:** first CT-P13 SC will be administered by pre-filled syringe (PFS) at Week 6. Further 24 doses of SC injections will be given every 2 weeks up to Week 54

The initially assigned dose will be adjusted to the optimal dose in all patients from Cohort 2, 3 and 4 if the optimal dose is confirmed after dose finding. Further SC injections with the optimal dose will be given up to Week 54.

Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

The patient assessment overview is illustrated in Figure 2**.**

Figure 2. Patient Assessment Overview

	Dose-loading		Maintenance[1]															
Week	**0**	**2**	**6**	**8**	**10**	**14**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**38**	**46**	**54**
Visit[2]	X	X	X	X[3]	X[3]	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X	X	X
Evaluation																		
Primary Pharmacokinetic[4]							←								→			
Efficacy	X	X	X			X	X								X			X
Pharmacokinetic	←																	→
Pharmacodynamic	X	X	X			X	X								X	X	X	X
Safety Evaluation	←																	→

1. Additional visits will only be made by patients who will need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed up to and including Week 30; a visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.
3. Only patients from Cohorts 2, 3, and 4 will make visits for additional pharmacokinetic assessment.
4. Visit window for primary PK assessment is allowed according to appendix1.

CT-P13 SC will be injected by a healthcare professional at each site visit (Weeks 6, 8, 10, 14, 22, 24, 26, 28, 30, 38, 46 and 54). After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate at any other weeks (Weeks 12, 16, 18, 20, 32, 34, 36, 40, 42, 44, 48, 50 and 52).

End-of-Study Visit: An End-of-Study Visit will occur 8 weeks after the last dose is received, either at the end of the Maintenance Phase or earlier if the patient withdraws from the study.

The schedule of events is presented in Appendix 1.

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), minimum, median, and maximum, unless otherwise specified. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data. SD will be presented to two more decimal places than the raw data. If the geometric mean and percent coefficient of variation (CV%) are to be presented, it will be set to the same decimal places as the mean. Confidence intervals (CI) obtained from statistical procedures will be displayed to two decimal places. In summary tables, all available decimal places will be used although rounded value is listed.

Categorical data will be summarized using numbers and percentages of patients. Percentages will be presented to one decimal place and will be suppressed when the count is zero. The denominator for all percentages will be the number of patients within the treatment group for the population of interest, unless otherwise specified.

All data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, patient number, and assessment date or visit date, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality signs will be displayed.

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

1) Recorded as collecting sample in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date/time 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/time from eCRF if not missing; if sample collection date/time 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.

5.1. Software

All analyses will be conducted using [redacted].
PK parameters will be calculated by noncompartmental methods using the appropriate validated software such as [redacted].

5.2. Sample Size

No formal sample size estimation was performed because no confirmatory analyses are planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) are considered to be sufficient to investigate the primary objective of this study (Section 3.1).

5.3. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for the randomization at Week 6. Biostatistician will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes. The randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL) and Week 6 body weight (≤70 kg vs. >70 kg). The randomization numbers will be blocked, and within each block the same number of patients will be allocated to each cohort group. Blinding is not included in Part 1 of this study because it is an open-label study.

5.4. Population of Analysis

Population to be used in analysis will be specified in related sections. The following patient populations are defined: Intent-to-Treat (ITT), All-Randomized, Efficacy, Pharmacokinetic (PK), Pharmacodynamics (PD) and Safety populations. Patients who have any major protocol

deviations (as defined in Section 5.6) may be excluded from the PK population. The relevant decision will be taken at the Data Review Meeting (DRM).

Analysis of the ITT population and All-Randomized population will be performed according to the treatment they were randomized to at Week 6. The other populations will be analyzed according to actual treatment group. The actual treatment group will be assigned according to their actual treatment, not according to the randomized cohort, even if there is a discrepancy between the actual administered dose and the randomized cohort. If there is a patient with such a discrepancy, the patient will be discussed during the DRM.

For randomized patients, data before randomization at Week 6 will be displayed by the treatment group based on randomized or actual administered study drug. If a patient discontinues the study before the randomization at Week 6, the patient will be listed under treatment group of Not Applicable and won't be included in summary tables.

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

5.4.1. Intent-to-Treat Population

The ITT population will consist of all enrolled patients. A patient will be considered to be enrolled if the patient is successfully screened based on the 'Screening Pass Y/N' page of the eCRF. In addition, a patient can be enrolled by an investigator's decision. Some of listings will be generated on the ITT population to include patients who discontinued the study prior to randomization at Week 6.

5.4.2. All-Randomized Population

The All-Randomized population will consist of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed. This will therefore include all patients who have been allocated randomization ID at Week 6 based on 'Randomization' page of eCRF.

5.4.3. Pharmacokinetic Population

The PK population will consist of the All-Randomized population who receive at least one full dose of study drug at Week 6 or thereafter and who have at least one PK concentration result after Week 6 treatment. The primary PK endpoint of the AUC_{τ} at steady state between Week 22 and Week 30 will be analyzed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population. A patient will be considered as receiving full dose if the actual administered dose (mg) of the patient is greater than or equal to prescribed dose (mg) based on 'Study Drug Administration' page of eCRF. If a patient doesn't receive full dose, the patient will be discussed during the DRM to confirm whether the patient can be considered as receiving full dose or not.

5.4.4. Pharmacodynamic Population

The PD population will consist of the All-Randomized population who receive at least one full dose (as defined in Section 5.4.3) of study drug at Week 6 or thereafter and who have at least

one PD result (Rheumatoid Factor (RF), Anti-cyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP) or Erythrocyte Sedimentation Rate (ESR)) after Week 6 treatment.

5.4.5. Efficacy Population

The Efficacy population will consist of the All-Randomized population who receive at least one full dose (as defined in Section 5.4.3) of study drug at Week 6 or thereafter and who have at least one efficacy evaluation result after Week 6 treatment. A patient will be considered as having an efficacy evaluation result if the patient is recorded as performing at least one of any assessment of the followings.

- Swollen/Tender Joint Count (ACR/DAS28)
- Health Assessment Questionnaire (HAQ)
- Visual Analogue Scales (VAS)

5.4.6. Safety Population

The Safety population will consist of all patients who received at least one (partial or full) dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter. A patient will be considered to have received a study drug if the patient is recorded as study drug administered or if a date of administration is recorded on the 'Study Drug Administration' page of the eCRF.

5.5. Definition of Baseline

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

5.6. Protocol Deviations

Protocol deviation will be categorized as "major" or "minor". Category of protocol deviation will be identified during the DRM. A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare.

Major protocol deviations are defined as follows:

- Mis-randomizations (defined as patients who received the another treatment than that to which they were assigned at any point during the study)

Patients who were mis-randomized will be excluded from the PK population. The major protocol deviations used for exclusion will be summarized for the All-Randomized population by treatment group. A listing of major protocol deviations 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 screening failure will be displayed along with the primary reason for screening failure.

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

- Inclusion/Exclusion Criteria Not Met
- Subject Withdrew Consent
- Others

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

The number of patients who were enrolled, treated in each phase, randomized, discontinued in each phase and completed the study will also be displayed on the All-Randomized population along with percentage, if applicable.

Patient disposition will be defined as follows:

- A patient will be considered to be enrolled if the patient is successfully screened based on the 'Screening Pass Y/N' page of the eCRF.
- A patient will be considered to have been treated in the dose-loading phase if it is recorded as 'Yes' on the 'Study Drug Administration' page of the eCRF at Week 0 and/or Week 2.
- A patient will be considered to be randomized if the patient was allocated a randomization ID at Week 6 based on the 'Randomization' page of the eCRF.
- A patient will be considered to have been treated in the maintenance phase if it is recorded as 'Yes' on the 'Study Drug Administration' page of the eCRF on or after Week 6.
- A patient will be considered to have completed the study if it is recorded that they completed ('Yes' box checked) on the 'Study Treatment Termination' page of the eCRF. Conversely, a patient is considered to have discontinued the study if it is recorded in the 'Study Treatment Termination' page of the eCRF that they did not complete ('No' box checked). If the patient who is considered to have discontinued the study has received a study drug administration at Week 6, the patient will be considered to have discontinued in the maintenance phase, otherwise, in the dose-loading phase.

The total number of patients who discontinued the study in the dose-loading phase will be presented by primary reason. The number and percentage of patients who discontinued the study in the maintenance phase will also be displayed by primary reason for discontinuation and treatment group. The reasons for discontinuation will be displayed using the following categories and ordering:

- Patient develops signs of disease progression
- Patient withdraws consent or refuses to continue treatment
- Adverse Event
- Significant protocol violations
- Lost to Follow-up
- Death
- Pregnancy
- Investigator decision
- Others

In addition, the time on study drug prior to discontinuation will also be summarized using descriptive statistics by treatment group, if applicable, for those patients who have discontinued study treatment prematurely in the dose-loading phase or maintenance phase, respectively. The treatment duration in days will be calculated as (date of last administration - date of first administration + 1).

The date of first administration will be taken as the earliest date recorded on the 'Study Drug Administration' page of the eCRF. The date of last dose will be taken as recorded on the 'Study Treatment Termination' page of the eCRF.

The patient disposition data collected for the ITT population will be listed by treatment group.

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics and Stratification Details

The following demographic measures will be summarized for the All-Randomized population by treatment group: age (years); sex (male, female); female fertility status (pre-menarche, surgically sterilized, post-menopausal, potentially able to bear children, other); race (Asian/oriental, Caucasian/white, African/black, 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 the screening visit.

Age will be automatically calculated in the 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.

The following stratification details will also be summarized for the All-Randomized population by treatment group: country (Estonia, Bulgaria, Latvia, Korea, Hungary, Russia, Ukraine, Bosnia, Poland, Czech, Lithuania); week 6 body weight ($\leq$ 70kg vs. $>$70kg); Week 2 serum CRP concentration ($\leq$0.6mg/dL vs. $>$0.6mg/dL). If there is a difference for data entered between IWRS and eCRF, the stratification factors will be summarized using the final data collected on the eCRF.

Demographics will be listed for the ITT population by treatment group. Stratification details will be listed for the All-Randomized 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 has any signs or symptoms of cardiac dysfunction, corresponding NYHA class will be selected. The criteria for congestive heart failure is defined as Table 2:

Table 2. 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 anginal 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 anginal 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 anginal pain.
IV (Severe)	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

All NYHA criteria assessment data will be presented in a listing by treatment group for the ITT population. Patients without signs or symptoms of cardiac dysfunction will be classed as “No Class” in the listing.

7.3. Hepatitis B and C and Human Immunodeficiency Virus -1 and -2

At screening, the following assessments 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) 1&2

Viral serology results will be summarized at Baseline (as defined in Section 5.5) by treatment group for the All-randomized population. A listing will be produced by treatment group for the ITT population.

7.4. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 20.0 or the higher version). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the All-randomized population. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by treatment group. Medical history will also be listed by treatment group for the ITT population.

7.5. Rheumatoid Arthritis History

Rheumatoid arthritis history is captured at the screening visit and is based on the Rheumatoid Arthritis Classification Criteria 2010 (Aletaha et al., 2010). The descriptive statistics of total score for the Rheumatoid Arthritis criteria and time since Rheumatoid Arthritis diagnosis will be tabulated for the All-Randomized population by treatment group. Time (years) since RA diagnosis will be calculated as [(date of first administration – date of diagnosis)/365.25]. If an incomplete rheumatoid arthritis diagnosis date is recorded for a patient this will be imputed using the latest possible date. That is, if the day is missing (i.e. XXMAR2017) the date will be the last day of the month (i.e. 31MAR2017). If the day and month are missing (i.e. XXXXX2017) the date will be set to the 31st December (i.e. 31DEC2017). If the imputed date is later than date of first administration, then it will be imputed using the date of administration. If the whole date is missing, the date will not be imputed and time since RA diagnosis will not be calculated. Rheumatoid Arthritis history will also be listed by treatment group for the ITT population.

7.6. Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria can be found in Sections 4.2 and 4.3 of the protocol (CT-P13 SC 3.5). Inclusion and exclusion criteria for each patient will be presented in separate listings for the ITT population by treatment group.

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. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

All medications except for the treatment of RA used during the study, as well as all medications taken within 30 days before date of first administration and until the last assessment date or EOS visit will be collected on the eCRF. All medications for the treatment of RA, from the diagnosis of disease until the last assessment date or EOS visit, will be collected on the eCRF. All medications will be coded according to the World Health Organization drug dictionary (WHO Drug Dictionary September 1, 2017 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 end date is after the date of death, the end date will be imputed as the date of death.

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

- Missing day: Assume the first day of the month.
  However, if the partial date and the date of first 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 administration is not after the stop date of the medication, set to the date of first administration. Otherwise, set to stop date of the medication.

- Missing day and month: Assume January 1st.
  However, if the partial date and the date of first administration lie within the same year and the date of first administration is not after the stop date of the medication, set to the date of first administration. Otherwise, set to stop date of the medication.

- Missing day, month and year: Assume date of first 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: UNJUN2017
  Medication end: 20OCT2017
  Date of first administration: 16OCT2017
  Medication start imputed: 01JUN2017
- Example 2:
  Medication start: UNOCT2017
  Medication end: 20OCT2017
  Date of first administration: 16OCT2017
  Medication start imputed: 16OCT2017
- Example 3:
  Medication start: UNOCT2017
  Medication end: 20OCT2017
  Date of first administration: 24OCT2017
  Medication start imputed: 20OCT2017

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 administration. A concomitant medication is defined as any medication that has an actual or imputed stop date on or after the date of first administration, marked as ongoing or missing. The actual or imputed start date of a concomitant medication can be before or after the date of first administration.

The prior medications will be summarized by treatment groups, 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 summaries will be repeated in separate tables for concomitant medications and just for concomitant medications in maintenance phase. A concomitant medication in maintenance phase is defined as a medication that has an actual or imputed stop date on or after the Week 6 administration date, marked as ongoing or missing in patients who are administered on or after Week 6.

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

8.1.1. 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 (week/mg) at first administration of treatment period and maintenance phase will be summarized. Summaries will be based on the Safety population 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 ITT population.

8.2. Exposure to Study Drug

The number and percentage of patients with dose administered at each scheduled dose week will be summarized by treatment group for the Safety population. 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. For patients who administered with the study drug, a table will be provided displaying descriptive statistics of the prescribed dose and actual dose administered by treatment group at each scheduled dose. Prescribed and actual administered dose per weight (mg/kg) for IV infusion and prescribed and actual administered dose (mg) for SC injection will be summarized. The dose per weight (mg/kg) will be calculated using the Prescribed Dose (mg) and Actual Administered Dose (mg) based on the 'Study Drug Administration' page of eCRF and Weight (kg) on the 'Vital Signs' page of eCRF. If the patient's weight is missing at the applicable visit, then the weight at the last available assessment for the patient will be used.

In addition, the total number of doses received and total administered dose (mg) during the dose-loading phase and maintenance phase will be summarized using descriptive statistics by treatment group for the Safety Population.

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

9. PHARMACOKINETIC ANALYSIS

All pharmacokinetic tables, listings and figures will be generated using all data on the PK population by treatment group unless otherwise specified.

9.1. Serum Concentrations

PK samples will be collected at pre-dose (prior to the beginning of the study treatment administration on dosing day) at the scheduled sampling time points. In addition, PK samples during the PK monitoring visit period (between Week 22 and Week 30) will also be collected at specific PK sampling time points presented in Table 3.

All patients in SC cohorts (Cohorts 2, 3 and 4) will be randomly assigned by IWRS at Week 14 in a 1:1 ratio to either of Group A or B to collect blood samples in the PK monitoring visit period:

- Group A (Cohorts 2A, 3A and 4A): frequent PK sampling at Weeks 22 and 26
- Group B (Cohorts 2B, 3B and 4B): frequent PK sampling at Weeks 24 and 28

Table 3. Steady state PK sampling Time points

Visit (Day)	Cohort 1	Cohorts 2, 3 and 4	
		Group A	Group B
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 3, 8 and 24 hr (±15 min) after SOI • 48 hr (±2 hr) after SOI • 96 hr (±4 hr) after SOI • 168 ±6 hr after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 26 (Day 182)	• 28 days (±1 day) after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 28 (Day 196)	• 42 days (±1 day) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection

Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

Individual serum concentrations, scheduled time, actual sampling time and deviations from scheduled time will be presented in a data listing by treatment group for the Safety population.

Serum concentrations of Infliximab will be summarized using descriptive statistics (n, mean, SD, CV%, geometric mean, minimum, median, and maximum) by treatment group at each scheduled collection visit and time point for the PK population. Geometric mean will not be reported if the dataset includes zero values. All concentrations below lower limit of quantification (BLQ) will be indicated in the data listing. For summary of serum concentration and calculation of PK parameters, BLQ prior to the first administration (Week 0, Dose 1) will be set to zero. All other BLQs after study drug exposure will be set to Lower Limit of Quantification (LLoQ).

Mean serum concentration versus scheduled sample time plots for study drugs will also be presented on both linear and semi-logarithmic scales by treatment group for the PK population. Additional plots showing the data collected during the PK monitoring visit period will be provided separately for better comparison between treatment groups for the PK population.

9.2. Pharmacokinetic Parameters

Individual serum concentration data over actual time data will be used to calculate PK parameters of infliximab by standard non-compartmental methods using [redacted]. For the calculation of PK parameters, BLQ will be handled using the rules described in Section 9.1. Actual time after dose (most recent dose) will be used for all PK analyses. However, for ease of presentation, scheduled sampling times will be used to present results in summary tables and figures.

Table 4. Pharmacokinetic Parameters for Infliximab

Primary Parameter (calculated between Week 22 and Week 30): AUC_{τ} will be calculated at Week 22 for Cohort 1 (IV), Week 22 and 26 for Group A of Cohort 2, 3 and 4 (SC), and Week 24 and 28 for Group B of Cohort 2, 3 and 4 (SC).	
$AUC_{\tau(SC)}$	Area under the concentration-time curve at steady state between over the actual SC dosing interval (14 days), calculated using the linear trapezoidal rule.
$AUC_{\tau(IV)}$	Area under the concentration-time curve at steady state between over the actual IV dosing interval (56 days), calculated using the linear trapezoidal rule.
Secondary Parameters (calculated between Week 22 and Week 30, if data allows): Secondary parameters except for $C_{trough,ss}$ will be calculated at Week 22 for Cohort 1 (IV), Week 22 and 26 for Group A of Cohort 2, 3 and 4 (SC), and Week 24 and 28 for Group B of Cohort 2, 3 and 4 (SC). $C_{trough,ss}$ will be calculated at Week 22 for Cohort 1 (IV), Week 22, 24, 26, 28 for Group A and B of Cohort 2, 3 and 4 (SC).	

AUC_{ss8W}	AUC exposure normalized to an 8-week interval, calculated over actual dosing interval (observed [τobs]), according to the following formula: - IV group: AUCτ [ng·h/mL]/ τobs [h]×1344 [h] - SC (A) group: $\left(\frac{AUC\tau \text{ at } W22}{\tau obs \text{ at } W22}+\frac{AUC\tau \text{ at } W26}{\tau obs \text{ at } W26}\right)/2 \times 1344$ [h] - SC (B) group: $\left(\frac{AUC\tau \text{ at } W24}{\tau obs \text{ at } W24}+\frac{AUC\tau \text{ at } W28}{\tau obs \text{ at } W28}\right)/2 \times 1344$ [h]
$C_{max,ss}$	Observed maximum serum concentration after dose administration
$T_{max,ss}$	Time of observed maximum serum concentration
$T_{1/2}$	Terminal half life
$C_{trough,ss}$	Trough concentration, calculated from the pre-dose of the next dose observed, if available.
MRT	Mean residence time, calculated as: MRT = ([$AUMC_\tau$ + τ (AUC_{inf} - AUC_τ)]/ AUC_τ) – 0.5 × (administration time) for IV infusion and MRT = ([$AUMC_\tau$ + τ (AUC_{inf} - AUC_τ)]/ AUC_τ) for SC administration Where AUC_{inf} is the area under the concentration-time curve from 0 extrapolated to infinity (AUC_{inf} = AUC_τ + $\frac{Last\ observed\ concentration\ over\ the\ dosing\ interval}{slope\ of\ the\ terminal\ phase}$), $AUMC_\tau$ is the area under the moment curve over the dosing interval, and τ is the dosing interval.
CL_{ss}	Clearance after IV dosing, calculated as: CL = $Dose_{IV}$ / $AUC_{\tau(IV)}$
CL/F_{ss}	Apparent clearance after SC dosing, calculated as: CL/F = $Dose_{SC}$ / $AUC_{\tau(SC)}$
$DNC_{max,ss}$	Dose normalized peak exposure at steady state, calculated as: C_{max}/total dose administered
Secondary Parameter (obtained over Week 0 to Week 54): C_{trough} will be obtained at all scheduled visit except Week 22 for Cohort 1 (IV), except Week 22, 24, 26, 28 for Group A and B of Cohort 2, 3 and 4 (SC).	
C_{trough}	Trough concentration, calculated from the pre-dose of the next dose observed, if available.

ss, steady state

The PK parameters will be presented in listings and summarized in tables by treatment group for the PK population. The PK primary parameter of the AUC_τ at steady state between Week 22 and Week 30 will also be summarized (n, mean, SD, CV%, geometric mean, minimum, median, and maximum) in patients who received all doses (full) of study drug up to Week 30 by treatment group for the PK population. Unreliable estimate values will be excluded from summary but listed with a flag.

10. PHARMACODYNAMIC ANALYSIS

All pharmacodynamic tables and listing will be generated using all data on the PD population by treatment group unless otherwise specified. The RF, anti-CCP, CRP and ESR will be recorded as numeric pharmacodynamic parameters. Any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all summary tables. In listing, original results containing inequality signs will be displayed. In the case where a duplicate measurement of the RF, anti-CCP, CRP and ESR is recorded within the same visit, the highest value will be used for summary as a conservative approach. All PD information will be listed by treatment group for the PD population.

10.1. Descriptive statistics of Pharmacodynamic parameters

Descriptive statistics will be provided for the RF, anti-CCP, CRP and ESR parameters (actual value and change from baseline) for the PD population by treatment group at each scheduled visit. Descriptive statistics will consist of n, mean, SD, Standard Error (SE), geometric mean, CV%, minimum, median and maximum.

RF results greater than 10 IU/ml will be considered as “positive” while those equal to or less than 10 IU/ml will be considered as “negative”. Anti-CCP results equal to or greater than 17 U/ml will be considered as “positive” while those less than 17 U/ml will be considered as “negative”. The number and percentage of patients within each category of the RF (Negative, Positive) and anti-CCP (Negative, Positive) parameter will be displayed in shift table from baseline to each post-baseline visit by treatment group for the PD population.

10.2. Figures and listings of Pharmacodynamic parameters

In addition, a plot will be presented showing the mean concentration and SE of the CRP and ESR at each scheduled visit for the PD population by treatment group.

All pharmacodynamic data for RF, anti-CCP, CRP and ESR will be listed by treatment group for the PD population at each scheduled visit. In addition, categorized results for RF and anti-CCP for the PD population will also be listed.

11. EFFICACY ANALYSIS

All efficacy tables and listings will be generated using all data on the Efficacy population by actual treatment group unless otherwise specified.

Efficacy will be assessed by the evaluation of the mean decrease in DAS28 (individual components, DAS28 [ESR], DAS28 [CRP]), EULAR response criteria, ACR criteria (individual components, ACR20, ACR50, ACR70 and hybrid ACR response), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), health assessment questionnaire (HAQ) at the each time points specified in the schedule of events (in Appendix 1).

11.1. DAS and EULAR Response Criteria

11.1.1. 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.

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 patient and visit, showing number of tender and swollen joints by category.

11.1.2. 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 Global Assessment of Disease Activity, the Patient's Assessment of pain and the Physician's Global Assessment of Disease Activity at each scheduled visit.

For these scales, descriptive statistics for actual value and change from baseline 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.

11.1.3. C-Reactive Protein and Erythrocyte Sedimentation Rate

The Descriptive statistics for actual value and change from baseline will be presented for both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) by treatment group at each scheduled visit. Note that CRP and ESR will also be summarized for the PD population by treatment group, and this is described in the pharmacodynamics section.

11.1.4. DAS28

Disease activity in 28 joints (DAS28) will be calculated in two ways at the each scheduled visit using the following two equations:

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

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

Where:

- TJC = number of tender joints (0-28): tender joint count (TJC)
- SJC = number of swollen joints (0-28): swollen joint count (SJC)
- ESR = ESR measurement (mm/h)
- CRP = CRP measurement (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 summarized at each scheduled visit. Data from the eCRF, 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.

11.1.5. EULAR Response Criteria

The European League Against Rheumatism Response (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

DAS28, disease activity score in 28 joints;
Reference: Fransen et al 2005

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

11.2. ACR20, ACR50, ACR70 Criteria and Hybrid ACR Response

11.2.1. 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.

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.

11.2.2. Health Assessment Questionnaire (HAQ) Estimate of Physical Ability

The arthritis-related functional disability will be measured using the disability index of the HAQ, a validated, self-administered form that assesses functional ability in a number of relevant areas, including the ability to dress, rise from bed, eat, walk, maintain personal hygiene, reach, grip and other activities on a scale ranging from 0 (without any difficulty) to 3 (unable to do). Scores range from 0 to 3, with higher scores indicating worse disability.

There are 8 categories within the Health Assessment Questionnaire:

- 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.

In order to compute the disability index:

(1) A score will be obtained for each category by taking the highest score recorded from the questions within the category. The maximum score is taken regardless of missing values in questions, i.e. at least one question must have an assigned score. If all questions have missing values, the score is recorded as missing.

(2) Additionally, an adjustment score is added for each category for use of aids/devices and/or help from another person using the tables below. If the score for a category is 0 or 1 after step (1), and any of the aids/devices/help from another person fields are marked, the score should be increased to 2. If a patient's highest score for that category is 2 or 3 already, it remains 2 or 3.

Table 6. Aids/Devices Items for HAQ Categories

Item	HAQ Category
Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)	Dressing & Grooming
Special or Built up chair	Arising
Built up or special utensils	Eating
Cane	Walking
Walker	Walking
Crutches	Walking
Wheelchair	Walking
Raised toilet seat	Hygiene
Bathtub seat	Hygiene
Bathtub bar	Hygiene
Long handled appliances in bathroom	Hygiene
Long handled appliances for reach	Reach
Jar opener (for jars previously opened)	Grip

Note: The assignment of devices to particular disability categories assumes that the devices are used only for their intended purposes.

Table 7. Help from another Person Items for HAQ Categories

Item	HAQ Category
Dressing & Grooming	Dressing & Grooming
Arising	Arising
Eating	Eating
Walking	Walking
Hygiene	Hygiene
Reach	Reach
Gripping and opening things	Grip
Errands and chores	Activities

(3) A minimum of 6 categories must have a score assigned in order for the HAQ estimate of physical ability to be derived. If there are only scores available for less than 6 categories, the HAQ estimate of physical ability cannot be computed and should be recorded as missing. If there are 6 or more categories with a score assigned, divide the summed category scores (using the adjustment score) by the number of categories answered to obtain the HAQ estimate of physical ability.

Descriptive statistics for actual value and change from baseline of the HAQ estimate of physical ability will be presented for the Efficacy population 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 all be displayed by treatment group and visit. A listing will also be provided by visit using VAS scale result, total length of VAS scale on the questionnaire and the standardized VAS (Section 11.1.2) to show the patient's score on the HAQ assessment of pain. (0-no pain, 100-severe pain).

11.2.3. ACR20, ACR50 and ACR70 criteria

The American College of Rheumatology (ACR) criteria are a standard measure of clinical activity in rheumatoid arthritis 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 following are fulfilled:

- A percentage decrease of at least 20% from baseline in the number of tender joints, and
- A percentage decrease of at least 20% from baseline in the number of swollen joints, and
- A percentage decrease of at least 20% from baseline on three 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

Any patient with missing component for the evaluation of ACR20 criteria or not satisfying the responder criteria will be considered as non-responder. The ACR50 and ACR70 are calculated 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 for the Efficacy population at each scheduled visit.

A listing will be provided by treatment group and visit, showing ACR20, ACR50 and ACR70 responder status at each visit.

11.2.4. Hybrid ACR Response

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 (Number of tender joints, Number of swollen joints, Pain (VAS), Disease activity (VAS), HAQ, 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, the post-baseline score is subtracted from the baseline score, and the percentage change in each measure determined.

(2) If a core set measure worsened by more than 100%, that percentage change is set to -100%

(3) The percentage change for all core set measures is averaged to give the mean % change in 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 percentage change in core set items calculated in step (3); the hybrid ACR score is where they intersect in the table.

Table 8. 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

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

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.

11.3. Clinical Disease Activity Index and Simplified Disease Activity Index

CDAI and SDAI are calculated at each scheduled visit as follows:

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

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

Note: Prior to calculation of the CDAI and SDAI, the Patient Global Assessment of Disease Activity and Physician Global Assessment of Disease Activity VAS results should be converted from 'mm' to 'cm'.

Descriptive statistics for actual value and change from baseline of CDAI and SDAI will be presented at each scheduled visit. In addition, a listing will be provided by treatment group and visit showing the CDAI and SDAI values.

11.4. 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 20.0 or the higher version) and the procedure date.

12. SAFETY ANALYSIS

All safety analyses will be performed in the Safety population by treatment group presenting data on adverse events (AEs), clinical laboratory results (clinical chemistry, hematology, urinalysis), complement (C3, C4) and total haemolytic complement, vital sign measurements, ECGs, hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and temperature), 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. All safety data will be listed for the ITT population unless otherwise specified.

12.1. 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 before exposure to study drug or any event already present that worsen in either intensity or frequency after exposure to study drug.

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 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) v4.03.

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

- Missing day (e.g. XXFEB2017): Assume the last day of the month. (e.g. 28FEB2017)

- Missing day and month (e.g. XXXXX2017): Assume December 31st. (e.g. 31DEC2017)
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as Missing.

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

- If the day of an Adverse Event is missing (e.g. XXFEB2017), 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 end date of the AE.
    - If the month and year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01FEB2017).
- If the day and month is missing (e.g. XXXXX2017), 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 end date of the AE.
    - If the year is not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2017).

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 end date of the AE.

Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date; TEAE flag, study period (dose-loading phase, maintenance phase); frequency (continuous, intermittent, transient); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); any treatment required (no, yes with specified treatment); intensity (CTCAE Grade 1 to 5); action taken with study drug (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn); relationship with study drug (unrelated, possible, probable, definite); whether the event was serious (no, yes); whether the AE is administration-related reaction (ARR) or injection site reaction (ISR); and infection/malignancy flag. All AEs will be listed.

In summaries, adverse events will be considered to be related if the relationship is possible, probable, or definite.

12.1.1. 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. The summaries will be repeated in separate tables for TEAEs occurred in maintenance phase. TEAEs occurred in maintenance phase is defined as any event not present before study drug administration at Week 6 or any event already present that worsens in either intensity or frequency after study drug administration at Week 6.

12.1.2. 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, whether an autopsy was performed (yes, no), whether a death certificate was completed (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). Also, days on study will be calculated as (date of last visit – date of first dose +1).

12.1.3. Serious Adverse Events

A 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 a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and 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. The summaries will be repeated in a separate table for TESAEs occurred in maintenance phase.

All SAEs will be listed including the variables detailed in Section 12.1. Serious criteria and SAE description will be presented in an additional information listing.

12.1.4. 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. The summaries will be repeated in a separate table for TEAEs leading to study drug discontinuation occurred in maintenance phase.

All TEAEs leading to study drug discontinuation will be listed including the variables detailed in Section 12.1.

12.1.5. Treatment-Emergent Adverse Events of Special Interest

The following TEAEs of special interest except for ARR and Delayed hypersensitivity will be summarized in separate tables and ARR and Delayed hypersensitivity will be summarized together in one table. 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. The summaries will be repeated in separate tables for TEAEs of special interest that occurred in maintenance phase. In addition, tables for signs and symptoms regarding ARR and ISR will be provided separately by SOC, PT (as coded by MedDRA version 20.0 or the higher version) and intensity. The summaries will be repeated in separate tables for TEAEs of special interest that occurred in Maintenance Phase.

- Infusion-related reactions/hypersensitivity/anaphylactic reactions [administration-related reactions]
  AEs classified as IRR in the eCRF and that occurred between start of administration and 24 hours from the study drug administration will be included. Stop time for IV infusion and start time for SC injection will be used for calculating time to ARR occurrence after study drug administration. If administration time or ARR start time is unknown, only administration date and ARR start date will be considered and AEs that occurred within 1 day after study drug administration will be classified as ARR.

  Note: IRR in the eCRF means administration related reaction (ARR).

- Delayed hypersensitivity
  AEs classified as IRR in the eCRF and that occurred after 24 hours from the study drug administration will be included. Stop time for IV infusion and start time for SC injection will be used for calculating time to ARR occurrence after study drug administration. If administration time or ARR start time is unknown, only administration date and ARR start date will be considered and AEs that occurred 2 or more days after study drug administration will be classified as Delayed hypersensitivity.

- Injection site reactions (ISR)
  AEs classified as ISR in the eCRF will be included.

- Infection
  AEs coded with a System Organ Class of 'Infections and Infestations' will be included.

- Malignancy
  AEs coded with a System Organ Class of ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps)’ excluding terms which includes ‘benign’ in High Level Group Term (HLGT), High Level Term (HLT), PT and Lowest Level Term (LLT). And it will be determined by medical review and included.

TEAEs classified as ARR and ISR will be presented in separate listings including the variables detailed in Section 12.1. Experienced Signs and symptoms will be presented in additional information listings for ARR and ISR, separately. Delayed hypersensitivity will be flagged in ARR listings. Infection and malignancy will be flagged in listings for AEs.

12.2. Clinical Laboratory Evaluations

Clinical laboratory (Clinical chemistry, hematology and urinalysis) test samples will be analyzed at the central laboratory at each scheduled visit. Erythrocyte Sedimentation Rate (ESR) samples will be analyzed at the local laboratory using kits supplied centrally. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration. All summaries will be based on the SI (System International) units provided by the central laboratory, no unit conversion will

be done. Results of clinical laboratory parameters listed in lab specification of the central laboratory will be tabulated by treatment group at each scheduled visit for the Safety population. All of the clinical laboratory results will be presented in listings for the ITT population.

Actual value and change from baseline of all numeric laboratory parameters including hematology, clinical chemistry and urinalysis (if applicable) will be summarized using descriptive statistics by laboratory category, test parameter and visit. For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality signs will be displayed.

The categorized results of laboratory parameters including urinalysis, clinical chemistry and hematology (if applicable) 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, 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 v 4.03 [6]. 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 with a result for each grade will be summarized by laboratory category, treatment group, CTCAE term and visit. Additional tables will be generated using the most severe grade after administration at Week 0 and Week 6, respectively. The most severe grade will be selected including all post-baseline scheduled, unscheduled and repeated visits.

Clinical chemistry, hematology and urinalysis data 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.

12.3. Complement (C3, C4) and Total Haemolytic Complement

Complement tests (C3, C4, and total haemolytic complement) will be assessed at Week 0. Additional assessment for complement (C3, C4, and total haemolytic complement) will be conducted when a patient experiences a delayed hypersensitivity reaction after 24 hours from study drug administration. All complement tests data will be presented in a listing by treatment group for the ITT population.

12.4. Vital Signs, Weight and BMI

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature), weight and BMI 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 beginning of the study drug administration
- 1 hour ($\pm$10 minutes) after the end of the study drug administration

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

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 for the Safety population. The criteria for clinically notable results are defined as follows:

Table 9. 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 (^{o}C)	<= 35.0	>= 38.0

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

12.5. Electrocardiograms

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 for the Safety population, 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 for the ITT population.

12.6. Physical Examination

Physical examinations will be performed on scheduled visit before the beginning of the study drug administration (on the same visit day as the study drug administration). 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
- 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 for the Safety population, 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 for the ITT population.

12.7. Tuberculosis Assessment

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

Results for IGRA will be classified as either "Positive", "Indeterminate" or "Negative". The number and percentage of patients with IGRA results will be summarized for Baseline (as defined in Section 5.5) and Treatment Period for the Safety population. All post-baseline results of IGRA will be reported in a Treatment Period category using the following methodology:

- If a patient has at least one result of "Positive" in the Treatment Period they will be considered as "Positive"
- If a patient has no "Positive" results and at least one result of "Indeterminate" in the Treatment Period then they will be considered as "Indeterminate"
- If a patient has the only "Negative" results in the Treatment Period then they will be considered as "Negative"

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 tuberculosis.

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

12.8. Local Site Pain

Local site pain measurements using 100 mm Visual Analogue Scale (VAS) will be performed immediately (not exceeding 1 hour) after the end of the study drug administration on scheduled visits beginning at Week 6. Local site pain data will be summarized using descriptive statistics

by treatment group and visit for the Safety population. All local site pain data will be listed by treatment group and visit for the ITT population.

12.9. Pregnancy Test

Pregnancy tests will be conducted and summarized only for female patients. Pregnancy tests consist of serum and urine pregnancy tests. Serum Pregnancy Tests will be performed by a central laboratory at Screening and EOS. Urine Pregnancy Tests will be performed at scheduled visits. Serum pregnancy test results will be classified as "Positive", "Inconclusive" or "Negative". Urine pregnancy test results will be classified as "Positive" or "Negative". If a urine pregnancy test result is "Positive", a confirmatory serum pregnancy test should be performed. The number and percentage of female patients who have pregnancy test results will be summarized by treatment group, visit and test for the Safety population. All pregnancy test results will be listed for each patient tested by treatment group and visit for the ITT population.

12.10. Immunogenicity

Serum sample for immunogenicity will be collected at Week 0, 6, 14, 22, 30, 38, 46, 54, and EOS. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24 hours of study drug administration. 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"}. For further characterization, the antibody level will be assessed by titration in samples that are "Positive" in the screening NAb assay.

The results of the final ADA and the screening NAb assay will be summarized. The number and percentage of patient will be presented by treatment group and test at each scheduled visit for the Safety population. A listing showing immunogenicity test results for each patient will be provided by treatment group and visit for the ITT population.

The ADA and NAb titer values of the CT-P13 tagged assay will be transformed using a $[\log_2(x/23)] + 1$ and $[\log_2(x/45)] + 1$ transformation, respectively. If the values in the data are in forms of inequality, the sign of inequality will be removed and then the values will be

transformed. Descriptive statistics of transformed ADA and NAb titer will be displayed by treatment group for the Safety population. The actual and transformed results of ADA and NAb titer for each visit will also be presented in the listing of immunogenicity results for the ITT population.

13. Changes in the Planned Analysis

13.1. Changes in the Protocol

1. Section 7.1.2 of the protocol states that the following secondary PK parameters for the study drug will be considered in Part 1 (between Week 22 and Week 30):

- **AUC_{ss8W}** : Total exposure over the 8 weeks interval from Week 22 to Week 30
- **C_{max}** : Observed maximum serum concentration after study drug administration
- **T_{max}** : Time of observed maximum serum concentration
- **$T_{1/2}$** : Terminal half life
- **C_{trough}** : Trough concentration (concentration before the next study drug administration)
- **MRT** : Mean residence time
- **CL** : Clearance after IV dosing
- **CL/F** : Apparent clearance after SC dosing
- **BA** : Bioavailability (absolute and/or relative)
- **AUCτ/DN** : Dose normalized total exposure over dosing interval (= AUCτ/total dose administered)
- **C_{max}/DN** : Dose normalized peak exposure (= C_{max}/total dose administered)

The BA and AUCτ/DN will not be considered as the secondary PK parameters in this analysis.

2. The formula (AUCτ [ng·h/mL]/ τobs [h]×1344 [h]) for AUC_{ss8W} was updated in the SAP from the protocol as in the following:

- IV group: AUCτ [ng·h/mL]/ τobs [h]×1344 [h]
- SC (A) group: $\left(\frac{AUC\tau\ at\ W22}{\tau\ at\ W22}+\frac{AUC\tau\ at\ W26}{\tau\ at\ W26}\right)/2$ ×1344 [h]
- SC (B) group: $\left(\frac{AUC\tau\ at\ W24}{\tau\ at\ W24}+\frac{AUC\tau\ at\ W28}{\tau\ at\ W28}\right)/2$ ×1344 [h]

14. Reference List

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15. APPENDICES

Appendix 1: Schedule of Events for Part 1

	Screening	Treatment Period												EOS[2]
Study Week		**0**	**2**	**6**	**8[1]**	**10[1]**	**14**	**22**	**PK Monitoring Visit[21]**	**30**	**38**	**46**	**54**	
Study Day	**–21 to –1**	**0**	**14**	**42**	**56**	**70**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**							**± 3 days**	**± 5 days**			
Cohort 1 treatment		**IV**	**IV**	**IV**			**IV**	**IV**		**IV**	**IV**	**IV**	**IV**	
Cohort 2, 3 and 4 treatment[3, 4]				**SC**	**SC[1]**	**SC[1]**	**SC**							
Informed consent	X													
Demography[5]	X													
Medical history[6]	X													
Hepatitis B & C and HIV-1 and -2[7]	X													
Inclusion and exclusion criteria	X	X[8]												
Randomization				X[8]										
Serum pregnancy test	X													X
Urine pregnancy test[9]		X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	
Clinical laboratory tests[10]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Chest x-ray[11]	X													
Interferon-γ release assay[12]	X									X[8]			X[8]	X
Physical examinations	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Vital signs and Weight[13]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
12-lead ECG	X			X			X			X			X	X
Efficacy assessment[14]														
Tender joint count (68 joints/28 joints)	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[15]
Swollen joint count (66 joints/28 joints)	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[15]
VAS pain score	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[15]
VAS global assessment of disease activity (patient/physician) score	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[15]
Health Assessment Questionnaire	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[15]
ESR (local)[16]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
CRP[16]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
VAS local site pain[17]				X			X	X		X			X	

Rheumatoid Factor	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X
Anti-cyclic citrullinated peptide	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X
Immunogenicity[18]		X[8]		X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X
Hypersensitivity monitoring[19]		X	X	X			X	X		X	X	X	X		
Complement (C3, C4) and Total Haemolytic Complement[20]		X[8]													
Pharmacokinetic blood sampling		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[21]	X[8]	X[8]	X[8]	X[8]	X[8]	
Previous/concomitant medications[22]	X														
TB clinical monitoring[23]	X														
AEs monitoring[24]	X														

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CRP, C-reactive protein; ECG, Electrocardiogram; ESR, erythrocyte sedimentation rate; EOS, end of study; HIV, human immunodeficiency virus; IV, intravenous; N/A; not applicable; PK, pharmacokinetic; QOL, quality of life; SC, subcutaneous; TB, tuberculosis; VAS, visual analogue scale.

1. Visits 4 and 5 (Week 8 and Week 10) will only be made by patients from Cohorts 2, 3 and 4 for additional pharmacokinetic assessment.
2. All EOS assessments will be completed 8 weeks after the last study drug administration.
3. First CT-P13 SC will be administered by PFS at Week 6 and further SC injections will be given every 2 weeks up to Week 54.
4. A dosing window of ±3 days is allowed up to and including Week 30; a dosing window of ±5 days is allowed after Week 30, including EOS.
5. Age, gender and race.
6. At Screening, patients will be assessed for the history of rheumatoid arthritis, respiratory disease, diabetes mellitus, congestive heart failure and etc.
7. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis. Hepatitis and HIV analysis will be performed at the central laboratory.
8. Assessed prior to study drug administration.
9. A urine pregnancy test for women of childbearing potential who have not been surgically sterilized will be used to confirm patients are not pregnant before study drug administration on each visit day 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.
10. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analysed at the central laboratory. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness.
11. 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 0) is available.
12. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period for the following patients:
    - Patient who has a history of active TB with sufficient documentation of complete resolution
    - Patient who has a history of latent TB with sufficient documentation of prophylaxis
    - Patient with a confirmed latent TB and enrolled after 30 days of latent TB prophylaxis during Screening
13. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented at Screening.
14. It is recommended that the joint count assessments are performed by the same physician when possible.
15. End-of-study assessments will only be performed if not done at Week 54.

16. Both ESR rate and CRP are considered to be an efficacy, pharmacodynamics and safety (clinical laboratory test) endpoint.
17. Patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug.
18. Serum samples for immunogenicity testing will be drawn before dosing of study drug. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
19. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and 1 hour (±10 minutes) after the end of the study drug administration) to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed. In addition, delayed hypersensitivity will be monitored after 24 hours of study drug administration, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema).
20. Additional serum samples for complement (C3, C4) and total haemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
21. If the investigator deems hospitalization necessary for the blood sample collection, patients should remain in the hospital until blood samples for pharmacokinetic analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized. Blood samples for pharmacokinetic analysis will be obtained at following time point;

Visit (Day)	Cohort 1	Cohorts 2, 3 and 4	
		Group A	Group B
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 3, 8 and 24 hr (±15 min) after SOI • 48 hr (±2 hr) after SOI • 96 hr (±4 hr) after SOI • 168 ±6 hr after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 26 (Day 182)	• 28 days (±1 day) after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection

		• 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	
Week 28 (Day 196)	• 42 days (±1 day) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)	

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

22. Use of all prior and concomitant medications for the treatment of rheumatoid arthritis, from the diagnosis of disease until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) patient enrolment until the last assessment date or End-of-Study Visit, will be recorded.
23. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay or chest x-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
24. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit. Where AEs are ongoing at the EOS visit (8 weeks after the last dose is received), the patient should be followed up for a further 30 days) regardless of the relationship to the study drug. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Adverse events of special interest (i.e. infusion-related reactions, injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Appendix 2: 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; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <100 - 80g/L	<8.0 g/dL; <80 g/L;	-
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
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	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
GGT increased	Gamma Glutamyl Transferase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hemoglobin increased	Hemoglobin		Increase in >0 - 2 gm/dL above			-

		High	ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
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	-
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L #	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L
Lymphocyte count decreased	Lymphocytes	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$/L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Neutrophil count decreased	Total 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

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	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/mm3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L

Note: The LLN and ULN values will be the normal ranges as provided by the central laboratory at each relevant transfer.
# indicates that this grade will not be used because this grade shares the same criteria due to exclusion of clinical input.