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

24th March 2019
Statistical Analysis Plan

Part 2 – Final Version 4.0

Prepared by:

[redacted]

Prepared by: _____ Date: ____/____/____

[redacted]

Approved by: _____ Date: ____/____/____

[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
ADA	Anti-Drug Antibody
AE	Adverse Event
AI	Auto Injector
Anti-CCP	Anticyclic Citrullinated Peptide
AUC_{τ}	Area Under the Concentration-Time Curve
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
C_{max}	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
HLGT	High Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
IGRA	Interferon Gamma Release Assay
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
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
SDAI	Simplified Disease Activity Index
SF-36	Short-Form Health Survey
SI	System International
SIAQ	Self Injection Assessment Questionnaire
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. (hereinafter referred to as "CELLTRION"). The clinical monitoring and medical writing are being performed under contract with [redacted], in collaboration with CELLTRION. Pharmacokinetics analysis is being performed under contract with [redacted], in collaboration with CELLTRION. The data management and statistical analysis are being performed by CELLTRION.

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 2 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 following clinical study reports (CSR) will be generated during entire Study Period:

- A report of all efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and safety data up to and including Week 30 only. The following data will be included.

<table>
<tr><th></th><th>Ongoing at Week 30</th><th>Withdrawal prior to Week 30</th></tr>
<tr><td>Scheduled visit (excluding EOS)</td><td>Up to and including Week 30</td><td>All scheduled visits before withdrawal</td></tr>
<tr><td>EOS</td><td>Not applicable</td><td rowspan="2">All available visits prior to the latest date of all patients' Week 30 visit dates</td></tr>
<tr><td>Unscheduled Visit</td><td>On or before date of Week 30 administration* for each patient</td></tr>
<tr><td>Non-visit based data (e.g. adverse events and medications)</td><td>All available data having a start date on or before the date of Week 30 administration* for each patient.
If available, the end date after the date of Week 30 administration* will also be included.</td><td>All available data having a start date on or before the latest date of all patients' Week 30 visit dates.
If available, the end date after the latest date of all patients' Week 30 visit date will also be included.</td></tr>
</table>

* If the date of Week 30 administration is missing, the date of Week 30 visit is used for cut-off date.

Note: Withdrawal patient at Week 30 is defined as a patient whose Week 30 visit date is recorded as date of last visit on the "Study Treatment Termination" eCRF page, will be included in category of "withdrawal prior to Week 30"

- A report of all efficacy, PK, PD, safety and usability data up to EOS (up to Week 54 for patients from the study for country specific B [Korea] and C [Bulgaria, Poland and Russia]) including all visit based data, and all available non-visit based data having a start date on or before the date of the following cut-off date. If available, the end date after the cut-off date will also be included. Each cut-off date is as follows:

	Patients from study for country specific B and C (up to Week 54)	**Patients from study excluding country specific B and C (up to EOS)**
Completion	Week 54 administration date for each patient (If the date of Week 54 administration is missing, the date of Week 54 visit is used)	EOS visit date for each patient
Early Withdrawal	the latest date of all completion patients' cut-off dates	

- A report of all efficacy, PK, PD, safety and usability 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 – 2nd February 2018
- Study Protocol Version 4.0 Country specific A.0 – 2nd February 2018
- Study Protocol Version 4.0 Country specific B.1 – 18th June 2018
- Study Protocol Version 4.0 Country specific C.1 – 2nd March 2018
- Study Protocol Version 4.0 Country specific C.2 – 10th September 2018
- Unique CRF Part 2 Version 4.0 – 22nd October 2018

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

3. Study Objective

Primary, secondary and tertiary objectives are described as below.

3.1. Primary Objective

The primary objective of this study is to demonstrate that CT-P13 SC is noninferior to CT-P13 IV at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-Reactive Protein [CRP]).

3.2. Secondary Objectives

The secondary objectives of this study are as following.

- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks)
- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54
- To evaluate usability of CT-P13 SC via Auto Injector (AI) from Week 46 to Week 54 (Protocol including country specific C only)
- To evaluate usability of CT-P13 SC via Pre-Filled Syringe (PFS) from Week 56 to Week 64 (Protocol including country specific C.2 only)

3.3. Tertiary Objective

The tertiary objective of this study is to evaluate biomarkers (optional).

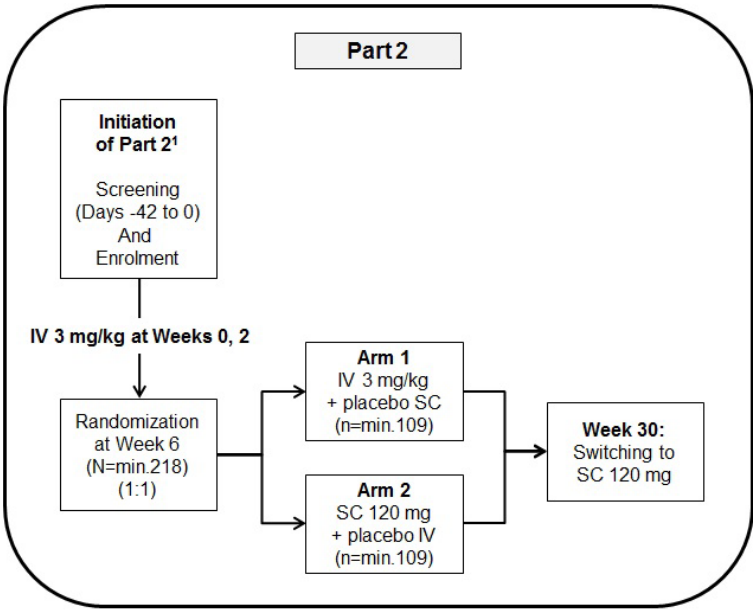
4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

The part 2 of this study is a randomized, multicenter, parallel group, Phase III study designed to evaluate efficacy, pharmacokinetics 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 RA who are not adequately responding to methotrexate administration over at least 3 months. Minimum 218 male or female patients with active RA will be randomly assigned at Week 6 in a 1:1 ratio to 1 of 2 treatment groups, CT-P13 SC with Placebo IV and CT-P13 IV with Placebo SC (minimum 109 patients per treatment group).

This study is designed to demonstrate noninferiority in efficacy between CT-P13 SC and CT-P13 IV. The overview of study design is illustrated in Figure 1.

Figure 1 Overview Study Design



IV, intravenous; SC, subcutaneous
1. Part 2 will be initiated based upon the independent data safety monitoring board (DSMB)'s review of the PK data as well as efficacy, PD and safety found over first 30 weeks from Part 1.

Part 2 will be initiated based upon the independent data safety monitoring board (DSMB)'s review of the PK data as well as efficacy, PD and safety found over the first 30 weeks from Part 1.

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) with a double-blinded period during Maintenance Phase up to Week 30 followed by an open-label period of 24 weeks and the EOS.

Screening: Screening will take place between Days −42 and 0, 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 CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on investigator's discretion will be randomly assigned to receive either CT-P13 SC with placebo IV or CT-P13 IV with placebo SC 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. A double-dummy design will be used to maintain blinding during the Maintenance Phase up to Week 30. The study will be unblinded at Week 30 for reporting purposes. The unblinded team will be predefined prior to performing the analyses. The study will remain blinded to the investigators, patients and predefined blinded team from the Sponsor and [redacted] until all patients have completed the study and the database has been finalized for study termination.

- **Arm 1**: further 3 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22) with placebo SC at Week 6 and every 2 weeks thereafter up to Week 28. CT-P13 IV will be then switched to CT-P13 SC via PFS at Week 30. Further doses of study treatment with CT-P13 SC via PFS will be given up to Week 54

- **Arm 2**: first CT-P13 SC will be administered by PFS at Week 6 and every 2 weeks thereafter up to Week 54 with placebo IV at Weeks 6, 14 and 22

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 TB.

The patient assessment overview is illustrated in Figure 2

Figure 2 Patient Assessment Overview

	Dose-loading		Maintenance[1]						
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**	**54**
Visit[2]	X	X	X	X	X	X	X	X	X
Evaluation									
Primary Efficacy					X				
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 need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed throughout the study period, including the EOS Visit.

CT-P13 SC via PFS (or placebo SC during double-blinded period) will be injected by a healthcare professional at each site visit (Weeks 6, 14, 22, 24~28 [for patients who will make visit for additional PK assessment], 30, 38, 46 and 54). After proper training in injection technique, patients may self-inject with CT-P13 SC via PFS (or placebo SC during double-blinded period) if their investigator determines that it is appropriate at any other weeks (Weeks 8, 10, 12, 16, 18, 20, 24~28 [for patients who will not make visit for additional PK assessment], 32, 34, 36, 40, 42, 44, 48, 50 and 52).

End-of-Study Visit: The End-of-Study (EOS) Visit will occur 2 weeks after the last dose of CT-P13 SC is received. For patients who early discontinue the study before Week 30, the EOS Visit will occur 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS visit will occur 2 weeks after the last CT-P13 SC is received.

The schedule of events is presented in Appendix 1-1.

4.2. Country Specific Study Design

4.2.1. Protocol including Country Specific A

There is no change in study design.

4.2.2. Protocol including Country Specific B

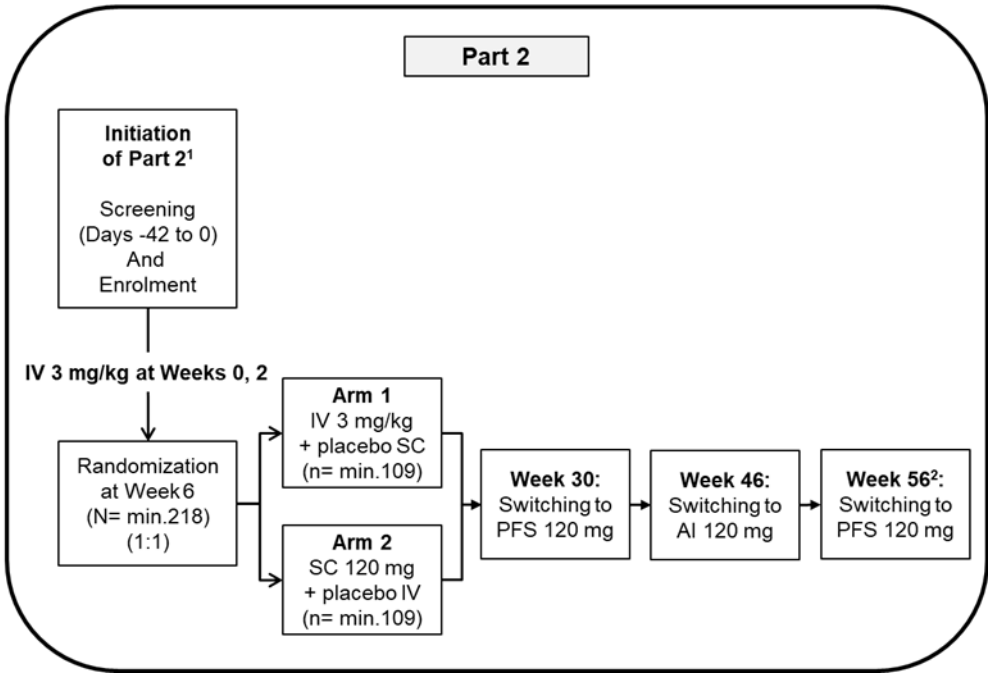
The changes in study design are as follows.

- Methotrexate between 10 to 25 mg/week is permissible.
- The 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.

4.2.3. Protocol including Country Specific C

Patients will be administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54, and patient who agreed with further administration will be switched back to CT-P13 SC via PFS at Week 56 according to protocol country specific C.2. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 64. The overview of study design is illustrated in Figure 3.

Figure 3 Overview of Study Design for Protocol including Country Specific C



IV, intravenous; SC, subcutaneous; PFS, Pre-filled Syringe; AI, Auto Injector
1. Part 2 will be initiated based upon the independent data safety monitoring board (DSMB)'s review of the PK data as well as efficacy, PD and safety found over first 30 weeks from Part 1.
2. Switching back to CT-P13 SC via PFS at Week 56 will be implemented at selected sites. (Protocol including country specific C.2 only)

Usability assessments will be performed additionally, and the patient assessment overview is illustrated in Figure 4.

Figure 4 Patient Assessment Overview for Protocol including Country Specific C

	Dose-loading		Maintenance[1]								
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**	**54**	**56**	**64**
Visit[2]	X	X	X	X	X	X	X	X	X	X	X
Evaluation											
Primary Efficacy					X						
Efficacy	X	X	X	X	X	X			X		
Pharmacokinetic	←	—	—	—	—	—	—	—	→		
Pharmacodynamic	X	X	X	X	X	X	X	X	X		
Safety Evaluation	←	—	—	—	—	—	—	—	—	—	→
Usability								←	—	—	→

1. Additional visits will only be made by patients who need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed throughout the study period, including the End-of-Study Visit.

CT-P13 SC via AI will be self-injected under observation of healthcare professional at each site visits (Week 46 and 54). Self-injection training will be provided at Week 46 prior to the first AI injection. After proper training in AI injection technique, patient may self-inject with CT-

P13 SC via AI at home at any other weeks (Weeks 48, 50 and 52). If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via AI. At Week 56, patients who agreed with protocol version 4.0 country specific C.2 will be switched back to CT-P13 SC via PFS and self-injection retraining will be provided prior to the Week 56 PFS injection. CT-P13 SC via PFS will be self-injected under observation of healthcare professional at Weeks 56 and 64. After proper training in PFS injection technique, patient may self-inject with CT-P13 SC via PFS at home at Weeks 58, 60 and 62. If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via PFS.

The schedule of events is presented in Appendix 1-2.

5. GENERAL STATISTICAL CONSIDERATIONS

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

- Minimum and maximum will be displayed without rounding from values in the source listing.
- Mean, median, geometric mean and percent coefficient of variation (CV%) will be rounded to one more decimal place than the maximum decimal place of values in the source listing.
- SD will be rounded to one more decimal place than mean.
- Point estimate and confidence intervals (CI) obtained from statistical procedures will be displayed to two decimal places.

Categorical data will be summarized using numbers and percentages of patients. Percentages will be rounded 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.

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

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] Version [redacted] or higher. Population PK model will be employed to estimate the individual subject PK parameters by a non-linear mixed effect PK model using [redacted] version [redacted] or higher.

5.2. Sample Size

The primary endpoint is the mean change from baseline in DAS28 (CRP) at Week 22. A sample size of 174 subjects (87 patients each in the CT-P13 SC and CT-P13 IV treatment groups) provide 80% power to demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the 97.5% one-sided confidence interval for the difference in the mean change from baseline of DAS28 (CRP) at Week 22. In the sample size calculation, noninferiority margin of -0.6, one-sided alpha level 2.5% and standard deviation of 1.4 were assumed. Considering 20% drop-out rate, minimum 218 patients (109 patients each in the CT-P13 SC and CT-P13 IV treatment groups) will be randomized.

5.3. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for the randomization at Week 6. Unblinded 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 (≤100 kg vs. >100 kg). The randomization numbers will be blocked, and within each block the same number of patients will be allocated to each treatment group.

This study will be double-blind. Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated by knowing the study drug status of the patient. In such cases, the investigator must contact the medical monitor. If the investigator is unable to contact the medical monitor, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data up to Week 30 have been entered into the database and the database up to Week 30 is finalized for analysis. The unblinded team will be predefined prior to performing the analyses. Final determination of the analysis sets will occur prior to the finalizing the database. While the study data are analyzed at Week 30, both the patient and physician and predefined blinded team from the Sponsor and [redacted] will be blinded until all patients have completed the study and the database has been finalized for study termination.

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), Safety, Usability populations. Patients to be excluded from analysis population because of major protocol deviation is defined in Section 5.6.

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 treatment group, even if there is a discrepancy between the actual administered dose and the randomized treatment group. If there is a patient with such a discrepancy, patients receiving at least one CT-P13 SC before Week 30 will be treated as CT-P13 SC treatment group. All other patients will be treated as CT-P13 IV treatment group. In addition, for the primary analysis of DAS28 (CRP) at Week 22, the adjusted treatment group will be defined based on the actual treatment between Week 6 (inclusive) and Week 22 (exclusive). For example, a patient receiving CT-P13 IV up to Week 22 and CT-P13 SC at Week 24 will be assigned to CT-P13 SC treatment group for the actual treatment group, CT-P13 IV treatment group for the adjusted treatment group.

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. Efficacy Population

The Efficacy population will consist of the All-Randomized population who receive at least one full dose of study drug (CT-P13 IV, CT-P13 SC) at Week 6 or thereafter and who have at least one efficacy evaluation result after Week 6 or thereafter treatment. A patient will be considered as receiving full dose if the actual administered dose (mg) of the patient is greater than or equal to 95% of prescribed dose (mg) based on 'Study Drug Administration' page of eCRF. 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)
- Short-Form Health Survey (SF-36)

A major protocol deviation that may affect the interpretation of study results of efficacy will be excluded from Efficacy population. Final determinations of the Efficacy population will be made at the blinded Data Review Meeting (DRM) held in accordance with ICH E9 Statistical principles for clinical trials.

5.4.4. Pharmacokinetic Population

The PK 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 (CT-P13 IV, CT-P13 SC) at Week 6 or thereafter and who have at least one PK concentration result after Week 6 or thereafter treatment.

5.4.5. 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 (CT-P13 IV, CT-P13 SC) 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 or thereafter treatment.

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.

5.4.7. Usability Population

The Usability population is defined as all patients who self-injected at least one (partial or full) dose of CT-P13 SC via AI from Week 46 to 54 or via PFS from Week 56 to 64 and who have at least one usability assessment.

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". A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare, and will be identified prior to study unblinding.

Major protocol deviations and population to be excluded are defined as follows:

- Mis-randomizations (Efficacy/PK populations): Patients who received the other treatment than that to which they were assigned at any point will be defined as mis-randomized. Only patients with mis-randomization before Week 22 administration will be excluded from Efficacy population. In addition, patients with mis-randomization before Week 30 administration will be excluded from PK population.

- Non-compliance of inclusion or exclusion criteria which affect efficacy result (Efficacy population): CELLTRION will identify via review of data sourced from the site monitoring database.

- Receipt of joint surgery, synovectomy or intra-articular injection before Week 22 (Efficacy population): CELLTRION will identify prior to database lock.

- Significant GCP non-compliance (All populations): CELLTRION will identify the sites which have been closed or patients who have been affected due to suspected scientific misconduct and/or serious GCP non-compliance. Some analysis population can be determined based on the details of the significant GCP non-compliance found after unblinding. Affected population will be discussed and determined during DRM and population to exclude the patients with significant GCP non-compliance will be specified in listing. In addition, a sensitivity analysis (Section 10.1.4.2) will be conducted considering the significant GCP non-compliance sites.

  Based on the discussion at Week 54 DRM, patients from [redacted] with Confirmed Scientific Misconduct issue will be excluded from the usability population only. The other populations will include the [redacted], and sensitivity analysis will be additionally performed for the primary analysis excluding the patients from the [redacted].

- Dose Skip (Efficacy population): If a patient who was continuing the study at Week 22 and skipped dose (more than two consecutive for SC injection, or more than one

for IV infusion) prior to Week 22, then the patient will be excluded from Efficacy population. Skipping administration of placebo will be ignored. CELLTRION will identify via review of exposure data.

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 failed at screening 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
- Patient 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: IV’ 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: IV’ page of the eCRF for Arm 1 and ‘Study Drug Administration: SC_PFS’ page of the eCRF for Arm 2 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 on or after Week 6, the patient will be considered to have discontinued in the maintenance phase, whereas if discontinuation occurred before the Week 6 administration, the patient will be considered to have discontinued 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: IV' 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, Chile, Spain and Peru); Week 6 body weight (≤100 kg vs. >100 kg); Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/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. These will be used as covariates in analysis of covariance (ANCOVA).

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 had cardiac disease, corresponding NYHA class will be selected. The criteria for congestive heart failure is defined as Table 1:

Table 1. New York Heart Association Functional Classification

Class	Symptoms
I (Mild)	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or 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

Patients who did not have cardiac disease will be classed as “No Class” in the listing. All NYHA criteria assessment data will be presented in a listing by treatment group for the ITT population.

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. If confirmatory test is conducted, the result of the confirmatory test will be used for the summary. All collected results will be listed.

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 [(the first administration date of study drug – 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 the first administration date of study drug, then it will be imputed using the first administration date of study drug. If the whole date is missing, the date will not be imputed and time since RA diagnosis will not be calculated. 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. BIOMARKER ASSESSMENTS (Optional)

For patients who sign a separate Informed Consent Form for the biomarker assessments, a blood sample for evaluation of any necessary genotypes will be collected before dosing on Day 0 of Week 0. These genes will include, but are not limited to FcγRIIIa.

Data for each genotype will be summarized by treatment group for the All-Randomized population. A listing will also be generated for the ITT population.

9. TREATMENTS AND MEDICATIONS

9.1. Prior and Concomitant Medications

All medications except for the treatment of RA used during the study, 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 concomitant medications will also be recorded when any Serious Adverse Drug Reactions (SADRs) occur after the EOS Visit. 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: IV' 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 following, and all other medications will be defined as concomitant medication.

- A medication checked as yes to "Is stop date before the first injection of study drug (Week 0)?" on eCRF, or
- A medication having actual/imputed stop date of medication before the first administration date.

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 separate tables will be generated for the concomitant medications during the entire study period and the maintenance phase, respectively. A concomitant medication in maintenance phase is defined as a concomitant medication that has missing stop date, an actual or imputed stop date on or after the Week 6 administration date, or marked as ongoing 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.

9.1.1. Co-administration of Methotrexate and Folic Acid

Data on co-administration of methotrexate and folic acid will be collected separately from all

other medications. The same rules for date imputation and definitions of prior and concomitant will apply. The number of patients with prior and concomitant administration of methotrexate or folic acid will be summarized separately. Additionally, the methotrexate dose (mg/week) at 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.

9.2. 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 along with the number and percentage of patients who are administered full or partial dose. 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: IV' page of eCRF and weight (kg) on the 'Kit Number Dispensation' 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: IV', 'Study Drug Administration: SC_PFS', 'Study Drug Administration: SC_PFS (W56~W64)' and 'Study Drug Administration: SC_AI' page of eCRF. Only study drug except for placebo will be presented in table and listing.

10. EFFICACY ANALYSIS

Primary efficacy analysis on DAS28 (CRP) at Week 22 will be conducted on both the Efficacy and the All-Randomized populations. In addition, primary efficacy analysis on DAS28 (CRP) at Week 22 will be repeated on the Efficacy population by the adjusted treatment group (as defined in Section 5.4). Sensitivity analysis by imputing missing values will be conducted on the All-Randomized population. If significant GCP non-compliance is identified after unblinding, an additional sensitivity analysis will be performed for primary efficacy analysis on DAS28 (CRP) at Week 22. It will be conducted by considering GCP non–compliance sites on both Efficacy and All-Randomized populations. All other efficacy tables will be generated on the Efficacy population by actual treatment group. All efficacy listings will be based on the All-Randomized population.

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) and Simplified Disease Activity Index (SDAI), health assessment questionnaire (HAQ) and Short-Form Health Survey (SF-36) at the each time points specified in the schedule of events (in Appendix 1-1 and Appendix 1-2).

10.1. DAS and EULAR Response Criteria

10.1.1. 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.

10.1.2. Visual Analogue Scale (VAS)

The VAS ranges from 0 to 100 mm, with higher scores indicating poorer status or more severe pain. A VAS is used to record the Patient's 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.

10.1.3. 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. CRP and ESR will be listed along with the other PD parameters (in Section 12) on All-Randomized population.

10.1.4. DAS28

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

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

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

Where:

- TJC28 = Tender Joint Count (0-28)
- SJC28 = Swollen Joint Count (0-28)
- ESR = ESR measurement (mm/h)
- CRP = CRP measurement (mg/L)
  Note: CRP in SI unit will be converted from 'mg/dL' to 'mg/L'
- GH = patient's global disease activity measured on VAS (0 – 100 mm)

Descriptive statistics for actual value and change from baseline in disease activity measured by DAS28 (ESR) and DAS28 (CRP) will be presented at each scheduled visit. DAS28 components, DAS28 value and change from baseline for both DAS28 (ESR) and DAS28 (CRP) will be listed. The DAS28 will be displayed to two decimal places.

10.1.4.1. Primary Analysis

Change (decrease) from baseline for ANCOVA will be defined as decrease from baseline and calculated as (DAS28 [CRP] at baseline – DAS28 [CRP] at Week 22). An ANCOVA comparing the change (decrease) from baseline of DAS28 (CRP) at Week 22 between two treatment groups, CT-P13 SC and CT-P13 IV, will be conducted on the Efficacy population and All-Randomized population, respectively. In addition, the ANCOVA will be repeated on the Efficacy population by the adjusted treatment group. The treatment will be considered as fixed effect, country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL), and Week 6 body weight (≤100 kg vs. >100 kg) will be considered as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region (Europe [Bosnia, Bulgaria, Estonia, Hungary, Latvia, Poland, Russia, Spain, and Ukraine], non-Europe [Korea, Chile, and Peru]) may be used instead. These fixed effect and covariates will be used in additional ANCOVA unless otherwise specified. The least squares mean and corresponding standard error of the change (decrease) from baseline in DAS28 (CRP) at Week 22 will be presented for each treatment group. A point estimate and 2-sided 95% CI for the treatment difference (CT-P13 SC 120 mg – CT-P13 IV 3 mg/kg) will also be provided.

10.1.4.2. Sensitivity Analysis

The descriptive summary (Section 10.1.4) and ANCOVA (Section 10.1.4.1) will be repeated for DAS28 (CRP) at Week 22 on All-Randomized population by imputing missing values based on the Multiple Imputation (MI) under the Missing At Random (MAR) assumption. Missing values in change from baseline of DAS28 (CRP) will be imputed using regression method with country (or region), Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL), and Week 6 body weight (≤100 kg vs. >100 kg) as covariates. Ten complete datasets will be created. The average of statistics from the 10 complete datasets will be presented.

If significant GCP non-compliance is identified after unblinding, the ANCOVA will be performed for DAS28 (CRP) at Week 22 by considering GCP non–compliance sites on both Efficacy and All-Randomized populations.

10.1.5. 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 2. European League Against Rheumatism Response Criteria

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

Reference: Fransen et al 2005

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

10.2. ACR20, ACR50, ACR70 Criteria and Hybrid ACR

10.2.1. 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.

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

General health status will be assessed using the Health Assessment Questionnaire (HAQ) consisting of the following 8 categories.

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

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

There are 3 steps to scoring the HAQ:

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

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

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

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

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

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

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

VAS scale result, total length of VAS scale on the questionnaire and the standardized VAS to show the patient's illness in the past week (0-no pain, 100-severe pain).

10.2.3. 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:

- At least 20% decrease from baseline in the number of tender and swollen joints, and
- At least 20% decrease 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 evaluated similarly to ACR20. However, a decrease of 50% and 70%, respectively, must be achieved.

The proportion of patients achieving clinical response according to the criteria for ACR20, ACR50 and ACR70 will be summarized at each scheduled visit. Denominator will be the number of patients on Efficacy population. A listing will be provided by treatment group and visit, showing ACR20, ACR50 and ACR70 responder status at each visit.

10.2.4. Hybrid ACR

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

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

The steps to calculate the hybrid ACR are as follows:

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

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

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

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

Table 4. Scoring Method for Hybrid ACR

	Mean % change in core set measures			
ACR Status	**<20**	**≥20, <50**	**≥50, <70**	**≥70**
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

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

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

10.3. Clinical Disease Activity Index and Simplified Disease Activity Index

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

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

Where:

- SJC28 = swollen joint count (0-28)
- TJC28 = tender joint count (0-28)
- PGA = patient global assessment of disease activity (0-10 cm)
- EGA = evaluator/physician global assessment of disease activity (0-10 cm)
- CRP = CRP measurement (mg/dL)

Note: Prior to calculation of the CDAI and SDAI, the PGA and EGA on VAS results should be converted from ‘mm’ to ‘cm’.

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.

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

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

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

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

- Physical Component Summary (PCS)
- Mental Component Summary (MCS).

The 8 subscale scores and 2 component summary scores will be derived using [redacted]. The scores of the SF-36 survey ranges from 0 (worst) to 100 (best), with a higher score indicating a better health-related quality of life.

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

10.5. Joint 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.

11. PHARMACOKINETIC ANALYSIS

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

11.1. Serum Concentrations

PK samples will be collected at pre-dose (prior to the beginning of the study treatment administration on dosing day) of each time points specified in the schedule of events (Appendix 1-1). 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 5.

All patients will be randomly assigned at Week 14 in a 1:1:1:1 ratio to one of the 4 groups, Group A, B, C or D, to collect blood samples at specific PK monitoring time points:

Table 5. Steady state PK sampling Time points

Visit (Day)	Group A	Group B	Group C	Group D
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 8 and 24 hr (±15 min) after SOI	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 48 hr (±2 hr) after SOI • 9 days after SOI at Week 22 (or 216 hr (±6 hr) after SOI)	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 96 hr (±4 hr) after SOI	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 7 days after SOI at Week 22 (or 168 hr (±6 hr) after SOI)
Week 24 (Day 168)	• N/A	• N/A	• 14 days (±1 day) after SOI at Week 22 *	• N/A
Week 26 (Day 182)	• N/A	• N/A	• N/A	• Pre-dose*
Week 28 (Day 196)	• 42 days (±1 day) after SOI at Week 22 *	• N/A	• N/A	• N/A
Week 30 (Day 210)	• Pre-dose* (or 56 days (±1 day) after SOI at Week 22**)			

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 descriptive summary of serum concentration, BLQ prior to the first administration (Week 0, Dose 1) will be treated as zero (0), and all other BLQ values will be set to Lower Limit of Quantification (LLoQ).

Mean serum concentration versus scheduled sample time plots for study drugs will 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.

11.2. Pharmacokinetic Parameters

Individual serum concentration data over actual time data will be used to calculate PK parameters of infliximab. Due to the sparse PK sampling time points, population PK model will be employed to estimate the individual subject PK parameters by a non-linear mixed effect PK model using [redacted] version [redacted] or higher. For the calculation of PK parameters, depending on the percentage of BLQ values alternative imputations methods will be explored and applied as deemed appropriate. A full dosing history will be used for PK parameter derivation.

The following PK endpoints between Week 22 and Week 30 will be estimated using population PK model:

- AUC_{τ}: Model predicted area under the concentration-time curve at steady state between Week 22 and Week 30
- C_{max}: Model predicted maximum serum concentration after study drug administration
- C_{trough}: Model predicted trough serum concentration

Specifically, $AUC_{Week22\text{-}30}$ of SC treatment group will be additionally estimated using population PK model due to different dosing interval of SC and IV administration. $AUC_{Week22\text{-}30}$ of SC treatment group will be compared with AUC_{τ} of IV treatment group.

The following PK endpoints will be obtained up to Week 54:

- C_{trough}: Observed trough serum concentration (concentration before the next study drug administration)

The PK parameters will be presented in listings and summarized in tables by treatment group for the PK population.

12. PHARMACODYNAMIC ANALYSIS

Pharmacodynamic (PD) parameters (Rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP], CRP and ESR) will be summarized displaying descriptive statistics for actual value and change from baseline on the PD population by treatment group at each scheduled visit specified in the blood sampling times (in Appendix 2). Descriptive statistics will consist of n, mean, SD, geometric mean, CV%, minimum, median and maximum. 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.

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

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

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

All PD data for RF, anti-CCP, CRP and ESR will be listed by treatment group on the All-Randomized population at each scheduled visit along with the categorized results for RF and anti-CCP.

13. 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), weight, BMI, 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.

13.1. Adverse Events

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

A treatment-emergent adverse event (TEAE) is defined as any event not present 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 Infusion related reaction (IRR), systemic injection reaction or delayed hypersensitivity; whether the AE is localized injection site reaction; infection/malignancy flag; and whether the AEs occured on or after Week 30. All AEs will be listed.

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

13.1.1. Incidence of Treatment-Emergent Adverse Events

The TEAEs during the study will be summarized by treatment group and SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE over all SOCs will also be displayed. The summaries will be repeated in separate tables for TEAEs occurred in maintenance phase and on or after Week 30, respectively. 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. In addition, TEAEs with PT reported for at least 3% of patients in either treatment group will be summarized separately.

13.1.2. Deaths

All patients who have a Serious Adverse Event (SAE) with serious criteria of "Death" will be presented in a listing and the following variables will be included; date of first/last dose, date of last visit, date of death, time to death from first/last dose, days on study, TEAE flag, SOC/ PT/ cause of death, whether an autopsy was performed (yes, no), whether a death certificate was completed (yes, no), relationship to study drug and whether the AEs occured on or after

Week 30. Time (days) to death from first/last dose will be calculated as (date of death – date of first/last dose + 1). In case of death during the study, days on study will be calculated as (date of death – date of first dose +1). Otherwise, days on study will be calculated as (date of last visit – date of first dose +1).

13.1.3. Serious Adverse Events

An SAE is defined as any event that is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or results in death. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient 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 and on or after Week 30, respectively.

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

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

All patients who have a TEAE with an action taken with study drug of "Drug Withdrawn" will be summarized by treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE leading to study drug discontinuation, using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE which led to study drug discontinuation will also be displayed. The summaries will be repeated in a separate table for TEAEs leading to study drug discontinuation occurred in maintenance phase and on or after Week 30, respectively.

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

13.1.5. Treatment-Emergent Adverse Events of Special Interest

The AEs of special interest are as following:

- Infusion related reaction (IRR), Systemic injection reaction and Delayed hypersensitivity
  AEs checked as Infusion related/anaphylactic reaction/hypersensitivity (ARR) in the eCRF will be classified as infusion related reaction (IRR), systemic injection reaction or Delayed hypersensitivity based on the date/time of latest administration, as shown in the table below. If administration time or AE start time is unknown, AEs that occurred within 1 day after study drug administration will be classified as IRR or systemic injection reaction, otherwise, will be classified as Delayed hypersensitivity.

The latest administration before AE	AE Occurrence Time	Classification
IV Infusion	between IV infusion start and after 24 hours of IV infusion end	Infusion related reaction
	after 24 hours of IV infusion end	Delayed hypersensitivity
SC Injection	between SC injection start and after 24 hours of SC injection start	Systemic injection reaction
	after 24 hours of SC injection start	Delayed hypersensitivity

- Localized injection site reaction
  AEs classified as injection site reactions (ISR) in the eCRF will be included.
- Infection
  AEs coded with a SOC of 'Infections and Infestations' will be included.
- Malignancy
  AEs coded with a SOC 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.

The IRR, Systemic injection reaction and Delayed hypersensitivity will be summarized together in one table, and the other TEAEs of special interest will be summarized in separate tables. These are displayed by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the most severe TEAE recorded at each levels of summarization. The total number of events and number of patients with at least one TEAE of special interest will also be displayed. In addition, tables for signs and symptoms regarding IRR, Systemic injection reaction and Localized Injection site reaction 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 a separate table for TEAEs of special interest occurred on or after Week 30.

TEAEs classified as IRR, Systemic injection reaction and Localized injection site reaction will be presented in separate listings including a subset of the variables detailed in Section 13.1. Experienced Signs and symptoms will be presented in additional information listings for IRR, Systemic injection reaction and Localized injection site reaction, separately. Delayed hypersensitivity will be flagged in IRR and Systemic injection reaction listings. Infection and malignancy will be flagged in listings for AEs.

13.2. 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 and ESR 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 treatment group, laboratory category, test parameter and visit.

The central laboratory test results for parameters including urinalysis, clinical chemistry and hematology (if applicable) are categorized with Normal and Abnormal and then will be summarized in a shift table from baseline to each scheduled visits. The number and percentage of patients will be displayed for post-baseline visits by treatment group, 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. 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 3. 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.

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

Complement (C3, C4) and total haemolytic complement will be assessed at Week 0. 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. All complement tests data will be presented in a listing by treatment group for the ITT population.

13.4. Vital Signs and Weight

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

During the double-blinded period, hypersensitivity will be assessed at the time points specified in the schedule of events (Appendix 1-1 and Appendix 1-2) and recorded at the following time points:

- Prior to the beginning of the SC formulation (either CT-P13 SC or placebo SC) injection
- 1 hour (±10 minutes) after the end of the IV formulation (either CT-P13 I V or placebo IV) infusion

All vital signs data and weight 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 6. Hypersensitivity Classification for Vital Signs

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

All vital signs data including hypersensitivity monitoring results, 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.

13.5. 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.

13.6. 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.

13.7. 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". If retest is conducted because the IGRA result is indeterminate, the result of the retest will be used for the summary. Both first and retest results will be listed. The number and percentage of patients with IGRA results will be summarized for baseline (as defined in Section 5.5) and Treatment Period for the Safety population. The all post-baseline result of IGRA in a Treatment Period including EOS will be reported by IGRA result at Baseline using the following methodology:

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

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.

13.8. 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. During the double-blinded period, local site pain will be assessed either immediately (within 15 minutes) after the end of SC injection (either CT-P13 SC or placebo SC) prior to receiving IV infusion (either CT-P13 IV or placebo IV) or immediately (not exceeding 1 hour) after the end of IV infusion (either CT-P13 IV or placebo IV). Local site pain data will be summarized using descriptive statistics by administration type, 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.

13.9. 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", "Negative" or "Inconclusive". 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 the results of serum and urine pregnancy test will be summarized by treatment group and visit (including EOS for serum pregnancy 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.

13.10. Immunogenicity

Serum sample for immunogenicity will be collected at Week 0, 6, 14, 22, 30, 38, 46, 54, and EOS visit. 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. In addition, proportion of patients who reported at least one ADA positive result after Week 0 administration in patients who had at least one ADA result after first administration, and had not any ADA positive result before first administration is presented. This will exclude result at EOS visit, and be repeated for NAb results. 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.

14. USABILITY ANALYSIS

All usability tables and listings will be generated using all data for the Usability population. Usability will be assessed by the evaluation of Self Injection Assessment Questionnaire (SIAQ), Self – Injection Assessment Checklist and Potential Hazards Checklist at each time points specified in the schedule of events (Appendix 1-2).

14.1. Self-Injection Assessment Questionnaire (SIAQ)

Usability will be assessed using the SIAQ prior and after self-injection of CT-P13 SC via AI from Week 46 to 54 and via PFS from Week 56 to Week 64 at the time points specified in the schedule of events (Appendix 1-2). The PRE module of the SIAQ is a 7-item questionnaire that investigates 3 domains such as feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection (each item graded on a 5-points). The POST module of the SIAQ is a 27-item questionnaire that assesses feelings about injection, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection (injection-site reactions), ease of use of the self-injection device (either AI or PFS), and satisfaction with self-injection. Each item graded on either a 5-point or 6-point scale.

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

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

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

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

The domain scores of PRE and POST module of SIAQ will be summarized using descriptive statistics by each scheduled visit and domain. A listing for PRE and POST module of SIAQ will be presented showing the raw scores for each questions and domain scores. The domain scores will be displayed to one decimal places

14.2. Successful Self-injection

Patients' ability to successfully follow the steps in the Instruction for Use to self-administer CT-P13 SC via AI from Week 46 to 54 and via PFS from Week 56 to Week 64 will be assessed using self-injection assessment checklist at the time points specified in the schedule of events (Appendix 1-2). The healthcare professional will observe the patient preform self-injection and complete the checklist within 15 minutes after patient's self-injection. Successful self-injection will be defined if P7, P9, P10 and P11 on both of the self-injection assessment checklists for SC via AI and PFS are checked as Yes. Summary table will display proportion of patients completing the successful self-injection and proportion of patients completing all instructions, respectively (14 instructions on the 'Self-Injection Assessment Checklist: SC_AI' page and 13 instructions on the 'Self-Injection Assessment Checklist: SC_PFS' page of the eCRF). All answers for checklists will be listed along with whether this injection is successful and all instructions are completed.

14.3. Hazard-Free Self-injection

The occurrence of observed or reported difficulties ('potential hazards') will be assessed using potential hazards checklist at the time points specified in the schedule of events (Appendix 1-2). The healthcare professional will observe the patient preform self-injection and complete the checklist within 15 minutes after patient's self-injection. Injection is considered as hazard-free self-injection if there is none of the hazard based on the 'Potential Hazard Checklist' page of the eCRF.

Summary table will display proportion of patients with hazard-free self-injection. All answers for 9 checklists will be listed along with whether this injection is hazard free.

15. Changes in the Planned Analysis

15.1. Changes in the Protocol

1. Usability population was added in the SAP from the protocol in country specific C to analyze the usability assessments.

2. The definitions of AUC_{τ}, C_{max} and C_{trough} was updated to clarify that the PK endpoints between Week 22 and 30 are model predicted values calculated by population PK model.

3. For the clarification of the systemic and localized reaction of the drug, the adverse event reported as "Administration Related Reaction" in eCRF and occurred within 1 day after study drug administration was classified as "Infusion Related Reaction" for IV infusion and "Systemic Injection Reaction" for SC injection. The AE reported as "Injection Site reaction" in eCRF was analysed as "Localized injection site reaction."

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17. Appendix

Appendix 1-1: Study Schedule of Events

	Screening	Treatment Period										EOS[1]
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[25]**	**30**	**38**	**46**	**54**	
Study Day	**–42 ~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**									
Arm 1 treatment[2, 3]		**IV**	**IV**	**IV + Placebo SC**	**IV + Placebo SC**	**IV + Placebo SC**	**Placebo SC**	**SC[4]**				
Arm 2 treatment[2, 3]				**SC + Placebo IV**	**SC + Placebo IV**	**SC + Placebo IV**	**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[9]	X											X
Urine pregnancy test[10]		X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	
Clinical laboratory tests[11]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Chest x-ray[12]	X											
Interferon-γ release assay[13]	X							X[8]			X[8]	X[17]
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[14]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
12-lead ECG[15]	X			X	X			X			X	X
Efficacy assessments:												
Tender joint count[16] (68 joints/28 joints)	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
Swollen joint count[16] (66 joints/28 joints)	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
VAS pain score	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
VAS global assessment of disease activity (patient and physician) score	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
Health Assessment Questionnaire	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
ESR (local)[18]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X

CRP[18]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
QOL (SF-36) assessment	X	X[8]		X[8]	X[8]	X[8]		X[8]			X[8]	X[17]
VAS local site pain[19]				X	X	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
Anti-cyclic citrullinated peptide	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Immunogenicity[20]		X[8]		X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Hypersensitivity monitoring[21]		X	X	X[22]	X[22]	X[22]		X	X	X	X	
Complement (C3, C4) and Total Haemolytic Complement[23]		X[8]										
Pharmacokinetic blood sampling[24]		X[8]	X[8]	X[8]	X[8]	X[8]	X[25]	X[8]	X[8]	X[8]	X[8]	
Biomarker[26]		X[8]										
Previous/concomitant medications[27]	X											
TB clinical monitoring[28]	X											
AEs monitoring[29]	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; QOL, quality of life; SC, subcutaneous; TB, tuberculosis; VAS, visual analogue scale.

1. The End-of-Study (EOS) Visit will occur 2 weeks after the last dose of CT-P13 SC is received. For patients who early discontinue the study before Week 30, all End-of-Study (EOS) assessments will be completed 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS assessments will be completed 2 weeks after the last CT-P13 SC is received. (In protocol version 4.0 country specific B.1, all EOS assessments will be completed 8 weeks after the last study drug administration.)
2. During the double-blinded period, SC formulation (either CT-P13 SC or placebo SC) will be injected initially prior to receiving IV infusion (either CT-P13 IV or placebo IV). IV infusion will be initiated immediately within 15 minutes after the completion of SC injection.
3. CT-P13 SC (or placebo SC during the double-blinded period) will be injected by a healthcare professional at each site visit (Weeks 6, 14, 22, 24~28 [for patients who will make visit for additional PK assessment], 30, 38, 46 and 54). After proper training in injection technique, patients may self-inject with CT-P13 SC (or placebo SC during the double-blinded period) if their investigator determines that it is appropriate at any other weeks (Weeks 8, 10, 12, 16, 18, 20, 24~28 [for patients who will not make visit for additional PK assessment], 32, 34, 36, 40, 42, 44, 48, 50 and 52).
4. CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30 for Arm 1. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 54.
5. Age, gender, ethnicity 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. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
8. Assessed/performed prior to study drug administration.
9. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS Visit.
10. A urine pregnancy test for women of childbearing potential 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.
11. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analyzed 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.

12. 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.
13. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period and at EOS 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
    - Patient with positive IGRA result during the study
14. 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.
15. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
16. An independent joint count assessor will be assigned to each site. It is recommended that the joint count assessments are performed by the same person, when possible, for all patients at each site throughout the entire study period. Standardizing training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records. Joint taken any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For the assessment, independent joint assessor will be informed about history of patient's joint surgery with the name of the surgery, date and location.
17. End-of-study assessment will be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54.
18. Both ESR rate and CRP are considered to be an efficacy, pharmacodynamics, and safety (clinical laboratory test) endpoint. CRP samples should be drawn at the same time as the clinical laboratory blood samples and ESR samples will be analyzed at the local laboratory using kits supplied centrally.
19. 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. During the double-blinded period, local site pain will be assessed at the following time points:
    - Immediately (within 15 minutes) after the end of SC injection (either CT-P13 SC or placebo SC) prior to receiving IV infusion (either CT-P13 IV or placebo IV)
    - Immediately (not exceeding 1 hour) after the end of IV infusion (either CT-P13 IV or placebo IV)
20. 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.
21. 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).
22. Hypersensitivity will be assessed prior to the beginning of the SC formulation (either CT-P13 SC or placebo SC) injection and 1 hour (±10 minutes) after the end of the IV formulation (either CT-P13 IV or placebo IV) infusion.
23. 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.
24. 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.
25. Blood samples for pharmacokinetic analysis will be obtained at the time point specified in Table 5.
26. Only for patients who sign a separate informed consent form for the biomarker study (genotypes). Testing will be performed at the assigned testing facilities.
27. Use of all prior and concomitant medications for the treatment of rheumatoid arthritis, from the diagnosis of disease until the last assessment date or EOS 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 EOS Visit, will be recorded. All concomitant medications will also be recorded when any SADRs occur after the EOS Visit.

28. 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.
29. Adverse events will be assessed from the date the ICF is signed until the last assessment date or EOS Visit. Where AEs are ongoing at the EOS visit, 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. Serious adverse drug reactions occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it will be followed up for a further 30 days. Adverse events of special interest (i.e. infusion related reaction, systemic injection reaction, localized injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Appendix 1-2: Study Schedule of Events for Protocol including Country Specific C

	Screening	Treatment Period												EOS[1]
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[25]**	**30**	**38**	**46**	**54**	**56**	**64**	
Study Day	**–42 ~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	**392**	**448**	
Visit Window		**N/A**		**± 3 days**										
Arm 1 treatment[2, 3]		**IV**	**IV**	**IV + Placebo SC**	**IV + Placebo SC**	**IV + Placebo SC**	**Placebo SC**	**SC[4]**		**SC via AI[5]**		**SC via PFS[6]**		
Arm 2 treatment[2, 3]				**SC + Placebo IV**	**SC + Placebo IV**	**SC + Placebo IV**	**SC**							
Informed consent	X													
Demography[7]	X													
Medical history[8]	X													
Hepatitis B & C and HIV-1 and -2[9]	X													
Inclusion and exclusion criteria	X	X[10]												
Randomization				X[10]										
Serum pregnancy test[11]	X													X
Urine pregnancy test[12]		X[10]	X[10]	X[810]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	
Clinical laboratory tests[13]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
Chest x-ray[14]	X													
Interferon-γ release assay[15]	X							X[10]			X[10]			X
Physical examinations	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
Vital signs and Weight[16]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
12-lead ECG[17]	X			X	X			X			X			X
Efficacy assessments:														

	Screening	Treatment Period											EOS[1]
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[25]**	**30**	**38**	**46**	**54**	**56**	**64**	
Study Day	**–42 ~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	**392**	**448**	
Visit Window		**N/A**		**± 3 days**										
Tender joint count[18] (68 joints/28 joints)	X	X[10]	X[10]	X[810]	X[10]	X[10]		X[10]			X[10]			X[19]
Swollen joint count[18] (66 joints/28 joints)	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
VAS pain score	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
VAS global assessment of disease activity (patient and physician) score	X	X[10]	X[10]	X[10]	X[10]	X[810]		X[10]			X[10]			X[19]
Health Assessment Questionnaire	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
ESR (local)[20]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
CRP[20]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
QOL (SF-36) assessment	X	X[10]		X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
VAS local site pain[21]				X	X	X		X	X	X	X			
Rheumatoid Factor	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
Anti-cyclic citrullinated peptide	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
Immunogenicity[22]		X[10]		X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
Hypersensitivity monitoring[23]		X	X	X[24]	X[24]	X[24]		X	X	X	X	X	X	
Complement (C3, C4) and Total Haemolytic Complement[25]		X[10]												
Pharmacokinetic blood sampling[26]		X[10]	X[10]	X[10]	X[10]	X[10]	X[27]	X[10]	X[10]	X[10]	X[10]			
Biomarker[28]		X[10]												
PRE- and POST-SIAQ[29]										X	X	X	X	
Self- injection assessment checklist[30]										X	X	X	X	
Potential Hazards Checklist[30]										X	X	X	X	
Previous/concomitant medications[31]	X													
TB clinical monitoring[32]	X													
AEs monitoring[33]	X													

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; AI, auto-injector; CRP, C-reactive protein; ECG, Electrocardiogram; ESR, erythrocyte sedimentation rate; EOS, end of study; HIV, human immunodeficiency virus; IV, intravenous; N/A, not applicable; PFS, pre-filled syringe; QOL, quality of life; SC, subcutaneous; SIAQ, self-injection assessment questionnaire; TB, tuberculosis; VAS, visual analogue scale.

1. The EOS assessments will be completed 2 weeks after the last dose of CT-P13 SC via PFS is received. For patients who early discontinue the study before Week 30, all EOS assessments will be completed 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS assessments will be completed 2 weeks after the last CT-P13 SC via PFS or AI is received.
2. During the double-blinded period, SC formulation (either CT-P13 SC or placebo SC) will be injected initially prior to receiving IV infusion (either CT-P13 IV or placebo IV). IV infusion will be initiated immediately within 15 minutes after the completion of SC injection.

3. CT-P13 SC via PFS (or placebo SC via PFS during the double-blinded period) will be injected by a healthcare professional at each site visit (Weeks 6, 14, 22, 24~28 [for patients who will make visit for additional PK assessment], 30 and 38). After proper training in injection technique, patients may self-inject with CT-P13 SC via PFS (or placebo SC via PFS during the double-blinded period) if their investigator determines that it is appropriate at any other weeks (Weeks 8, 10, 12, 16, 18, 20, 24~28 [for patients who will not make visit for additional PK assessment], 32, 34, 36, 40, 42 and 44).
4. CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30 for Arm 1. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 44.
5. Patients will be administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54. CT-P13 SC via AI will be self-injected under observation of healthcare professional at each site visits (Week 46 and 54). Self-injection training will be provided at Week 46 prior to the first AI injection. After proper training in AI injection technique, patient may self-inject with CT-P13 SC via AI at home at any other weeks (Weeks 48, 50 and 52).
6. Switching back to CT-P13 SC via PFS at Week 56 will be implemented at selected sites. At Week 56, patients will be switched back to CT-P13 SC via PFS and self-injection retraining will be provided prior to the Week 56 PFS injection. CT-P13 SC via PFS will be self-injected under observation of healthcare professional at Week 56 and 64. After proper training in PFS injection technique, patient may self-inject with CT-P13 SC via PFS at home at Weeks 58, 60 and 62.
7. Age, gender, ethnicity and race.
8. At Screening, patients will be assessed for the history of rheumatoid arthritis, respiratory disease, diabetes mellitus, congestive heart failure and etc.
9. 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. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
10. Assessed/performed prior to study drug administration.
11. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS Visit.
12. A urine pregnancy test for women of childbearing potential 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.
13. 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.
14. 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.
15. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period and at EOS for the following patient:
    - 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
    - Patient with positive IGRA result during the study
    - If the patient early discontinued the study at Week 30 and was assessed IGRA, no IGRA test is required at EOS visit.
16. 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.
17. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
18. An independent joint count assessor will be assigned to each site. It is recommended that the joint count assessments are performed by the same person, when possible, for all patients at each site throughout the entire study period. Standardizing training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records. Joint taken any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For the assessment, independent joint assessor will be informed about history of patient's joint surgery with the name of the surgery, date and location.
19. End-of-study assessment will be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54.

20. Both ESR rate and CRP are considered to be an efficacy, pharmacodynamics, and safety (clinical laboratory test) endpoint. CRP samples should be drawn at the same time as the clinical laboratory blood samples and ESR samples will be analysed at the local laboratory using kits supplied centrally.
21. 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. During the double-blinded period, local site pain will be assessed at the following time points:
    - Immediately (within 15 minutes) after the end of SC injection (either CT-P13 SC or placebo SC) prior to receiving IV infusion (either CT-P13 IV or placebo IV)
    - Immediately (not exceeding 1 hour) after the end of IV infusion (either CT-P13 IV or placebo IV)
22. 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.
23. 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).
24. Hypersensitivity will be assessed prior to the beginning of the SC formulation (either CT-P13 SC or placebo SC) injection and 1 hour (±10 minutes) after the end of the IV formulation (either CT-P13 IV or placebo IV) infusion.
25. 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.
26. 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.
27. Blood samples for pharmacokinetic analysis will be obtained at the time point specified in Table 5.
28. Only for patients who sign a separate informed consent form for the biomarker study (genotypes). Testing will be performed at the assigned testing facilities.
29. PRE-SIAQ will be completed by patient prior to self-injection of CT-P13 SC and POST-SIAQ will be completed by patient after self-injection of CT-P13 SC at every injection (AI: Week 46, 48, 50, 52 and 54; PFS: 56, 58, 60, 62 and 64). Patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of study drug and POST-SIAQ immediately (not exceeding 1 hour) after the administration of study drug.
30. The healthcare professional will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection at Week 46, 54, 56 and 64. If additional training in either AI or PFS technique is given, checklist should be additionally assessed.
31. Use of all prior and concomitant medications for the treatment of rheumatoid arthritis, from the diagnosis of disease until the last assessment date or EOS 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 EOS Visit, will be recorded. All concomitant medications will also be recorded when any SADRs occur after the EOS Visit.
32. 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.
33. Adverse events will be assessed from the date the ICF is signed until the last assessment date or EOS Visit. Where AEs are ongoing at the EOS visit, 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. Serious adverse drug reactions occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it will be followed up for a further 30 days. Adverse events of special interest (i.e. infusion related reaction, systemic injection reaction, localized injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Appendix 2: Blood Sampling Times for Pharmacodynamic and Safety Assessments

Study Period		PD		Safety				Biomarker
Week	Day	CRP, ESR	RF, anti-CCP	Clinical Laboratory Analysis	IGRA	Immunogenicity	Complement (C3, C4) and Total Haemolytic Complement	
Screening	-42 ~	Time not specified[2]	Time not specified[2]	Time not specified[2]	Time not specified[2]	-	-	-
0	0	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]
2	14	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	N/A	Additional serum sampling if delayed hypersensitivity occurs after 24 hours of study drug administration	-
6	42	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]		-
14	98	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]		-
22	154	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]		-
30	210	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]		-
38	266	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]		-
46	322	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	-	Pre-treatment[1]		-
54	378	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]		-
56[3]	392	-	-	Pre-treatment[1]	-	-	-	-
64[3]	448	-	-	Pre-treatment[1]	-	-	-	-
EOS[4]		Time not specified[2]	Time not specified[2]	Time not specified[2]	Time not specified[2]	Time not specified[2]		-

Abbreviations: anti-CCP, Anti-cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EOS, end of study; IGRA, Interferon-γ release assay; RF, rheumatoid factor.

1. Pre-treatment: Blood samples will be obtained prior to the study drug administration.
2. Time not specified: Blood samples will be obtained any time during the day.
3. Protocol including country specific C only.
4. The EOS assessments will be completed 2 weeks after the last dose of CT-P13 SC via AI is received. For patients who early discontinue the study before Week 30, all EOS assessments will be completed 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS assessments will be completed 2 weeks after the last CT-P13 SC via PFS or AI is received. (In protocol version 4.0 country specific B.1, the EOS assessment will be completed 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.) For the IGRA, EOS assessment will be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54 (Excluding protocol for country specific C.2).

Appendix 3: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <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	High	Increase in >0 - 2 gm/dL above 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	-

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
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.